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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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1 **Title:** Protocol for Project Recovery: Cardiac Surgery - Leveraging Digital
2 Platform for Efficient Collection of Longitudinal Patient-Reported Outcome Data
3 Towards Improving Postoperative Recovery
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25 longitudinal, latent class
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1
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3 39
4 40 **Abstract** (287/300)
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6
7 41 Introduction
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10 42 Improving postoperative patient recovery after cardiac surgery is a priority,
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12 43 but our current understanding of individual variations in recovery and factors
13
14 44 associated with poor recovery is limited. We are using a health-information
15
16 45 exchange platform to collect patient-reported outcome measures (PROMs) and
17
18 46 wearable device data to phenotype recovery patterns in the 30-day period after
19
20 47 cardiac surgery hospital discharge, to identify factors associated with these
21
22 48 phenotypes and to investigate phenotype associations with clinical outcomes.
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29 50 Methods and analysis
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32 51 We designed a prospective cohort study to enroll 200 patients undergoing
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34 52 valve, coronary artery bypass graft, or aortic surgery at a tertiary center in the
35
36 53 U.S. We are enrolling patients postoperatively after the intensive care unit (ICU)
37
38 54 discharge, and delivering electronic surveys directly to patients every 3 days for
39
40 55 30 days after hospital discharge. We will conduct medical record reviews to
41
42 56 collect patient demographics, comorbidity, operative details and hospital course
43
44 57 using the Society of Thoracic Surgeons (STS) data definitions. We will use phone
45
46 58 interview and medical record review data for adjudication of survival,
47
48 59 readmission, and complications. We will apply group-based trajectory modeling
49
50 60 to the time-series PROM and device data to classify patients into distinct
51
52 61 categories of recovery trajectories. We will evaluate whether certain recovery
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62 pattern predicts death or hospital readmissions, as well as whether clinical
63 factors predict a patient having poor recovery trajectories. We will evaluate
64 whether early recovery patterns predict the overall trajectory at the patient-level.

65

66 Ethics and dissemination

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

72

73 **Strengths and limitations of this study**

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

1
2
3 83 Text (4081 words)
4

5 84 **Background**
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7
8 85 Improving postoperative patient recovery is a priority. Readmission rates
9
10 86 in the post-operative period are high. Moreover, in the United States, the
11
12 87 expansion of episode-based payments and performance measures is increasing
13
14 88 interest in the post-acute experience of patients^{1,2}. However, we generally lack
15
16 89 systematically-collected information on the experience of patients in the post-
17
18 90 acute period, as few studies rigorously collecting information using established
19
20 91 patient-reported outcomes measures (PROMs). We have, for example, little
21
22 92 information about the variation of the trajectories of recovery and the factors most
23
24 93 strongly associated with better outcomes³.
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28 94 The assessment of the patient experience can provide important insights
29
30 95 into the process of recovery that is not evident through clinical outcomes or
31
32 96 intermittent clinical office visits. PROMs and wearable devices can provide
33
34 97 complementary information by providing measurements of how the patient's
35
36 98 experience and functional status change over time⁴. Current digital platforms
37
38 99 allow us to efficiently collect PROMs and wearable-generated data at high
39
40 100 frequencies and with little cost and burden. These automated data collection
41
42 101 approaches may minimize the bias introduced by clinician-directed patient
43
44 102 interviews⁵. Such a platform is highly suited to obtain repeated measures to
45
46 103 characterize a time-dependent process such as recovery⁶.
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51 104 Cardiac surgery is an ideal area for the study of recovery. Many patients
52
53 105 have good outcomes, but the limited existing evidence suggests a wide variation
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3 106 in the post-operative experience of these patients⁷. However, these patients'
4
5 107 experience has been poorly studied, as most studies of recovery simply assess
6
7 108 deaths and complications.
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10 109 Characterizing the recovery from the patient perspective is important for
11
12 110 many reasons. First, shared decision-making and informed consent should be
13
14 111 guided not only by the risk of mortality and complications but also by the recovery
15
16 112 experience. Understanding variations in recovery could enable the early
17
18 113 identification of people who are struggling and require additional attention.
19
20 114 Recovery data from the patient perspective may enable remote monitoring after
21
22 115 the procedure to selectively and preemptively intervene on those at high risk of
23
24 116 poor recovery to improve outcomes. Characterization of recovery can also be
25
26 117 used to identify patient, surgeon, procedural, and institutional factors that are
27
28 118 associated with different patterns. With this information we can identify modifiable
29
30 119 risk factors for poor recovery.
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35 120 Thus, at this juncture, there are several notable gaps in knowledge. First,
36
37 121 although recovery occurs over time, most studies of recovery included a small
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39 122 number of timepoints, and the recovery trajectory phenotypes remains poorly
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41 123 defined³. Cohort-level average of recovery trajectories is a common way of
42
43 124 reporting³ and can indicate how patients recover on average⁷, but it obscures
44
45 125 individual variation such as rapid early recovery, gradual recovery, or initial
46
47 126 recovery followed by a decline. Second, we have limited understanding of how
48
49 127 recovery trajectories vary by patient factors, operation types, center or surgeon
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3 128 characteristics, procedural processes, and complications, which limit
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5 129 opportunities to identify high risk patients preemptively and intervene.
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8 130 Accordingly, our overall objective is to characterize short-term trajectories
9
10 131 of patient recovery after cardiac surgery using PROMs and wearable data. We
11
12 132 are conducting a prospective study to characterize trajectories of postoperative
13
14 133 recovery in multiple domains after cardiac surgery. The specific aims of this study
15
16 134 are to: 1) leverage a digital data platform to collect PROM and wearable device
17
18 135 data to bring forth the variable individual recovery trajectories, 2) describe distinct
19
20 136 classes of recovery trajectories and clinical factors associated with the classes,
21
22 137 and 3) to evaluate whether early postoperative recovery trajectory predicts later
23
24 138 recovery trajectory. In addition, we will investigate optimal ways to manage
25
26 139 missing data specific to these time-series data This study is a step toward using
27
28 140 this approach to prospectively monitor and preemptively identify patients at risk of
29
30 141 poor recovery and facilitate intervention to reduce the risk of adverse events.
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36 37 143 **Methods**

38 144 *Design Overview*

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40
41 145 This is a prospective cohort study of patients who are undergoing valve,
42
43 146 CABG, or aortic surgery at a tertiary center in the U.S. We chose the operations
44
45 147 because they are the most common cardiac operations performed⁸. We are
46
47 148 enrolling patients postoperatively after ICU discharge in order to ensure clinical
48
49 149 stability, and we electronically delivering surveys directly to patients every 3 days
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52 150 for 30 days after hospital discharge to study patient trajectories in multiple
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3 151 domains characterizing recovery. The closing phone interview after 30 days,
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5 152 electronic medical record review, and linkage to the Society of Thoracic
6
7 153 Surgeons database are used to confirm survival, readmission, and complications.
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9
10 154 The closing interview asks about details of readmissions if they occurred,
11
12 155 patients' overall satisfaction with the study, and whether their experience was
13
14 156 well captured by the summary of their PROM data. We will apply group-based
15
16 157 trajectory modeling to the longitudinal PROM data to identify distinct categories of
17
18 158 recovery trajectories in a data-driven fashion. We also identify predictors of
19
20 159 protracted recovery trajectory and evaluate whether early recovery patterns (<10
21
22 160 days) predict the overall trajectory (30 days) at the patient-level. The Yale
23
24 161 Institutional Review Board approved this study.
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30 31 163 *Patient Population*

32
33 164 This study began in January 2019 and is ongoing. The study is taking
34
35 165 place at Yale-New Haven Hospital, a tertiary center in the United States, where
36
37 166 over 1,100 cardiac surgeries are performed annually. Inclusion criteria are
38
39 167 patients of age 18 and older who are undergoing coronary artery bypass grafting
40
41 168 (CABG), valve replacement or repair, or aortic operations. Exclusion criteria are
42
43 169 those who undergo heart transplant, extracorporeal membrane oxygenation
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45 170 (ECMO), adult congenital operations, or ventricular assist device implantation, as
46
47 171 these patient populations tend to have a longer course of intensive care unit
48
49 172 stay⁹, precluding the timely enrollment necessary to capture immediate
50
51 173 postoperative recovery. We also excluded those who do not own a smartphone
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3 174 or a tablet or those who do not speak or read English, because the digital
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5 175 platform for PROM data collection relies on patients responding to surveys
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7 176 displayed on web browser via email or text, and the surveys were written in
8
9
10 177 English language. We do not allow proxy for survey response and consequently
11
12 178 excluded patients who were not able to respond by themselves as determined by
13
14
15 179 the research assistant.

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17 180

181 *Recruitment*

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

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

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5 198 *PROM instrument and administration*

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7
8 199 We use 24-item quality of recovery (QoR-24) to characterize patients'
9
10 200 postoperative recovery in various domains. The questionnaire consists of 24
11
12 201 items that were developed and validated in inpatient and outpatient surgical
13
14 202 populations¹⁰⁻¹³. The instrument was previously adapted into a mobile format and
15
16 203 was successfully used to administer the survey daily for 14 days^{11, 12}. We added 3
17
18 204 items to QoR-24 to capture the self-reported time patients went to sleep, the time
19
20 205 they awakened, and their global perception of how much they have 'recovered' in
21
22 206 a 0-100% scale. The resulting 27-item questionnaire takes 2-4 minutes to
23
24 207 complete, making its frequent administration feasible (Supplementary Material
25
26 208 S2). Among the published studies in cardiac surgery, this study will have the
27
28 209 highest number of PROM data points collected in the first postoperative month³.

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33 21034
35 211 *Digital data platform*

36
37 212 We are delivering surveys on the day of enrollment and every 3 days for
38
39 213 30 days. This method provides detailed longitudinal data across multiple domains
40
41 214 of recovery (Figure 2). To facilitate data organization and scheduled survey
42
43 215 delivery, we use Hugo (Me2Health, LLC, Guilford CT, USA) a patient-centered
44
45 216 health data sharing platform, which has a customizable survey delivery function
46
47 217 and reminder feature to facilitate data collection. Hugo platform allows for
48
49 218 automated delivery of surveys without researchers having to directly contact
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51 219 patients, which facilitates high-frequency data collection. Additionally, it imports
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3 220 data from connected wearable devices to facilitate centralization of patient health
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5 221 data. The patients retain access to their own data in a cloud-based account.
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10 223 *Identifying common reasons for low response rate*

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12 224 Recognizing that the survey response will be incomplete for some
13
14 225 participants, we have conducted a phone interview with the first 22 patients to
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16 226 learn reasons for low responses and identify strategies to minimize the barriers
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18 227 toward survey response for subsequent participants. In the first 22 patients, we
19
20 228 identified 5 with response rate of <50% and conducted recorded phone
21
22 229 interviews. Our interview guide (Supplementary Material S3) contained questions
23
24 230 to elucidate technical barriers, differential preferences for engagement, and or
25
26 231 any other issues precluding survey completion. We also asked whether the
27
28 232 length of the questionnaire or types of questions asked made it difficult to
29
30 233 complete the survey. Two members of the research team (CB and MM)
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32 234 evaluated the interview recordings to identify common reasons for low response
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34 235 rate. This suggested the potential importance of reminder to maintain patient
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36 236 engagement. We modified the protocol to contact all participants approximately
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38 237 10 days after enrollment.
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49 240 *Additional clinical data and adjudication of hospitalization and survival*

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51 241 Additionally, we are using the Society of Thoracic Surgeons (STS) Adult
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53 242 Cardiac Surgery Database data specifications to retrospectively collect clinically
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3 243 relevant data in this patient population. Pre-specified candidate predictors in this
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5 244 database will be used to identify clinical predictors of recovery trajectories (Table
6
7 245 1). The STS database contains patient demographics, comorbidities, presenting
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10 246 clinical status, operative details, and postoperative mortality and morbidity up to
11
12 247 30 days after the time of operation¹⁴. These data are routinely collected at Yale
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14
15 248 New Haven Hospital.

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17 249 We will determine mortality and hospital readmissions by several
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19 250 approaches: review of hospital records, review of cardiac surgery clinic notes,
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21 251 and conducting closing phone interviews with the patient or contact person
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24 252 previously identified.

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27 28 254 *Patient Involvement*

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31 255 Prior to launching the study, we interviewed 5 patients both in pre and
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33 256 postoperative settings to evaluate whether the frequency of survey delivery and
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35 257 PROM instrument were likely to adequately capture their experience of recovery.
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38 258 All patients agreed that the frequency of questionnaire administration and the
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40 259 length of the PROM instrument were reasonable and provided face validity that
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42 260 the questionnaire captured aspects of recovery that were important to the
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45 261 patients. Additionally, this article is authored with a patient (LG) who participated
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47 262 in the study to reflect his perspective on the study design and experience in
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49 263 responding to the surveys.

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52 53 265 *Sample size*

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3 266 The study sample target is 200 patients. Adequate sample size for studies
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5 267 using group-based trajectory modeling depends on the dataset's
6
7 268 representativeness of the population of interest¹⁵. Therefore, the concept of
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9 269 statistical power traditionally used for sample size calculation does not apply to
10
11 270 latent class analyses. We may generate a larger simulation dataset from the
12
13 271 measured patient trajectory data to perform a split-sample testing, evaluating
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15 272 whether trajectories generated from the derivation sample would allow for
16
17 273 satisfactory categorization of the testing dataset. Additionally, the study setting is
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19 274 scalable to increase the sample size by increasing the enrollment period, should
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21 275 a larger sample size become necessary.
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27 277 *Analytical approach – group-based trajectory modeling*

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29
30 278 The resulting dataset is a complex time-series data, with each patient having 10
31
32 279 data points (one every three days) at different postoperative times for each item. A
33
34 280 practical approach to dimension reduction is group-based trajectory modeling, which is a
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36 281 type of latent class analysis that groups similar patient trajectories according to a number
37
38 282 of features derived from the time-series data^{16, 17}. This approach allows for dimension
39
40 283 reduction of the complex time-series data into several distinct classes of recovery
41
42 284 trajectories. These trajectories can be labeled according to the observed clinical
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44 285 phenotype of trajectories, for example 'fast recovery,' 'average recovery,' or 'protracted
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46 286 recovery,'. This data-driven categorization enables additional regression modeling to
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48 287 identify predictors of patients belonging to a certain class of recovery path.
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3 288 The dataset will be classified into distinct categories of trajectories at domain
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5 289 level, using group-based trajectory modeling^{16, 17}. Traj package on R¹⁸ or Proc Traj
6
7 290 package on SAS¹⁵, performs trajectory modeling by first extracting 24 features of patient-
8
9 291 level trajectory, selecting a subset of features that describes the overall trajectory, and
10
11 292 identifying optimal number of classes to group the trajectories based on the longitudinal
12
13 293 k-means method. The 24 features include range, mean change per unit time, and slope of
14
15 294 the linear model (Table 2), which have been demonstrated to discriminate between stable-
16
17 295 unstable, increasing-decreasing, linear-nonlinear, and monotonic-nonmonotonic patterns
18
19 296 of trajectories¹⁸. K-means method partitions the time-series data into k groups such that
20
21 297 the mean squared error distance of each data point from the assigned cluster is
22
23 298 minimized¹⁹. The optimal number of clusters is determined by the minimization of
24
25 299 Bayesian information criterion, which signifies the balance between model's complexity
26
27 300 and the ability to describe the dataset. This process yields distinct classes of patient
28
29 301 trajectories in a data-driven fashion. Trajectories will be identified separately for the 5
30
31 302 domains and 1 global recovery measure.
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40 304 *Analytical approach – missing data*

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42 305 Because missing data are inevitable in longitudinal PROMs, there is a
43
44 306 need employ an appropriate handling of missing data. Multiple imputation prior to
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46 307 latent class analysis may yield a less biased estimate of the resulting trajectories.
47
48 308 An alternative approach used in group-based trajectory models assumes the data
49
50 309 are missing at random (MAR) and generates the maximum likelihood of the
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52 310 model parameters²⁰. MAR is valid when the response attrition is independent of
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3 311 the group membership. However, patient attrition is oftentimes dependent on
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5 312 clinical characteristics and likely related to the class of trajectory itself. An
6
7 313 extension of the model allows for modeling of attrition across trajectory groups²¹,
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9 314 permitting dropout probability to vary as a function of covariates or observed
10
11 315 outcomes prior to dropout and yields a more robust estimate of the probability of
12
13 316 group membership. As such, we will perform sensitivity analysis to compare the
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15 317 trajectories generated via raw data vs. data preprocessed with multiple
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17 318 imputation vs. trajectories generated via trajectory model accounting for response
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19 319 attrition.
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26 321 **Results**

27
28 322 Between January and May 2019, we have enrolled 22 patients who
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30 323 completed the 30-day follow-up. In this cohort, median age was 58.5 years
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32 324 (interquartile range 53.5-67.0) and 7 (32%) were women. There were 9 (41%)
33
34 325 mitral valve repair cases and 6 isolated or concomitant CABG (27%).
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40 327 *Barriers to completing surveys*

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42 328 Of the 22 patients enrolled, 3 (14%) did not complete any surveys, 19
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44 329 (86%) completed at least 3 surveys, and 17 patients (77%) completed at least 6
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46 330 of 11 delivered surveys (>50% of delivered surveys). Of the 5 patients who
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48 331 completed less than half of the surveys, we successfully contacted 4, and 1 could
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50 332 not be reached after 5 attempts. All 4 reported that the major barriers precluding
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52 333 survey completion were their clinical conditions: 2 described readmissions as an
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3 334 overwhelming event that made them feel continuing survey participation
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5 335 challenging, and 2 described not feeling well in general, which precluded
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7 336 participation. All 4 patients noted that text or email reminders might have been
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10 337 helpful to sustain participation. Based on these responses, we modified the
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12 338 protocol to contact all participants approximately 10 days after enrollment to
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14 339 improve engagement and resolve any patient-specific issues in completing the
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16
17 340 surveys.
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19 341

20 21 342 *Clinical outcomes*

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24 343 There were no deaths during follow-up. Two (9%) patients experienced at
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26 344 least 1 hospital readmission. Figure 2 depicts the breadth in recovery trajectories
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28 345 in pain, sleep, ability to take care of own hygiene, and perception of overall
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30 346 recovery in five patients with complete response.
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34 348 *Patient perspective*

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36
37 349 An author (LG) participated in this study as he underwent cardiac surgery.
38
39
40 350 He noted that the length and frequency of the questionnaire was reasonable and
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42 351 helped him to be more aware of the recovery process because responding to the
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44 352 questions facilitated introspection on his progress across different domains. He
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47 353 recommended that the study platform feedback the data to study participants,
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49 354 such as a visual summary of the trajectory or response for patients to better
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51 355 gauge their progress. Additionally, he noted that responses may differ across the
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54 356 time of the day, as he was able to better function physically in the afternoon
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3 357 compared with in the morning. Finally, he suggested the potential value of
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5 358 reviewing the questionnaire during preoperative counseling to highlight important
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8 359 aspects of recovery to provide better patient and family expectations.
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10 360 Investigators plan on providing a brochure to the clinic that contains this
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12 361 information.
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17 363 **Discussion**

19 364 This study will provide time-series data on short-term recovery after
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21 365 cardiac surgery using PROM instruments complemented by clinical records
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23 366 obtained via the STS database and electronic health records. This study will
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25
26 367 provide one of the highest density of postoperative PROM data in existing
27
28 368 cardiac surgery literature³, and it will characterize the variability in individual
29
30 369 recovery processes with a high temporal resolution. This study will be important
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33 370 in closing knowledge gaps around patient-level variations in trajectories because
34
35 371 prior studies have mostly focused on changes in PROM scores at a limited
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38 372 number of time points³ or reporting group-level aggregate of longitudinal recovery
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40 373 data^{7, 22}. Because recovery is an individual, variable, and time-dependent
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42 374 process, we designed our data collection and analytical approach to capture such
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44
45 375 features important to recovery.

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47 376 This study has the potential to make a variety of contributions toward
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49 377 improving post-acute phase of care. First, we will be able to develop a
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51 378 preliminary nomogram of postoperative recovery for each domain and overall
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54 379 perception of recovery, which would be instrumental for patients and clinicians to
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3 380 gauge the breadth of possible recovery trajectories to facilitate informed shared
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5 381 decision-making. Second, identifying predictors of accelerated or protracted
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7 382 recovery, as classified by group-based trajectory model, may allow for
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10 383 individualized prediction of the postoperative recovery course to better inform the
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12 384 patients and family members. Third, early detection of recovery signals related to
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14 385 adverse events, such as mortality and readmission, may eventually facilitate
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16 386 preemptive intervention and focused monitoring of patients at an elevated risk for
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19 387 such events. Our design of the longitudinal PROM data collection allows for
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21 388 incremental update of such prediction as patients progress through the phase of
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23 389 recovery.

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26 390 There are many challenges to the successful acquisition of patient
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28 391 measurements during recovery: efficient administration of PROMs in a way that
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30 392 does not require prohibitive amount of resources, minimizing selection bias
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32 393 originating from barriers to survey completion, handling of missing data that
33
34 394 inevitably occurs in PROMs, and summarizing the complex data in a way that is
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36 395 interpretable to surgeons and patients²³. Additionally, the use of wearables and
37
38 396 device data require active patient participation in periodically charging the device,
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40 397 wearing them correctly, and reliably syncing the device to the server for data
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42 398 uploads. Moreover, there is a need to provide value to the patients for providing
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44 399 their recovery profile, such as giving them access to their health data in a
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46 400 meaningful way.

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51 401 The resulting data collection, analytical, and output platforms have the
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53 402 potential of being implemented in the clinical setting where an integration of
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3 403 incrementally increasing PROM and clinical data provides the near-real time
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5 404 estimate of individual patient risk of adverse post-operative events. Such a model
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7 405 may allow for triggering of preemptive clinical intervention. An output may
8
9 406 assimilate a form of clinical dashboard within the electronic health record system,
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11 407 which may be monitored at a centralized location where a trained clinician
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13 408 reviews high-risk cases filtered by the algorithm to further evaluate whether the
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15 409 patient condition warrants an intervention. Together, this workflow has a
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17 410 tremendous potential to improve post-acute phase of care following surgery.
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412 *Lessons Learned from the initial experience*

26 413 Through this first group of enrolled patients, we learned that most of the
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28 414 patients approached were willing to participate and consented to the study. By
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30 415 streamlining the enrollment process, the enrollment time shortened from over 1
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32 416 hour on the first patient to approximately 10-15 minutes for the current
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34 417 enrollment. The overall response rate is acceptable, with 77% of the participants
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36 418 completing more than half of the delivered surveys independently without any
37
38 419 intervention by researchers. Challenging recovery course, including readmissions
39
40 420 may have interfered with patient engagement. While this would have resulted in
41
42 421 an underrepresentation of those with protracted recovery or with complications,
43
44 422 our preliminary data show we were able to capture variations in the trajectories of
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46 423 recovery.

51 424 To sustain patient engagement through challenging recovery course, we
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53 425 implemented a protocol for a research assistant to call the patient around 10
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3 426 days after enrollment to troubleshoot any issues and reemphasize the
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5 427 importance of their participation. We believe that once the survey becomes part
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7 428 of clinical workflow with clinicians monitoring and responding to the PROM
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10 429 response, patient response rate would improve further.

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12 430 We modified the enrollment protocol to reduce the enrollment time,
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14 431 because to some patients, the complexity and prolonged time spent for
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16 432 enrollment discouraged signups. Initial protocol for enrollment required patients
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18 433 to download an app and register. This resulted in a wide range of time spent for
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20 434 enrollment between 15 minutes and 90 minutes, with longer enrollment owing to
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22 435 technical challenges. These challenges include patients forgetting the password
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24 436 for app download, having to reset the password, and not having immediate email
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26 437 access to check account confirmation emails. Because our cardiac surgery
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28 438 patient population tended to be older, these technical challenges may have been
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31 439 pronounced. By not including the app download and allowing for the research
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33 440 assistant to enroll the patient via an online form with their permission, the
34
35 441 enrollment time shortened significantly to 10-15 minutes.

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38 442 Examining the initial individual data on recovery, there were wide
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40 443 variations in the trajectories of recovery even among only 5 patients. The
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42 444 variation suggests that the instrument we used was sensitive to capturing such
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44 445 differences. We also noted variations in improvement over time across different
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46 446 domains of recovery, where overall perception of recovery seemed to have a
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48 447 steady improvement pattern, while pain varied between consecutive
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50 448 measurements in some patients.
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5 450 *Limitations*

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7 451 There are several limitations to this study. First, the single-center tertiary
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9 452 care setting limits the sample size and applicability of the findings to patients
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11 453 cared for in different settings. A multi-center study following the current study
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13 454 would address this limitation and evaluate whether the findings at our center are
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15 455 comparable to findings in other centers. Additionally, group-based trajectory
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17 456 modeling will classify patients into distinct trajectories based on similar recovery
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19 457 patterns, and this analytical approach may allow for generalization of the
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21 458 variations in the trajectories as long as our sample represents the breadth of the
22
23 459 possible variation in recovery.

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25 460 Another limitation is the exclusion of patients who cannot participate for
26
27 461 various reasons. The use of digital platform is advantageous in reducing the
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29 462 resource intensity for data collection, but leads to exclusion of patients who do
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31 463 not own mobile devices, which likely affects older patients disproportionately. As
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33 464 the number of adults using mobile devices is increasing²⁴, we believe this will
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35 465 become less of a limitation over time. Initiating this study now despite this
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37 466 limitation is important to establish a platform that may become the standard of
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39 467 postoperative care when the vast majority of patient population own digital
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41 468 devices in a predictably near future. Those who cannot participate due to lack of
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43 469 interest represent an important population that may be distinct in characteristics
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45 470 and risk profiles. We plan on minimizing the non-participation for the lack of
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47 471 interest by intermittent phone check-ins to sustain interests and identify barriers
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3 472 to inform strategies to increase engagement. In following studies, we may
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5 473 consider other forms of incentives to participate, if this population is indeed
6
7 474 distinct and large in proportion. Additionally, when the PROM data are integrated
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10 475 into routine clinical care, patient engagement will likely increase substantially
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12 476 because they will be more inspired to share these data if they are used by their
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14 477 clinicians.

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17 478 Finally, postoperative enrollment and retrospective assessment of
18
19 479 preoperative health status, as opposed to preoperative enrollment, may introduce
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21 480 recall bias. We decided on postoperative enrollment, because preoperative
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23 481 enrollment precluded standardized enrollment of patients operated on under non-
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25 482 elective settings. Given the retrospective assessment of baseline health status
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27 483 takes place on the first postoperative survey, we believe the recall bias is
28
29 484 minimized owing to the temporal proximity.

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34 35 486 **Conclusion**

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37 487 This study will generate highly granular, longitudinal PROM data to
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39 488 characterize individual trajectories of patient recovery after cardiac surgery.
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41 489 Digital data sharing platforms promise to minimize the patient and researcher
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43 490 burden in administering and completing PROMs, allowing for characterization of
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45 491 granular progression of patients' state of health over time in the postoperative
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47 492 period. Implementation of such study is complex but feasible, and it will serve as
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49 493 an important platform to facilitate clinical use of PROM data to improve the
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51 494 overall patient recovery.
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5 496 **Authors contributions**
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8 497 MM, HMK, SD, and AG developed the study and research question. MM
9
10 498 and HMK developed analytical strategy with inputs from BJM, GCL, and
11
12 499 YZ. SIC and ES guided refining the enrollment strategy and interpretation
13
14 500 of the phone interview responses. LAG provided patient perspective on the
15
16 501 study protocol and interpretation of the preliminary results. All authors
17
18 502 developed and approved the final manuscript before submission.
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20 503

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23
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31 510 **Competing interest statement**
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40 518 sports motion analysis and activity monitoring" and a patent to
41 519 US20180315507A1 is pending.
42
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44 521 Services to support quality measurement programs; was a recipient of a research
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46 523 develop methods for post-market surveillance of medical devices; was a recipient of
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50 527 Center for Health Information for work to advance intelligent disease prevention and
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52 529 in Beijing; receives payment from the Arnold & Porter Law Firm for work related to
53 530 the Sanofi clopidogrel litigation, from the Ben C. Martin Law Firm for work related to
54 531 the Cook Celect IVC filter litigation, and from the Siegfried and Jensen Law Firm for
55 532 work related to Vioxx litigation; chairs a Cardiac Scientific Advisory Board for
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3 533 UnitedHealth; was a participant/participant representative of the IBM Watson Health
4 534 Life Sciences Board; is a member of the Advisory Board for Element Science, the
5 535 Advisory Board for Facebook, and the Physician Advisory Board for Aetna; and is the
6 536 co-founder of HugoHealth, a personal health information platform, and co-founder of
7 537 Refactor Health, an enterprise healthcare AI-augmented data management company.
8 538
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For peer review only

625 **Tables and Figures**

626 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			

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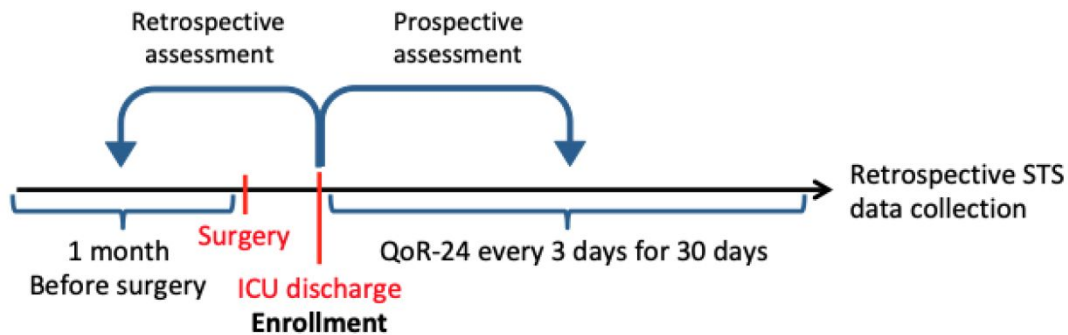
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629 Table 2: 24 features of trajectory used in group-based trajectory model

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

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631 Figure 1: Timing of patient enrollment and PROM administration

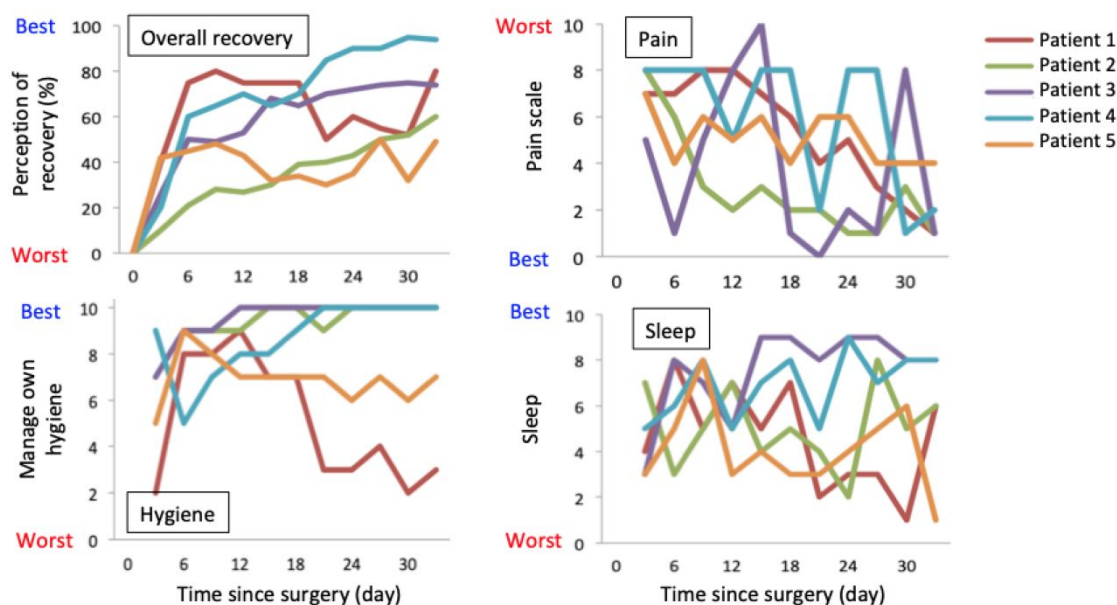


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633 The figure shows the timing of patient enrollment and PROM administration over
 634 the clinical course. Baseline function is assessed by retrospectively asking the
 635 patient about their state of health during 1 month prior to the operation.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

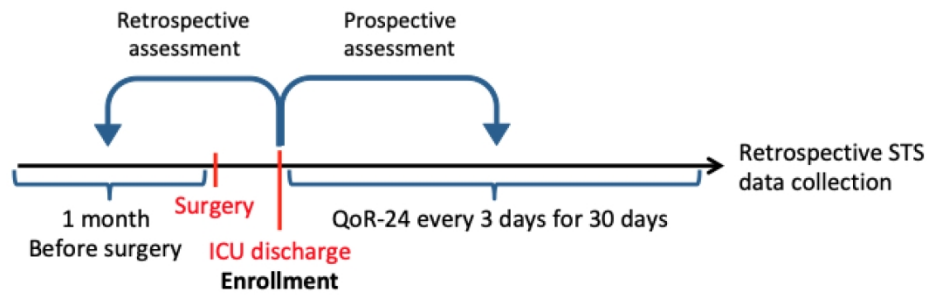
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639 Figure 2: Sample trajectories of recovery in 5 patients

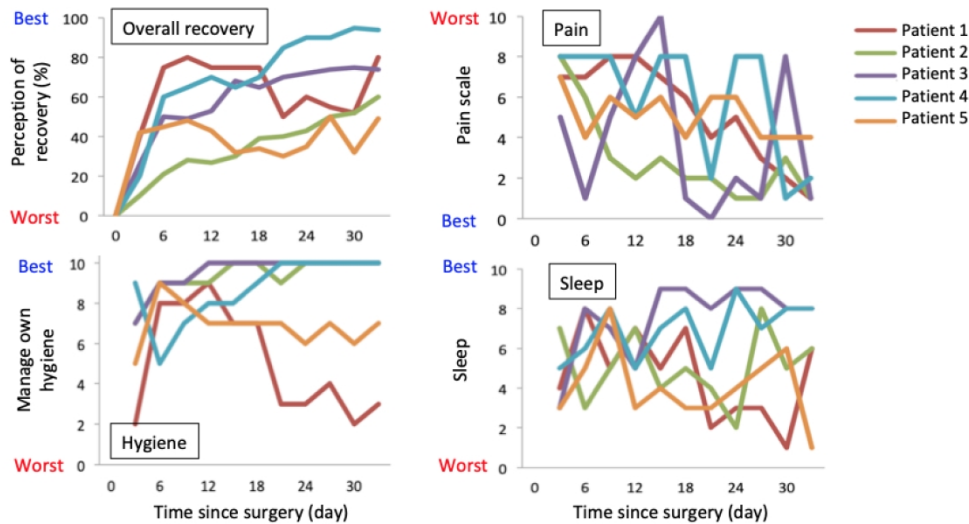


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641 The figures display trajectories of recovery in different domains in 5 patients.
 642 Each color corresponds to the same patient. Overall recovery is the patient's
 643 perception of overall recovery in 0 to 100% scale. Pain in surgical site is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



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.



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 dizzy
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#:

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3 **COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A**
4 **RESEARCH PROJECT**
5 **200 FR. 4 (2016-2)**
6 **YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL**
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10 **Study Title:** Understanding Recovery After Cardiac Surgery
11

12 **Principal Investigator:** Arnar Geirsson, MD
13

14 Associate Professor of Surgery (Cardiac)

15 Yale School of Medicine

16 Best Contact Number: 475-201-8349
17

18 **Funding Source:** None
19

20 **What is this study about?**
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22
23 You are invited to take part in a research study to understand how you recover after heart
24 surgery. We use an app to centralize your healthcare information from multiple sources so it is
25 easy for you and researchers to understand your health status and how you are doing after the
26 surgery. You have been asked to take part in this study because you are planned to undergo or
27 have undergone cardiac surgery at Yale New Haven Hospital (YNHH). If you agree to take part
28 in this study, you will be asked to answer questionnaire through a mobile application platform
29 called Hugo. Through Hugo, you will be asked to answer short questionnaires on your
30 smartphone or email for up to 90 days.
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33 This research study will examine the ability of the mobile health application, Hugo, to
34 quickly and securely obtain healthcare information from multiple sources to monitor your
35 outcomes after a procedure. Among the advantages of this system are that, with your permission,
36 we will be able to access your records at multiple health systems. The risks for this study are
37 similar to the risks associated with traditional research methods: you are sharing your personal
38 health information with researchers and there is a risk to your privacy. However, researchers will
39 only be able to view the health data that you sync with the Hugo platform. There will also be
40 audit logs of who has accessed your data via Hugo and other safeguards that do not exist with
41 paper and faxed records. Researchers will also access your records within the YNHH electronic
42 medical record (EMR) system. This access is to allow the researchers to confirm that your data
43 has fully come into the Hugo, and that there are no major missing data points.
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47 In order to decide whether you would like to be a part of this research study you should
48 know enough about its risks and benefits to make an informed decision. This consent form gives
49 you detailed information about the study, which a member of the research team will discuss with
50 you. This discussion should review all aspects of this research, especially the confidentiality
51 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.

HIC#:

- 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 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.

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

HIC#:

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2
3 required to comply with HIPAA but is required to maintain the confidentiality of your
4 information as described in the privacy notice to be provided when you sign up for Hugo.
5

6 This authorization to use and disclose your health information collected during your participation
7 in this study will never expire.
8
9

10 **Voluntary Participation and Withdrawal**

11
12 Participating in this study is voluntary and you are free to choose not to take part in this study.
13 **Declining to participate or withdrawing will involve no penalty or loss of benefits to which**
14 **you are otherwise entitled** (such as your health care outside the study, the payment for your
15 health care, and your health care benefits). It will not harm your relationship with your own
16 doctors or with Yale-New Haven Health or the care that you receive.
17
18

19 If you do become a study participant, you are free to stop and withdraw from this study at any
20 time during its course.
21

22
23 To withdraw from the study, you can call a member of the research team to let them know that
24 you would no longer like to take part. The telephone number to do this is 475-201-8349. You
25 may also email the intent to makoto.mori@yale.edu.
26

27 When you withdraw from this study, no new health information identifying you will be gathered
28 after that date. Information that has already been collected may still be used until the end of the
29 research study, as necessary to ensure the integrity of the study and/or study oversight.
30
31

32 **Questions**

33
34 We have used some technical terms in this form. Please feel free to ask about anything you don't
35 understand and to consider this research and the consent form carefully – as long as you feel is
36 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.

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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1 **Title:** Protocol for Project Recovery: Cardiac Surgery – A Single-center Cohort
2 Study Leveraging Digital Platform to Characterize Longitudinal Patient-Reported
3 Postoperative Recovery Patterns
4

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

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1
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3 39
4 40 **Abstract** (287/300)
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6
7 41 Introduction
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9 42 Improving postoperative patient recovery after cardiac surgery is a priority,
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11 43 but our current understanding of individual variations in recovery and factors
12
13 44 associated with poor recovery is limited. We are using a health-information
14
15 45 exchange platform to collect patient-reported outcome measures (PROMs) and
16
17 46 wearable device data to phenotype recovery patterns in the 30-day period after
18
19 47 cardiac surgery hospital discharge, to identify factors associated with these
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21 48 phenotypes and to investigate phenotype associations with clinical outcomes.
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28 50 Methods and analysis
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30 51 We designed a prospective cohort study to enroll 200 patients undergoing
31
32 52 valve, coronary artery bypass graft, or aortic surgery at a tertiary center in the
33
34 53 U.S. We are enrolling patients postoperatively after the intensive care unit (ICU)
35
36 54 discharge, and delivering electronic surveys directly to patients every 3 days for
37
38 55 30 days after hospital discharge. We will conduct medical record reviews to
39
40 56 collect patient demographics, comorbidity, operative details and hospital course
41
42 57 using the Society of Thoracic Surgeons (STS) data definitions. We will use phone
43
44 58 interview and medical record review data for adjudication of survival,
45
46 59 readmission, and complications. We will apply group-based trajectory modeling
47
48 60 to the time-series PROM and device data to classify patients into distinct
49
50 61 categories of recovery trajectories. We will evaluate whether certain recovery
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52 62 pattern predicts death or hospital readmissions, as well as whether clinical
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63 factors predict a patient having poor recovery trajectories. We will evaluate
64 whether early recovery patterns predict the overall trajectory at the patient-level.

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66 Ethics and dissemination

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

73

74 **Strengths and limitations of this study**

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

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3 84 Text (4081 words)
4

5 85 **Background**
6

7
8 86 Improving postoperative patient recovery is a priority. Readmission rates
9
10 87 in the post-operative period are high. Moreover, in the United States, the
11
12 88 expansion of episode-based payments and performance measures is increasing
13
14 89 interest in the post-acute experience of patients^{1,2}. However, we generally lack
15
16 90 systematically-collected information on the experience of patients in the post-
17
18 91 acute period, as few studies rigorously collecting information using established
19
20 92 patient-reported outcomes measures (PROMs). We have, for example, little
21
22 93 information about the variation of the trajectories of recovery and the factors most
23
24 94 strongly associated with better outcomes³.
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27

28 95 The assessment of the patient experience can provide important insights
29
30 96 into the process of recovery that is not evident through clinical outcomes or
31
32 97 intermittent clinical office visits. PROMs and wearable devices can provide
33
34 98 complementary information by providing measurements of how the patient's
35
36 99 experience and functional status change over time⁴. Current digital platforms
37
38 100 allow us to efficiently collect PROMs and wearable-generated data at high
39
40 101 frequencies and with little cost and burden. These automated data collection
41
42 102 approaches may minimize the bias introduced by clinician-directed patient
43
44 103 interviews⁵. Such a platform is highly suited to obtain repeated measures to
45
46 104 characterize a time-dependent process such as recovery⁶.
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51 105 Cardiac surgery is an ideal area for the study of recovery. Many patients
52
53 106 have good outcomes, but the limited existing evidence suggests a wide variation
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3 107 in the post-operative experience of these patients⁷. However, these patients'
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5 108 experience has been poorly studied, as most studies of recovery simply assess
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7 109 deaths and complications.
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10 110 Characterizing the recovery from the patient perspective is important for
11
12 111 many reasons. First, shared decision-making and informed consent should be
13
14 112 guided not only by the risk of mortality and complications but also by the recovery
15
16 113 experience. Understanding variations in recovery could enable the early
17
18 114 identification of people who are struggling and require additional attention.
19
20 115 Recovery data from the patient perspective may enable remote monitoring after
21
22 116 the procedure to selectively and preemptively intervene on those at high risk of
23
24 117 poor recovery to improve outcomes. Characterization of recovery can also be
25
26 118 used to identify patient, surgeon, procedural, and institutional factors that are
27
28 119 associated with different patterns. With this information we can identify modifiable
29
30 120 risk factors for poor recovery.
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35 121 Thus, at this juncture, there are several notable gaps in knowledge. First,
36
37 122 although recovery occurs over time, most studies of recovery included a small
38
39 123 number of timepoints, and the recovery trajectory phenotypes remains poorly
40
41 124 defined³. Cohort-level average of recovery trajectories is a common way of
42
43 125 reporting³ and can indicate how patients recover on average⁷, but it obscures
44
45 126 individual variation such as rapid early recovery, gradual recovery, or initial
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47 127 recovery followed by a decline. Second, we have limited understanding of how
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49 128 recovery trajectories vary by patient factors, operation types, center or surgeon
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3 129 characteristics, procedural processes, and complications, which limit
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5 130 opportunities to identify high risk patients preemptively and intervene.
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8 131 Accordingly, our overall objective is to characterize short-term trajectories
9
10 132 of patient recovery after cardiac surgery using PROMs and wearable data. We
11
12 133 are conducting a prospective study to characterize trajectories of postoperative
13
14 134 recovery in multiple domains after cardiac surgery. The specific aims of this study
15
16 135 are to: 1) leverage a digital data platform to collect PROM and wearable device
17
18 136 data to bring forth the variable individual recovery trajectories, 2) describe distinct
19
20 137 classes of recovery trajectories and clinical factors associated with the classes,
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22 138 and 3) to evaluate whether early postoperative recovery trajectory predicts later
23
24 139 recovery trajectory. In addition, we will investigate optimal ways to manage
25
26 140 missing data specific to these time-series data This study is a step toward using
27
28 141 this approach to prospectively monitor and preemptively identify patients at risk of
29
30 142 poor recovery and facilitate intervention to reduce the risk of adverse events. The
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32 143 purpose of this study protocol summary is to describes a new approach to
33
34 144 studying recovery in order to address the knowledge gap as well as to prespecify
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36 145 our approach.
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44 147 **Methods**

46 148 *Design Overview*

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48
49 149 This is a prospective cohort study of patients who are undergoing valve,
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51 150 CABG, or aortic surgery at a tertiary center in the U.S. We chose the operations
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53 151 because they are the most common cardiac operations performed⁸ while having
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3 152 different patient and operative characteristics, such as the use of deep
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5 153 hypothermic circulatory arrest, to potentially provide insights into the recovery
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7 154 pattern associated with such variations. Subgroup analysis will be conducted to
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10 155 evaluate whether there is a distinct patient experience by operation types. We
11
12 156 are enrolling patients postoperatively after ICU discharge in order to ensure
13
14 157 clinical stability, and we electronically delivering surveys directly to patients every
15
16 158 3 days for 30 days after hospital discharge to study patient trajectories in multiple
17
18 159 domains characterizing recovery. The closing phone interview after 30 days,
19
20 160 electronic medical record review, and linkage to the Society of Thoracic
21
22 161 Surgeons database are used to confirm survival, readmission, and complications.
23
24
25 162 The closing interview asks about details of readmissions if they occurred,
26
27 163 patients' overall satisfaction with the study, and whether their experience was
28
29 164 well captured by the summary of their PROM data. We will apply group-based
30
31 165 trajectory modeling to the longitudinal PROM data to identify distinct categories of
32
33 166 recovery trajectories in a data-driven fashion. We also identify predictors of
34
35 167 protracted recovery trajectory and evaluate whether early recovery patterns (<10
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37 168 days) predict the overall trajectory (30 days) at the patient-level. The Yale
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39 169 Institutional Review Board approved this study (IRB # 2000025689).
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47 171 *Patient Population*

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49 172 This study began in January 2019 and is ongoing. The study is taking
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51 173 place at Yale-New Haven Hospital, a tertiary center in the United States, where
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53 174 over 1,100 cardiac surgeries are performed annually. Inclusion criteria are
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3 175 patients of age 18 and older who are undergoing coronary artery bypass grafting
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5 176 (CABG), valve replacement or repair, or aortic operations. Exclusion criteria are
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7 177 those who undergo heart transplant, extracorporeal membrane oxygenation
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9
10 178 (ECMO), adult congenital operations, or ventricular assist device implantation, as
11
12 179 these patient populations tend to have a longer course of intensive care unit
13
14 180 stay⁹, precluding the timely enrollment necessary to capture immediate
15
16
17 181 postoperative recovery. We also excluded those who do not own a smartphone
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19 182 or a tablet or those who do not speak or read English, because the digital
20
21 183 platform for PROM data collection relies on patients responding to surveys
22
23 184 displayed on web browser via email or text, and the surveys were written in
24
25 185 English language. We do not allow proxy for survey response and consequently
26
27 186 excluded patients who were not able to respond by themselves as determined by
28
29 187 the research assistant.
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32
33 188 In order to provide the sense of patient selection resulting from these
34
35 189 criteria, we will compare patient characteristics of those who were approached
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37 190 and were and were not able to participate in the study for any reasons.
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41 42 192 *Recruitment*

43
44 193 Recruitment takes place postoperatively after the patient has left the
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46 194 intensive care unit (ICU) for the step-down or floor unit (Figure 1). We chose to
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48 195 enroll patients postoperatively, as opposed to preoperatively, because
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50 196 postoperative enrollment allows for enrollment of patients who undergo surgery
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52 197 under non-elective settings. Recruitment after transfer from the ICU setting
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3 198 ensures clinical stability. A research assistant (RA) visits the patient and after
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5 199 confirming the patient is eligible to participate and following the description of the
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7 200 study procedure, obtains written informed consent (Supplementary Material S1)
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10 201 from all study participants. The informed consent form states that all personal
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12 202 information, survey response, and any medical records are confidential, will not
13
14 203 be shared, and will be stored in an encrypted database.
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17 204 We iteratively refined the enrollment process to minimize the onboarding
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19 205 time, which includes obtaining informed consent and signup process directed by
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21 206 the RA on a tablet device to enter patient name and email address or phone
22
23 207 number and takes approximately 10-15 minutes.
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26 208

27 28 209 *PROM instrument and administration*

29
30 210 We use 24-item quality of recovery (QoR-24) to characterize patients'
31
32 211 postoperative recovery in various domains. The questionnaire consists of 24
33
34 212 items that were developed and validated in inpatient and outpatient surgical
35
36 213 populations in terms of convergent validity with visual analogue scale, construct
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38 214 validity compared with length of hospital stay and sex-based difference, along
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40 215 with good internal consistency and test-retest reliability¹⁰⁻¹³. We chose QoR-24
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42 216 among 5 other PROMs developed specifically to measure postoperative
43
44 217 recovery. QoR-24 possessed many qualities advantageous for the purpose of our
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46 218 study, including the robust validation of psychometric property, extensive use
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48 219 cases in various surgical populations, ability for self-administration, and the ease
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50 220 of interpreting item-wise scores (Supplementary Table 1-2). The instrument was
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3 221 previously adapted into a mobile format and was successfully used to administer
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6 222 the survey daily for 14 days^{11, 12}. We added 3 items to QoR-24 to capture the
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9 223 self-reported time patients went to sleep, the time they awakened, and their
10
11 224 global perception of how much they have 'recovered' in a 0-100% scale. The
12
13 225 resulting 27-item questionnaire takes 2-4 minutes to complete, making its
14
15 226 frequent administration feasible (Supplementary Material S2). Among the
16
17 227 published studies in cardiac surgery, this study will have the highest number of
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19 228 PROM data points collected in the first postoperative month³.
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25 230 *Digital data platform*

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27 231 We are delivering surveys on the day of enrollment and every 3 days for
28
29 232 30 days. This method provides detailed longitudinal data across multiple domains
30
31 233 of recovery (Figure 2). To facilitate data organization and scheduled survey
32
33 234 delivery, we use Hugo (Me2Health, LLC, Guilford CT, USA) a patient-centered
34
35 235 health data sharing platform, which has a customizable survey delivery function
36
37 236 and reminder feature to facilitate data collection. Hugo platform allows for
38
39 237 automated delivery of surveys without researchers having to directly contact
40
41 238 patients, which facilitates high-frequency data collection. Additionally, it imports
42
43 239 data from connected wearable devices to facilitate centralization of patient health
44
45 240 data. The patients retain access to their own data in a cloud-based account.
46
47 241 Hugo does not fall under the Covered Entity that Health Insurance Portability and
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49 242 Accountability Act (HIPAA) regulates, but employs all the security measures that
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51 243 would be required by HIPAA had it been a Covered Entity.
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245 *Identifying common reasons for low response rate*

246 Recognizing that the survey response will be incomplete for some
247 participants, we have conducted a phone interview with the first 22 patients to
248 learn reasons for low responses and identify strategies to minimize the barriers
249 toward survey response for subsequent participants. In the first 22 patients, we
250 identified 5 with response rate of <50% and conducted recorded phone
251 interviews. Our interview guide (Supplementary Material S3) contained questions
252 to elucidate technical barriers, differential preferences for engagement, and or
253 any other issues precluding survey completion. We also asked whether the
254 length of the questionnaire or types of questions asked made it difficult to
255 complete the survey. Two members of the research team (CB and MM)
256 evaluated the interview recordings to identify common reasons for low response
257 rate. This suggested the potential importance of reminder to maintain patient
258 engagement. We modified the protocol to contact all participants approximately
259 10 days after enrollment. We will continue to conduct this phone interview for
260 patients with low response rate and describe engagement and barriers to
261 participation in the final cohort. Survey response rate and time spent to complete
262 each survey will be reported descriptively to evaluate the degree of patient
263 engagement. This approach likely allows us to identify patients who either did not
264 respond or completed the survey in an unrealistically short time that may not
265 represent a meaningful response.

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3 267 *Additional clinical data and adjudication of hospitalization and survival*
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5 268 Additionally, we are using the Society of Thoracic Surgeons (STS) Adult
6
7 269 Cardiac Surgery Database data specifications to retrospectively collect clinically
8
9 270 relevant data in this patient population. Pre-specified candidate predictors in this
10
11 271 database will be used to identify clinical predictors of recovery trajectories (Table
12
13 272 1). The STS database contains patient demographics, comorbidities, presenting
14
15 273 clinical status, operative details, and postoperative mortality and morbidity up to
16
17 274 30 days after the time of operation¹⁴. These data are routinely collected at Yale
18
19 275 New Haven Hospital. At our program, 30-day mortality rates for isolated aortic
20
21 276 valve replacement and isolated CABG are stable around 1%, with 30-day
22
23 277 readmission rate of about 10%, which are slightly lower than the national
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25 278 average.
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31 279 We will determine mortality and hospital readmissions by several
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33 280 approaches: review of hospital records, review of cardiac surgery clinic notes,
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35 281 and conducting closing phone interviews with the patient or contact person
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37 282 previously identified.
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42 284 *Patient Involvement*
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44 285 Prior to launching the study, we interviewed 5 patients both in pre and
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46 286 postoperative settings to evaluate whether the frequency of survey delivery and
47
48 287 PROM instrument were likely to adequately capture their experience of recovery.
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50 288 All patients agreed that the frequency of questionnaire administration and the
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52 289 length of the PROM instrument were reasonable and provided face validity that
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3 290 the questionnaire captured aspects of recovery that were important to the
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5 291 patients. Additionally, this article is authored with a patient (LG) who participated
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7 292 in the study to reflect his perspective on the study design and experience in
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10 293 responding to the surveys.

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14 295 *Sample size*

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16
17 296 The study sample target is 200 patients. Adequate sample size for studies
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19 297 using group-based trajectory modeling depends on the dataset's
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21 298 representativeness of the population of interest¹⁵. Therefore, the concept of
22
23 299 statistical power traditionally used for sample size calculation does not apply to
24
25 300 latent class analyses. We may generate a larger simulation dataset from the
26
27 301 measured patient trajectory data to perform a split-sample testing, evaluating
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29 302 whether trajectories generated from the derivation sample would allow for
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31 303 satisfactory categorization of the testing dataset. Additionally, the study setting is
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33 304 scalable to increase the sample size by increasing the enrollment period, should
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35 305 a larger sample size become necessary.

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42 307 *Analytical approach – group-based trajectory modeling*

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46 308 The resulting dataset is a complex time-series data, with each patient
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49 309 having 10 data points (one every three days) at different postoperative times for
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51
52 310 each item. A practical approach to dimension reduction is group-based trajectory

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3 311 modeling, which is a type of latent class analysis that groups similar patient
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7 312 trajectories according to a number of features derived from the time-series data¹⁶,
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10 313 ¹⁷. This approach allows for dimension reduction of the complex time-series data
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14 314 into several distinct classes of recovery trajectories. These trajectories can be
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17 315 labeled according to the observed clinical phenotype of trajectories, for example
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21 316 'fast recovery,' 'average recovery,' or 'protracted recovery,'. This data-driven
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24 317 categorization enables additional regression modeling to identify predictors of
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28 318 patients belonging to a certain class of recovery path.

31 319 The dataset will be classified into distinct categories of trajectories at
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35 320 domain level, using group-based trajectory modeling^{16, 17}. Traj package on R¹⁸ or
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38 321 Proc Traj package on SAS¹⁵, performs trajectory modeling by first extracting 24
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42 322 features of patient-level trajectory, selecting a subset of features that describes
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45 323 the overall trajectory, and identifying optimal number of classes to group the
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49 324 trajectories based on the longitudinal k-means method. The 24 features include
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52 325 range, mean change per unit time, and slope of the linear model (Table 2), which
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56 326 have been demonstrated to discriminate between stable-unstable, increasing-

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3 327 decreasing, linear-nonlinear, and monotonic-nonmonotonic patterns of
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7 328 trajectories¹⁸. K-means method partitions the time-series data into k groups such
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10 329 that the mean squared error distance of each data point from the assigned
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14 330 cluster is minimized¹⁹. The optimal number of clusters is determined by the
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17 331 minimization of Bayesian information criterion, which signifies the balance
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21 332 between model's complexity and the ability to describe the dataset. This process
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24 333 yields distinct classes of patient trajectories in a data-driven fashion. Trajectories
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28 334 will be identified separately for the 5 domains and 1 global recovery measure.

31 335 With the characterization of trajectories, we will then fit multinomial logistic
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33 336 regression models using clinical variables outlined in Table 1, including patient
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35 337 demographics, comorbidity, and postoperative event such as complications and
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38 338 ICU readmissions, to identify predictors of patients belonging to each trajectory
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40 339 class. As some variables interact with each other, such as history of chronic lung
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42 340 disease increasing the risk of postoperative pneumonia, which likely impacts the
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45 341 recovery experience, we plan to stratify the cohort with and without the index
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47 342 complications defined by the STS (prolonged ventilation, renal failure, sternal
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49 343 wound infection, pneumonia, stroke, all-cause reoperation). Further analyses on
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51 344 interaction and mediation effects likely requires a larger sample size and are of
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54 345 interest in the future.

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5 347 *Analytical approach – missing data*
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7 348 Because missing data are inevitable in longitudinal PROMs, there is a
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10 349 need employ an appropriate handling of missing data. Multiple imputation prior to
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12 350 latent class analysis may yield a less biased estimate of the resulting trajectories.
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14 351 An alternative approach used in group-based trajectory models assumes the data
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16 352 are missing at random (MAR) and generates the maximum likelihood of the
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18 353 model parameters²⁰. MAR is valid when the response attrition is independent of
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20 354 the group membership. However, patient attrition is oftentimes dependent on
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22 355 clinical characteristics and likely related to the class of trajectory itself. An
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24 356 extension of the model allows for modeling of attrition across trajectory groups²¹,
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26 357 permitting dropout probability to vary as a function of covariates or observed
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28 358 outcomes prior to dropout and yields a more robust estimate of the probability of
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30 359 group membership. As such, we will perform sensitivity analysis to compare the
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32 360 trajectories generated via raw data vs. data preprocessed with multiple
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34 361 imputation vs. trajectories generated via trajectory model accounting for response
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36 362 attrition.
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45 364 **Results**

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47 365 Between January and May 2019, we have enrolled 22 patients who
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49 366 completed the 30-day follow-up. In this cohort, median age was 58.5 years
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51 367 (interquartile range 53.5-67.0) and 7 (32%) were women. There were 9 (41%)
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53 368 mitral valve repair cases and 6 isolated or concomitant CABG (27%).
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5 370 *Barriers to completing surveys*

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7 371 Of the 22 patients enrolled, 3 (14%) did not complete any surveys, 19
8 372 (86%) completed at least 3 surveys, and 17 patients (77%) completed at least 6
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10 373 of 11 delivered surveys (>50% of delivered surveys). Of the 5 patients who
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12 374 completed less than half of the surveys, we successfully contacted 4, and 1 could
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14 375 not be reached after 5 attempts. All 4 reported that the major barriers precluding
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16 376 survey completion were their clinical conditions: 2 described readmissions as an
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18 377 overwhelming event that made them feel continuing survey participation
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20 378 challenging, and 2 described not feeling well in general, which precluded
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22 379 participation. All 4 patients noted that text or email reminders might have been
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24 380 helpful to sustain participation. Based on these responses, we modified the
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26 381 protocol to contact all participants approximately 10 days after enrollment to
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28 382 improve engagement and resolve any patient-specific issues in completing the
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30 383 surveys.

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32 38433
34 385 *Clinical outcomes*

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36 386 There were no deaths during follow-up. Two (9%) patients experienced at
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38 387 least 1 hospital readmission. Figure 2 depicts the breadth in recovery trajectories
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40 388 in pain, sleep, ability to take care of own hygiene, and perception of overall
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42 389 recovery in five patients with complete response.

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46 391 **Discussion**

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3 392 This study will provide time-series data on short-term recovery after
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5 393 cardiac surgery using PROM instruments complemented by clinical records
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7 394 obtained via the STS database and electronic health records. This study will
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10 395 provide one of the highest density of postoperative PROM data in existing
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12 396 cardiac surgery literature³, and it will characterize the variability in individual
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14 397 recovery processes with a high temporal resolution. This study will be important
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16 398 in closing knowledge gaps around patient-level variations in trajectories because
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18 399 prior studies have mostly focused on changes in PROM scores at a limited
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20 400 number of time points³ or reporting group-level aggregate of longitudinal recovery
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22 401 data^{7, 22}. Because recovery is an individual, variable, and time-dependent
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24 402 process, we designed our data collection and analytical approach to capture such
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26 403 features important to recovery.

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30 404 This study has the potential to make a variety of contributions toward
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32 405 improving post-acute phase of care. First, we will be able to develop a
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34 406 preliminary nomogram of postoperative recovery for each domain and overall
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36 407 perception of recovery, which would be instrumental for patients and clinicians to
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38 408 gauge the breadth of possible recovery trajectories to facilitate informed shared
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40 409 decision-making. Second, identifying predictors of accelerated or protracted
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42 410 recovery, as classified by group-based trajectory model, may allow for
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44 411 individualized prediction of the postoperative recovery course to better inform the
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46 412 patients and family members. Third, early detection of recovery signals related to
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48 413 adverse events, such as mortality and readmission, may eventually facilitate
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50 414 preemptive intervention and focused monitoring of patients at an elevated risk for
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3 415 such events. Our design of the longitudinal PROM data collection allows for
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5 416 incremental update of such prediction as patients progress through the phase of
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7 417 recovery.

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10 418 There are many challenges to the successful acquisition of patient
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12 419 measurements during recovery: efficient administration of PROMs in a way that
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14 420 does not require prohibitive amount of resources, minimizing selection bias
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16 421 originating from barriers to survey completion, handling of missing data that
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18 422 inevitably occurs in PROMs, and summarizing the complex data in a way that is
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20 423 interpretable to surgeons and patients²³. Additionally, the use of wearables and
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22 424 device data require active patient participation in periodically charging the device,
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24 425 wearing them correctly, and reliably syncing the device to the server for data
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26 426 uploads. Moreover, there is a need to provide value to the patients for providing
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28 427 their recovery profile, such as giving them access to their health data in a
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30 428 meaningful way.

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33 429 The resulting data collection, analytical, and output platforms have the
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35 430 potential of being implemented in the clinical setting where an integration of
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37 431 incrementally increasing PROM and clinical data provides the near-real time
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39 432 estimate of individual patient risk of adverse post-operative events. Such a model
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41 433 may allow for triggering of preemptive clinical intervention. An output may
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43 434 assimilate a form of clinical dashboard within the electronic health record system,
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45 435 which may be monitored at a centralized location where a trained clinician
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47 436 reviews high-risk cases filtered by the algorithm to further evaluate whether the
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3 437 patient condition warrants an intervention. Together, this workflow has a
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5 438 tremendous potential to improve post-acute phase of care following surgery.
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10 440 *Lessons Learned from the initial experience*

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12 441 Through this first group of enrolled patients, we learned that most of the
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14 442 patients approached were willing to participate and consented to the study. By
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16 443 streamlining the enrollment process, the enrollment time shortened from over 1
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18 444 hour on the first patient to approximately 10-15 minutes for the current
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20 445 enrollment. The overall response rate is acceptable, with 77% of the participants
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22 446 completing more than half of the delivered surveys independently without any
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24 447 intervention by researchers. Challenging recovery course, including readmissions
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26 448 may have interfered with patient engagement. While this would have resulted in
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28 449 an underrepresentation of those with protracted recovery or with complications,
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30 450 our preliminary data show we were able to capture variations in the trajectories of
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32 451 recovery.
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38 452 To sustain patient engagement through challenging recovery course, we
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40 453 implemented a protocol for a research assistant to call the patient around 10
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42 454 days after enrollment to troubleshoot any issues and reemphasize the
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44 455 importance of their participation. By the protocol, research assistant making this
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46 456 call does not act in clinical capacity and does not provide clinical evaluation or
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48 457 advise, which is an important boundary for this call to not act as an intervention to
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50 458 alter recovery course. We believe that once the survey becomes part of clinical
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3 459 workflow with clinicians monitoring and responding to the PROM response,
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5 460 patient response rate would improve further.
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7 461 We modified the enrollment protocol to reduce the enrollment time,
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9 462 because to some patients, the complexity and prolonged time spent for
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11 463 enrollment discouraged signups. Initial protocol for enrollment required patients
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13 464 to download an app and register. This resulted in a wide range of time spent for
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15 465 enrollment between 15 minutes and 90 minutes, with longer enrollment owing to
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17 466 technical challenges. These challenges include patients forgetting the password
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19 467 for app download, having to reset the password, and not having immediate email
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21 468 access to check account confirmation emails. Because our cardiac surgery
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23 469 patient population tended to be older, these technical challenges may have been
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25 470 pronounced. By not including the app download and allowing for the research
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27 471 assistant to enroll the patient via an online form with their permission, the
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29 472 enrollment time shortened significantly to 10-15 minutes.
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35 473 Examining the initial individual data on recovery, there were wide
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37 474 variations in the trajectories of recovery even among only 5 patients. The
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39 475 variation suggests that the instrument we used was sensitive to capturing such
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41 476 differences. We also noted variations in improvement over time across different
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43 477 domains of recovery, where overall perception of recovery seemed to have a
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45 478 steady improvement pattern, while pain varied between consecutive
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47 479 measurements in some patients.
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53 481 *Limitations*
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3 482 There are several limitations to this study. First, the single-center tertiary
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5 483 care setting limits the sample size and applicability of the findings to patients
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7 484 cared for in different settings. A multi-center study following the current study
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9 485 would address this limitation and evaluate whether the findings at our center are
10
11 486 comparable to findings in other centers. Additionally, group-based trajectory
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13 487 modeling will classify patients into distinct trajectories based on similar recovery
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15 488 patterns, and this analytical approach may allow for generalization of the
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17 489 variations in the trajectories as long as our sample represents the breadth of the
18
19 490 possible variation in recovery.

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24 491 Another limitation is the exclusion of patients who cannot participate for
25
26 492 various reasons. The use of digital platform is advantageous in reducing the
27
28 493 resource intensity for data collection, but leads to exclusion of patients who do
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30 494 not own mobile devices, which likely affects older patients disproportionately. As
31
32 495 the number of adults using mobile devices is increasing²⁴, we believe this will
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34 496 become less of a limitation over time. Initiating this study now despite this
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36 497 limitation is important to establish a platform that may become the standard of
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38 498 postoperative care when the vast majority of patient population own digital
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40 499 devices in a predictably near future. Those who cannot participate due to lack of
41
42 500 interest or technological barrier represent an important population that may be
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44 501 distinct in characteristics and risk profiles. While acknowledging the selection
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46 502 bias originating from this inclusion threshold, we believe there is a need to initiate
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48 503 collection of patient-centered outcome measures in the proposed approach, in
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50 504 order to further engage hospitals and programs for a broader implementation of
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3 505 this approach in the context of extremely limited evidence base. We plan on
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5 506 minimizing the non-participation for the lack of interest by intermittent phone
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7 507 check-ins to sustain interests and identify barriers to inform strategies to increase
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9 508 engagement. While recognizing that clinical implementation of this protocol would
10
11 509 preclude the use of incentives, in following studies, we may consider other forms
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13 510 of incentives to participate, if this population is indeed distinct and large in
14
15 511 proportion. Additionally, when the PROM data are integrated into routine clinical
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17 512 care, patient engagement will likely increase substantially because they will be
18
19 513 more inspired to share these data if they are used by their clinicians.
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24 514 Finally, postoperative enrollment and retrospective assessment of
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26 515 preoperative health status, as opposed to preoperative enrollment, may introduce
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28 516 recall bias. We decided on postoperative enrollment, because preoperative
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30 517 enrollment precluded standardized enrollment of patients operated on under non-
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32 518 elective settings. Given the retrospective assessment of baseline health status
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34 519 takes place on the first postoperative survey, we believe the recall bias is
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36 520 minimized owing to the temporal proximity.
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41 42 522 **Conclusion**

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44 523 This study will generate highly granular, longitudinal PROM data to
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46 524 characterize individual trajectories of patient recovery after cardiac surgery.
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48 525 Digital data sharing platforms promise to minimize the patient and researcher
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50 526 burden in administering and completing PROMs, allowing for characterization of
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52 527 granular progression of patients' state of health over time in the postoperative
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3 528 period. Implementation of such study is complex but feasible, and it will serve as
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5 529 an important platform to facilitate clinical use of PROM data to improve the
6
7 530 overall patient recovery.
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10 531

11 532 **Authors contributions**

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14 533 MM, HMK, SD, and AG developed the study and research question. MM and
15
16 534 HMK developed analytical strategy with inputs from BJM, GCL, and YZ. SIC, CB,
17
18 535 and ES guided refining the enrollment strategy and interpretation of the phone
19
20 536 interview responses. LAG provided patient perspective on the study protocol and
21
22 537 interpretation of the preliminary results. All authors developed and approved the
23
24 538 final manuscript before submission.
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43 546 **Competing interest statement**

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46
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50
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6
7 553 Mortazavi reported having a patent US10201746B1 approved for "Near-realistic
8
9 554 sports motion analysis and activity monitoring" and a patent to
10
11 555 US20180315507A1 is pending.
12
13
14 556 Dr. Krumholz works under contract with the Centers for Medicare & Medicaid
15
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17
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21
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23
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25
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27
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29
30 564 disease prevention and health promotion; collaborates with the National Center
31
32 565 for Cardiovascular Diseases in Beijing; receives payment from the Arnold &
33
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35
36 567 C. Martin Law Firm for work related to the Cook Celect IVC filter litigation, and
37
38 568 from the Siegfried and Jensen Law Firm for work related to Vioxx litigation; chairs
39
40 569 a Cardiac Scientific Advisory Board for UnitedHealth; was a
41
42 570 participant/participant representative of the IBM Watson Health Life Sciences
43
44 571 Board; is a member of the Advisory Board for Element Science, the Advisory
45
46 572 Board for Facebook, and the Physician Advisory Board for Aetna; and is the co-
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48 573 founder of HugoHealth, a personal health information platform, and co-founder of
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3 574 Refactor Health, an enterprise healthcare AI-augmented data management
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5 575 company.

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For peer review only

663 **Tables and Figures**

664 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		

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667 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

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3 670 Figure 1: Timing of patient enrollment and PROM administration
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10 673 The figure shows the timing of patient enrollment and PROM administration over
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12 674 the clinical course. Baseline function is assessed by retrospectively asking the
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14 675 patient about their state of health during 1 month prior to the operation. 24-item
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16 676 Quality of Recovery questionnaire is administered every 3 days for 30 days
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18 677 following discharge from the intensive care unit.
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24 680 Figure 2: Sample trajectories of recovery in 5 patients
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30 683 The figures display trajectories of recovery in different domains in 5 patients.
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32 684 Each color corresponds to the same patient. Overall recovery is the patient's
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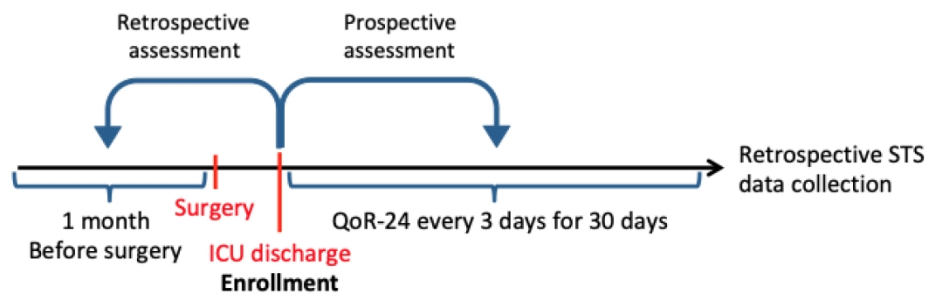
34 685 perception of overall recovery in 0 to 100% scale. Pain in surgical site is reported
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36 686 in 0 to 10 point scale, with 10 representing the worst pain. Being able to take care
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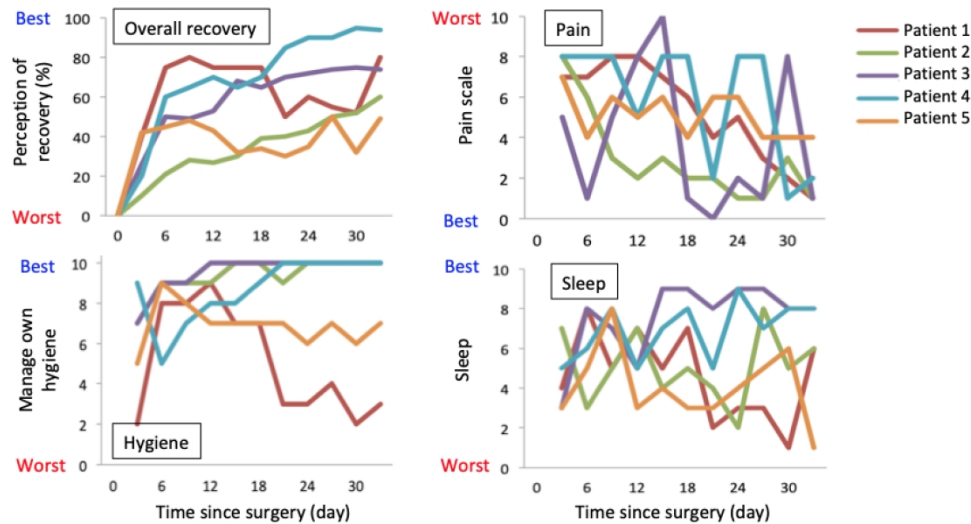
38 687 of own hygiene is reported in 0 to 10 point scale, with 10 representing complete
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40 688 independence in managing own hygiene. Patient's perception of sleep quality is
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42 689 reported in 0 to 10 point scale, with 10 being the best sleep.
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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.



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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3 **COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A**
4 **RESEARCH PROJECT**
5 **200 FR. 4 (2016-2)**
6 **YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL**
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10 **Study Title:** Understanding Recovery After Cardiac Surgery
11

12 **Principal Investigator: Arnar Geirsson, MD**
13 Associate Professor of Surgery (Cardiac)
14 Yale School of Medicine
15 Best Contact Number: 475-201-8349
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17

18 **Funding Source:** None
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20 **What is this study about?**
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22
23 You are invited to take part in a research study to understand how you recover after heart
24 surgery. We use an app to centralize your healthcare information from multiple sources so it is
25 easy for you and researchers to understand your health status and how you are doing after the
26 surgery. You have been asked to take part in this study because you are planned to undergo or
27 have undergone cardiac surgery at Yale New Haven Hospital (YNHH). If you agree to take part
28 in this study, you will be asked to answer questionnaire through a mobile application platform
29 called Hugo. Through Hugo, you will be asked to answer short questionnaires on your
30 smartphone or email for up to 90 days.
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33 This research study will examine the ability of the mobile health application, Hugo, to
34 quickly and securely obtain healthcare information from multiple sources to monitor your
35 outcomes after a procedure. Among the advantages of this system are that, with your permission,
36 we will be able to access your records at multiple health systems. The risks for this study are
37 similar to the risks associated with traditional research methods: you are sharing your personal
38 health information with researchers and there is a risk to your privacy. However, researchers will
39 only be able to view the health data that you sync with the Hugo platform. There will also be
40 audit logs of who has accessed your data via Hugo and other safeguards that do not exist with
41 paper and faxed records. Researchers will also access your records within the YNHH electronic
42 medical record (EMR) system. This access is to allow the researchers to confirm that your data
43 has fully come into the Hugo, and that there are no major missing data points.
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47 In order to decide whether you would like to be a part of this research study you should
48 know enough about its risks and benefits to make an informed decision. This consent form gives
49 you detailed information about the study, which a member of the research team will discuss with
50 you. This discussion should review all aspects of this research, especially the confidentiality
51 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.

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- 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 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.

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

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3 required to comply with HIPAA but is required to maintain the confidentiality of your
4 information as described in the privacy notice to be provided when you sign up for Hugo.
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6 This authorization to use and disclose your health information collected during your participation
7 in this study will never expire.
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10 **Voluntary Participation and Withdrawal**

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12 Participating in this study is voluntary and you are free to choose not to take part in this study.
13 **Declining to participate or withdrawing will involve no penalty or loss of benefits to which**
14 **you are otherwise entitled** (such as your health care outside the study, the payment for your
15 health care, and your health care benefits). It will not harm your relationship with your own
16 doctors or with Yale-New Haven Health or the care that you receive.
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19 If you do become a study participant, you are free to stop and withdraw from this study at any
20 time during its course.
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22
23 To withdraw from the study, you can call a member of the research team to let them know that
24 you would no longer like to take part. The telephone number to do this is 475-201-8349. You
25 may also email the intent to makoto.mori@yale.edu.
26

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

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34 We have used some technical terms in this form. Please feel free to ask about anything you don't
35 understand and to consider this research and the consent form carefully – as long as you feel is
36 necessary – before you make a decision.
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3 **Authorization and Permission**
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5 I have read (or someone has read to me) this form and have decided to participate in the project
6 described above. Its general purposes, the particulars of my involvement and possible hazards
7 and inconveniences have been explained to my satisfaction. My signature also indicates that I
8 have received a copy of this consent form.
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10
11 By signing this form, I give permission to the researchers to use [and give out] information about
12 me for the purposes described in this form. By refusing to give permission, I understand that I
13 will not be able to be in this research.
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17 Print Name of Participant: _____
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20 Signature: _____
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24 Date: _____
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28 If after you have signed this form you have any questions about your privacy rights, please
29 contact the Yale Privacy Officer at 203-432-5919.
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32 If you have further questions about this project or if you have a research-related problem, you
33 may contact the Research Associate, Makoto Mori, at 475-201-8349 or at
34 makoto.mori@yale.edu. If you would like to talk with someone other than the researchers to
35 discuss problems, concerns, and questions you may have concerning this research, or to discuss
36 your rights as a research participant, you may contact the Yale Human Investigation Committee
37 at 203-785-4688.
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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