PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for Project Recovery: Cardiac Surgery – A Single-center Cohort Study Leveraging Digital Platform to Characterize Longitudinal Patient-Reported Postoperative Recovery Patterns
AUTHORS	Mori, Makoto; Brooks, Cornell; Spatz, Erica; Mortazavi, Bobak; Dhruva, Sanket; Linderman, George; Grab, Lawrence; Zhang, Yawei; Geirsson, Arnar; Chaudhry, Sarwat; Krumholz, Harlan

VERSION 1 – REVIEW

REVIEWER	Vivek Rao University of Toronto. Canada
REVIEW RETURNED	24-Feb-2020

GENERAL COMMENTS	The authors have submitted a study protocol describing their efforts to determine patient related factors and wearable device data that predicts clinical outcomes following cardiac surgery. The authors provide limited data in their first 22 patients out of a planned 200 patient enrollment. I applaud the authors for their investigations in this area, but I have particular concerns with this manuscript. 1. In my opinion, study protocols should be published when they involve large multi-centre, multi-national clinical trials to avoid major funding agencies (NIH, NHS, CIHR, etc) from supporting similar studies that are earlier in their stage of development. This study is a single centre, almost retrospective study in that patients are enrolled after their surgery. I think a similar larger study involving multiple sites would be competitive for national funding and thus I personally see no value in publishing this study design and preliminary results. 2. Point #1 notwithstanding, I do have enthusiasm for this study and would welcome a manuscript describing their final results. To that end, I have a few suggestions with respect to study design and inclusion/exclusion factors. - I agree with the inclusion of isolated CABG, VALVE and combined VALVE-CABG cases as these patient populations are relatively homogeneous. In contrast, aortic operations can vary in their complexity and patient demographics. The latter group may include patients with Hereditary syndromes (as Yale is a recognized center of excellence for aortic surgery). These patients may have additional comorbidities associated with their aortopathy that adversely affects their PROMs, but has little to do with the actual surgery. Furthermore, some of these patients will require deep hypothermia and circulatory arrest which will also confound their postoperative recovery. I recommend excluding aortic surgery from this study. The actual predictive model incorporating all PROMs and wearable device data is not described. Similarly, the PROMs are not all externally validated and thus reproducibility and generalizability

	remain a concern. How do the authors intend to handle patients with postoperative complications such as dialysis, wound infections, stroke, etc? Clearly these complications will affect recovery but may not be accounted for in a model that only examines PROMs and wearable device data. One may argue that their PROMs may be skewed against recovery due to their postoperative course. 3. Why not include preoperative demographics into the predictive model? I would assume that age, urgency of operation and other preoperative co-morbidities would predict recovery. In summary, I wish the authors well on the completion of this interesting study. I have some suggestions for the execution of this trial, despite the fact that the trial is underway. As stated above, I don't see value in the independent publication of the study protocol and rationale.

REVIEWER	Massimo Chello Università Campus Bio-Medico di Roma, Rome, Italy
REVIEW RETURNED	07-Mar-2020

GENERAL COMMENTS	The reviewer has no comment.

REVIEWER	Yuki Nakamura Department of Surgery, University of Iowa, USA
REVIEW RETURNED	16-Mar-2020

GENERAL COMMENTS	The protocol is well-organized and well-written. I have several questions and comments as follows: 1. How is the chance of death or hospital readmission within 30 days after ICU discharge at your institution? Not from your preliminary 22 patients, but rather do you have data from more patients? 2. You modified the protocol to contact all participants 10 days after enrollment to improve engagement and resolve any issued in completing the surveys. Do you think that this also affects patients' outcome/readmission rate? I wonder the contact made on 10 days after enrollment may function not only to improve survey engagement but also to become an opportunity to check whether a patient is doing well or not, which may affect your outcomes. For example, if a patient says she/he is not doing well, an interviewer may provide some medical advice. It may be that a call 10 days after ICU discharge asking how a patient is doing might be a best way to evaluate the patient recovery and to facilitate intervention for adverse events. 3. How are you handling patients who need ICU readmission during the same hospitalization after enrollment? 4. As you pointed out, I think selection bias would be a huge issue in your study after considering your preliminary study. Are you going to analyze patients who do not take part in or do not complete surveys because of lack of interest, having no smartphones, frailty, or not in the mood for your surveys? 5. I do not think considering some incentives for participation is the right thing to do because such a system will not be sustainable, especially if you want to integrate this system into your routine clinical care.

REVIEWER	adrienne boissy

	Cleveland Clinic
REVIEW RETURNED	01-May-2020

GENERAL COMMENTS	Thank you for this study and your hard work advancing the understanding of engagement for cardiac patients. The study is well designed,and strength is in the planned evaluation, as well as pairing subjective with objective input. and the manuscript captures the preliminary results. Having all the results would make the paper more robust in its data collection - I wonder what the additional burden of reporting finalized data is and whether you would consider wrapping it all in one manuscript. Also, You have a section in Page 16 called patient perspective, wherein the author became a patient s and offers their perspective. I would submit that this is not the best example to provide for a patient perspective, ie someone with extensive healthcare knowledge and expertise on the disease process. Would be ideal to actually interview another patient for his piece or remove. Lastly, patient engagement research hinges on not simply opening the email or consenting, but completion of all the tasks being requested. True engagement includes motivation and confidence to manage one's condition and the work would be strengthened by including the gold standard measurement of the Patient Activation Measure - this would help tease out selection bias regarding digitally savvy patients who are highly activated to manage their health, especially given the nature of this study. There are many lessons from how best to engage patients (knowing their own goals for health, aligning communication and its frequency to their preferences, etc) that I dont see mentioned here. the informed consent says HUGO is not a HIPAA compliant platform and that patient data is going into the Cloud (line 221). How did we ensure patients understood this and how many accessed their own data? Page 13-14 and 24 have formatting issues Thank you for the opportunity to review

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1, Vivek Rao

1. In my opinion, study protocols should be published when they involve large multi-centre, multi-national clinical trials to avoid major funding agencies (NIH, NHS, CIHR, etc) from supporting similar studies that are earlier in their stage of development. This study is a single centre, almost retrospective study in that patients are enrolled after their surgery. I think a similar larger study involving multiple sites would be competitive for national funding and thus I personally see no value in publishing this study design and preliminary results.

Response: We appreciate these comments and generally agree. We opted to submit this Methods paper because of its novelty and the value in describing in detail how we are conducting a longitudinal study of recovery with frequent patient-generated and patient-reported information – and the use of latent class models to define recovery phenotypes. We have recently published the paucity of studies focusing on recovery – and there is little guidance about how to conduct these studies. Therefore, this

contribution is intended not only to pre-specify our approach (which is the usual reason for a Methods paper), but perhaps more importantly to describe a new approach to studying recovery. We have now made this point clearer in the Introduction.

Changes: The end of the introduction section now includes the following sentence to clarify the main purpose of publishing this study protocol manuscript, 'The purpose of this study protocol summary is to describes a new approach to studying recovery in order to address the knowledge gap as well as to prespecify our approach.' (line 144-)

2. Point #1 notwithstanding, I do have enthusiasm for this study and would welcome a manuscript describing their final results. To that end, I have a few suggestions with respect to study design and inclusion/exclusion factors.
- I agree with the inclusion of isolated CABG, VALVE and combined VALVE-CABG cases as these patient populations are relatively homogeneous. In contrast, aortic operations can vary in their complexity and patient demographics. The latter group may include patients with Hereditary syndromes (as Yale is a recognized center of excellence for aortic surgery). These patients may have additional comorbidities associated with their aortopathy that adversely affects their PROMs, but has little to do with the actual surgery. Furthermore, some of these patients will require deep hypothermia and circulatory arrest which will also confound their postoperative recovery. I recommend excluding aortic surgery from this study.

Response: Thank you for your enthusiasm for this study and for this comment considering the particular patient population seen at our center. We agree with the reviewer's point that aortic surgery patient population and operative features may differ from those of CABG or valve cohorts. This was considered at the time of study design and we decided to proceed including patients who underwent aortic operation, because we felt there would be lessons learned from comparing the recovery pattern of patients undergoing different CABG or valve and aortic operations, including those who undergo deep hypothermic circulatory arrest. As the recruitment of these group of participants was logistically feasible, we felt it would be a missed opportunity not to enroll patients who underwent aortic operation. We have always intended to assess this group separately to determine if the recovery experience is different from the other patients.

Changes: The Design Overview section of the Methods section now reads as the following: 'We chose the operations because they are the most common cardiac operations performed8 while having different patient and operative characteristics, such as the use of deep hypothermic circulatory arrest, to potentially provide insights into the recovery pattern associated with such variations. Subgroup analysis will be conducted to evaluate whether there is a distinct patient experience by operation types.' (line 150-)

3. The actual predictive model incorporating all PROMs and wearable device data is not described. Similarly, the PROMs are not all externally validated and thus reproducibility and generalizability remain a concern.

Response: We agree that the manuscript would benefit from more information about our analytic approach. As described in the previous version, the first step is to use the time-series PROM data to define trajectory classes using group-based trajectory model. We have added information about the next step, which is to treat the trajectory classes as an outcome to identify clinical predictors of the membership in a particular trajectory class, using multinomial logistic regression. This approach would allow us to estimate coefficients of each predictor variable towards the probability of membership in each trajectory class. This approach has strong precedence in time-series data used in other clinical

domains.

In terms of the psychometric property of the PROM tool, the Quality of Recovery questionnaire has a strong evidence base in terms of validity testing, including convergent validity, construct validity, internal consistency, and test-retest reliability. Importantly, the instrument was chosen among 6 candidate instruments that were all developed to measure postoperative recovery after evaluating various properties. Specific properties of each candidate instrument including the Quality of Recovery questionnaire are summarized in new Supplementary Table 1-2. Briefly, we chose the instrument because it gave the assessment of the most comprehensive recovery domains with evaluation of the psychometric property that was most extensive among the 6 candidate instruments. Other favorable property included the ability to self-administer, involving inpatient surgery as a development cohort, the interpretability of item-wise score on Likert scale, and extensive use case publications in broad surgical populations.

Changes: The section describing the model specification now reads: 'The questionnaire consists of 24 items that were developed and validated in inpatient and outpatient surgical populations in terms of convergent validity with visual analogue scale, construct validity compared with length of hospital stay and sex-based difference, along with good internal consistency and test-retest reliability10-13. We chose QoR-24 among 5 other PROMs developed specifically to measure postoperative recovery. QoR-24 possessed many qualities advantageous for the purpose of our study, including the robust validation of psychometric property, extensive use cases in various surgical populations, ability for self-administration, and the ease of interpreting item-wise scores (Supplementary Table 1-2).'

4. How do the authors intend to handle patients with postoperative complications such as dialysis, wound infections, stroke, etc? Clearly these complications will affect recovery but may not be accounted for in a model that only examines PROMs and wearable device data. One may argue that their PROMs may be skewed against recovery due to their postoperative course.

Response: Thank you for raising this point. We agree that it is important to incorporate clinical factors including postoperative complications in the model, specifically considering the potential mediation and interaction effects of certain variables that you alluded to. The main purpose of the study is to understand different recovery phenotype, and subsequent steps would try to understand this in causal inference framework, as it would require much larger sample size. For this study, we plan to stratify the data (subgroup analysis specifically on those without complications, for example) and possibly use mixed effects model to evaluate this. Feasibility and inferential value of such analysis largely depends on the final sample size and distribution of the recruited cohort. Additionally, as in response to your third comment above, the second step of this analysis, the use of multinomial model to identify predictors of patients belonging to each trajectory class, was missing in the prior version. As stated in response to your third question, we revised this section to include the details of the model, specifically highlighting that we will fit the model using clinical variables including complications.

Changes: Analytical approach section now includes the following sentence: 'As some variables interact with each other, such as history of chronic lung disease increasing the risk of postoperative pneumonia, which likely impacts the recovery experience, we plan to stratify the cohort with and without the index complications defined by the STS (prolonged ventilation, renal failure, sternal wound infection, pneumonia, stroke, all-cause reoperation). Further analyses on interaction and mediation effects likely requires a larger sample size and are of interest in the future.' (line 325-)

5. Why not include preoperative demographics into the predictive model? I would assume that age, urgency of operation and other preoperative co-morbidities would predict recovery.

Response: We agree with this point and the description of this aspect of the model was inadequate in the prior version. We revised this description in response, outlining the fact that we will consider fitting the model using preoperative patient and clinical variables.

Changes: The Analytical approach section now includes the following sentence: 'With the characterization of trajectories, we will then fit multinomial logistic regression models using clinical variables outlined in Table 1, including patient demographics, comorbidity, and postoperative event such as complications and ICU readmissions, to identify predictors of patients belonging to each trajectory class.' (line 321-)

Reviewer: 3, Yuki Nakamura

The protocol is well-organized and well-written. I have several questions and comments as follows:
1. How is the chance of death or hospital readmission within 30 days after ICU discharge at your institution? Not from your preliminary 22 patients, but rather do you have data from more patients?

Response: We agree this is a contextually important information. The incidence of 30-day mortality at our center is about 1% for isolated CABG or isolated AVR, which are slightly lower than the national average reported by the STS. The incidence of 30-day readmission is approximately 10% for isolated or concomitant CABG, which is also comparable to the national average. We would like to note that it is somewhat challenging to estimate the incidence of such events in our study participants based on our center's all-comer data, because of the likely selection towards younger and perhaps healthier participants.

Changes: We modified the methods section to provide this contextual information: 'The STS database contains patient demographics, comorbidities, presenting clinical status, operative details, and postoperative mortality and morbidity up to 30 days after the time of operation14. These data are routinely collected at Yale New Haven Hospital. At our program, 30-day mortality rates for isolated aortic valve replacement and isolated CABG are stable around 1%, with 30-day readmission rate of about 10%, which are slightly lower than the national average.'

2. You modified the protocol to contact all participants 10 days after enrollment to improve engagement and resolve any issued in completing the surveys. Do you think that this also affects patients' outcome/readmission rate? I wonder the contact made on 10 days after enrollment may function not only to improve survey engagement but also to become an opportunity to check whether a patient is doing well or not, which may affect your outcomes. For example, if a patient says she/he is not doing well, an interviewer may provide some medical advice. It may be that a call 10 days after ICU discharge asking how a patient is doing might be a best way to evaluate the patient recovery and to facilitate intervention for adverse events.

Response: We agree with the potential for the 10-day follow-up to become an intervention. The research assistant who has been conducting the follow-up call at 10 days is not allowed by the study protocol to act in the clinical capacity, and this way, we restrict that the nature of this call to be an assessment of barriers to completing surveys mostly to resolve technical challenges.
We also agree with the reviewer's comment that this phone call mechanism as a possible way to improve recovery process. While interesting and plausible, we focused on evaluating the potential value in the semi-automated approach to recovery data collection, which we believe to have a much higher scalability potential from human resource perspective.

Changes: To elaborate on the nature of this call highlighting the above point, we modified the Discussions section to read as the following: ‘To sustain patient engagement through challenging recovery course, we implemented a protocol for a research assistant to call the patient around 10 days after enrollment to troubleshoot any issues and reemphasize the importance of their participation. By the protocol, research assistant making this call does not act in clinical capacity and does not provide clinical evaluation or advise, which is an important boundary for this call to not act as an intervention to alter recovery course.’

3. How are you handling patients who need ICU readmission during the same hospitalization after enrollment?

Response: We keep the patients who are readmitted to the ICU in the study and record such events. We have considered excluding this population but that did not make sense for our purpose of characterizing the range of postoperative recovery irrespective of the degree of complications and readmission needs. Instead, we will collect information regarding readmission and complications and evaluate their associations with different patterns of recovery. With regards to the concern for missing data during ICU readmission, the proposed group-based trajectory model takes into account of the missing data and as long as the patient has at least 3 data points, the trajectory can be included in the model. As stated in the manuscript, multiple imputation also remains an option to handle such missingness.

Changes: We added the following sentence to clarify our intent to use postoperative complications including readmissions as the following: ‘With the characterization of trajectories, we will then perform multinomial logistic regression to identify clinical variables, including postoperative event such as complications and ICU readmissions, that may be associated with the likelihood of patients belonging to each trajectory class.’

4. As you pointed out, I think selection bias would be a huge issue in your study after considering your preliminary study. Are you going to analyze patients who do not take part in or do not complete surveys because of lack of interest, having no smartphones, frailty, or not in the mood for your surveys?

Response: Yes, this has been our plan and we appreciate you raising this point. We agree that we should address it in the protocol. We plan to analyze the characteristics of patients who were approached and were and were not able to participate in this study to provide the sense of the selection at play with such a study design.

Changes: We added the following sentence under Patient population section to clarify this point: ‘In order to provide the sense of patient selection resulting from these criteria, we will compare patient characteristics of those who were approached and were and were not able to participate in the study for any reasons.

5. I do not think considering some incentives for participation is the right thing to do because such a system will not be sustainable, especially if you want to integrate this system into your routine clinical care.

Response: Thank you for this comment. We meant to say that in the context of a research project that incentives might be helpful. If this system is integrated into clinical care there will be an incentive

embedded because the patients' clinicians will be using the data and that will be a benefit in their recovery. We have made this information clearer in our revision: xxx

Reviewer: 4, adrienne boissy

1. Thank you for this study and your hard work advancing the understanding of engagement for cardiac patients. The study is well designed, and strength is in the planned evaluation, as well as pairing subjective with objective input. and the manuscript captures the preliminary results. Having all the results would make the paper more robust in its data collection - I wonder what the additional burden of reporting finalized data is and whether you would consider wrapping it all in one manuscript.

Response: Thank you very much for this encouraging comment with regards to the importance of the study. We considered delivering this study's findings in a single manuscript. However, as we feel the study design is quite complex and the word count of this manuscript describing the methods and implementation of the protocol alone is already quite long, we felt there is a value to publishing this protocol paper.

2. Also, you have a section in Page 16 called patient perspective, wherein the author became a patient s and offers their perspective. I would submit that this is not the best example to provide for a patient perspective, ie someone with extensive healthcare knowledge and expertise on the disease process. Would be ideal to actually interview another patient for his piece or remove.

Response: We agree with this comment and removed the patient perspective section.

Changes: We removed the section in question

3. Lastly, patient engagement research hinges on not simply opening the email or consenting, but completion of all the tasks being requested. True engagement includes motivation and confidence to manage one's condition and the work would be strengthened by including the gold standard measurement of the Patient Activation Measure - this would help tease out selection bias regarding digitally savvy patients who are highly activated to manage their health, especially given the nature of this study. There are many lessons from how best to engage patients (knowing their own goals for health, aligning communication and its frequency to their preferences, etc) that I don't see mentioned here.

Response: Thank you for this important point. We agree that our current design lacks quantitative assessment of the degree of patient engagement. By examining the survey completion rate and the time spent to complete each survey, we have indirect ways of assessing patient engagement. For example, patients who do not respond or who speeds through the questions by responding with the same value would have unrealistically short completion time, and such values could be used as a marker of engagement. We plan to use such metrics to descriptively report on engagement.
We also acknowledge that there is a selection bias related to digital savviness and the level of engagement as the reviewer noted, and to improve the sense of the population to which our findings may apply, we will report the characteristics of those who were and were not able to enroll, along with the reasons for not being enrolled. This information is being collected at the time of enrollment. Although the technical barrier likely introduces selection bias, as identified in our prior systematic review, the quality and volume of existing evidence is extremely limited on this topic and we hope that evidence generated from this study will be a step towards further engaging hospitals and surgical programs for a more systematic implementation of such a patient-centered evaluation of

postoperative recovery, which in turn can result in a more robust data collection accounting for different levels of patient engagement. We also plan to report on the reasons of difficult engagement through phone interview of patients who had low response rate, similar to the pilot data on phone interview (under 'Identifying common reasons for low response rate') that we reported in the manuscript that led to modification of the protocol.

Changes: We added the following sentences in the 'Identifying common reasons for low response rate': 'Survey response rate and time spent to complete each survey will be reported descriptively to evaluate the degree of patient engagement. This approach likely allows us to identify patients who either did not respond or completed the survey in an unrealistically short time that may not represent a meaningful response.' We also added the following sentence describing our approach to assess engagement and barriers, similar to what we have described in our pilot phase: 'We will continue to conduct this phone interview for patients with low response rate and describe engagement and barriers to participation in the final cohort.'
We also modified the Limitations section to include the following sentence: 'Those who cannot participate due to lack of interest or technological barrier represent an important population that may be distinct in characteristics and risk profiles. While acknowledging the selection bias originating from this inclusion threshold, we believe there is a need to initiate collection of patient-centered outcome measures in the proposed approach, in order to further engage hospitals and programs for a broader implementation of this approach in the context of extremely limited evidence base.'

4. the informed consent says HUGO is not a HIPAA compliant platform and that patient data is going into the Cloud (line 221). How did we ensure patients understood this and how many accessed their own data?

Response: Thank you for this important point. The language regarding Hugo platform being not HIPAA compliant was placed specifically because Hugo does not fall under the definition of a "Covered Entity" that HIPAA regulates. However, Hugo actually has all the safeguards required by HIPAA in terms of security and privacy. This information is also available at Hugo website (https://hugo.health/security). Therefore, that practically speaking, the fact that Hugo is not regulated by HIPAA and therefore by definition is not HIPAA compliant does not mean that patient data is handled any differently than it would had this platform been HIPAA compliant (which would require Hugo to be defined under Covered Entity).
At the time of obtaining consent, we try our best to be explicit and detailed about the content of the consent form, including that data share elements, cloud storage, and the nature of the platform. As you point out, these concepts can be complex and we currently do not have objective ways to assess their level of understanding, other than verbally confirming at the time of consenting that they understood what is being described. However, as described above, we believe that the practicality of HIPAA compliance does not apply to Hugo and it is more important to describe the process Hugo takes to ensure data security, which we do in the consenting process.
In terms of data access, we do not review participants' access activity to their own data and the exact number is unknown.

Changes: The following sentence is added to Digital data platform section of the manuscript. "Hugo does not fall under the Covered Entity that Health Insurance Portability and Accountability Act (HIPAA) regulates, but employs all the security measures that would be required by HIPAA had it been a Covered Entity."

5. Page 13-14 and 24 have formatting issues

Response: They have all been reformatted with uniform font type, size, and double spacing.

Changes: Corresponding pages have been reformatted.

VERSION 2 – REVIEW

REVIEWER	Yuki Nakamura University of Iowa, USA
REVIEW RETURNED	31-Jul-2020

GENERAL COMMENTS	Thank you for your revisions and hard work.