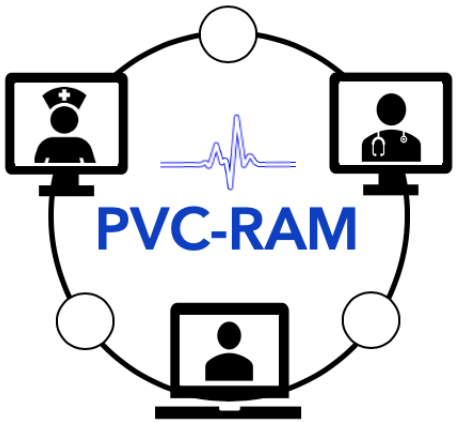
ONLINE-ONLY SUPPLEMENT 2



Post discharge after surgery Virtual Care with Remote Automated Monitoring technology (PVC-RAM) Trial

STATISTICAL ANALYSIS PLAN

Version 1.0
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LIST OF ABBREVIATIONS

CI: confidence interval
COVID-19: Coronavirus Disease 2019
PVC-RAM: Post discharge after surgery Virtual Care with Remote Automated Monitoring technology
RAM: remote automated monitoring
RCT: randomized controlled trial
SAP: Statistical Analysis Plan

1. INTRODUCTION

At the start of the Coronavirus Disease 2019 (COVID-19) pandemic, many hospitals cancelled elective surgeries for various reasons (e.g., reduce the risk of COVID-19 transmission, facilitate physical distancing, preserve personal protection equipment, and maximize bed availability for patients with COVID-19); however, throughout the pandemic, the need for semi-urgent (e.g., oncology), urgent (e.g., hip fracture), and emergent (e.g., abdominal aortic aneurysm rupture) surgeries has remained. Patients discharged after non-elective (i.e., semi-urgent, urgent, or emergent) surgeries are at substantial risk of hospital re-admissions, presentation to emergency departments or urgent-care centres, or death in the 30 days following discharge.[1-3] Many centres have now resumed elective surgeries. To facilitate management of the backlog of individuals waiting for elective surgeries, ensure hospital capacity for patients with COVID-19, and minimize the spread of COVID-19, there is a need to reduce non-elective surgical patients' subsequent use of acute-hospital care. A strong rationale and encouraging evidence suggest that virtual care with remote automated monitoring (RAM) will increase days alive at home, in adults discharged after surgery.

The trial described in this Statistical Analysis Plan (SAP), the Post discharge after surgery Virtual Care with Remote Automated Monitoring technology (PVC-RAM) Trial, was a parallel group randomized controlled trial (RCT) among adults discharged after non-elective surgery that evaluated the effect of virtual care with RAM versus standard care on the 31-day outcome of days alive at home.

This SAP describes the statistical methods for the PVC-RAM Trial. It contains definitions of analysis sets, key derived variables and it provides a technical and detailed elaboration of the principal features of the planned analyses (e.g., dealing with missing data). The SAP will be finalized without knowledge of any emerging results by trial treatment group. The final version of the SAP will be signed off before database freeze.

2. TRIAL DESCRIPTION

2.1 Study Design

The PVC-RAM trial is a multicentre RCT of 900 patients being discharged from the hospital after non-elective surgery. Patients are randomized to virtual care with RAM for 30 days after randomization or standard care. PVC-RAM will determine the effects of virtual care with RAM technology versus standard care. Patients, healthcare providers, and data collectors will be aware of patients' treatment assignment. Outcome adjudicators will be masked to treatment allocation. Outcome ascertainment will occur through direct patient follow-up and administrative data obtained from the Institute for Clinical Evaluative Sciences and the Canadian Institute of Health Information.

3. STUDY OBJECTIVES

3.1 Primary objective

- To determine, in adults being discharged after undergoing non-elective surgery, the effect of virtual care with RAM technology compared to standard care on days alive at home during 31 days of follow-up.

3.2 Secondary objectives

- To determine, during 31 days of follow-up, the effect of virtual care with RAM technology on the following secondary outcomes:
    - 1. hospital re-admission;
    - 2. emergency department visit;
    - 3. urgent-care centre visit;
    - 4. acute-hospital care (i.e., a composite of hospital re-admission and emergency department or urgent-care centre visit);
    - 5. brief acute-hospital care (i.e., acute-hospital care that lasts <24 hours);
    - 6. all-cause hospital days;
    - 7.medication error detection;
    - 8. medication error correction; and
    - 9. death.
- To determine the effect of virtual care with RAM technology compared to standard care on pain at 7, 15, and 30 days and 6 months after randomization, measured via the Brief Pain Inventory-Short Form.

3.3 Tertiary objectives

- To determine, during 31 days of follow-up, the effect of virtual care with RAM technology on the following tertiary outcomes:
    - 1. health services utilization-related costs;
    - 2. patient-level cost of recovery;
    - 3. re-operation;
    - 4. arrhythmia resulting in electrical cardioversion;
    - 5. acute renal failure resulting in dialysis;
    - 6. respiratory failure;
    - 7. infection;
    - 8. surgical site infection;
    - 9. life-threatening, major, or critical-organ bleeding;
    - 10. ileus;
    - 11. myocardial infarction;
    - 12. clinically important atrial fibrillation;
    - 13. symptomatic proximal venous thrombo-embolism;
    - 14. stroke;
    - 15. non-fatal cardiac arrest;
    - 16. clostridium difficile-associated diarrhea;
    - 17. indwelling device inappropriately left in a patient;
    - 18. COVID-19 infection;
    - 19. delirium;
    - 20. surgeon, family physician, or specialist in-person clinic visit;
    - 21. surgeon, family physician, or specialist virtual clinic visit;
    - 22. sepsis; and
    - 23. acute heart failure.
- To determine, the 6-month effect of virtual care with RAM technology on the following tertiary outcomes:

- 1. the secondary outcomes;
- 2. COVID-19 infection;
- 3. surgeon, family physician, or specialist in-person clinic visit;
- 4. surgeon, family physician, or specialist virtual clinic visit; and
- 5. health services utilization-related costs.

4. OUTCOMES

Outcome adjudicators (expert physicians), blind to treatment allocation, will adjudicate the following outcomes: 1. days alive at home; 2. brief acute-hospital care; 3. all-cause hospital days; 4. delirium; 5. sepsis; 6. acute heart failure; 7. myocardial infarction; 8. stroke; 9. non-fatal cardiac arrest; 10. clinically important atrial fibrillation; 11. symptomatic pulmonary embolism; 12. symptomatic proximal deep venous thrombosis; 13. bleeding; and 14. ileus. All statistical analyses involving these outcomes will use the adjudicated decisions. Unrefuted events are events that undergo adjudication and the adjudicator does not refute the event or events reported by centres that do not undergo adjudication. All outcomes are defined in Table 1.

The day of randomization is day 0 of follow-up and the day after randomization is day 1 of follow-up after randomization, etc. Because patients are followed from the day of randomization (i.e., day 0 of follow-up) until day 30 after randomization, patients have 31 days of follow-up for the main analyses that are the focus of this SAP. Study personnel will contact all study patients at 31 days to collect outcome data. The economic and long-term (i.e., 6 month) outcomes, mentioned above, will not be discussed further in this SAP. There will be a separate SAP for the economic and long-term outcomes.

4.1 Primary Outcome

The primary outcome is

- days alive at home during the 31-day follow-up

4.2 Secondary Outcomes

Secondary outcomes during the 31-day follow-up include: 1. hospital re-admission; 2. emergency department visit; 3. urgent-care centre visit; 4. acute-hospital care; 5. brief acute-hospital care; 6. all-cause hospital days; 7. medication error detection; 8. medication error correction; and 9. death. An additional secondary outcome is pain, assessed at days 7, 15, and 30 after randomization. We expect to detect more medication errors and corrections in the intervention group compared to the control group and would interpret this as an improvement in care.

4.3 Tertiary Outcomes

Tertiary outcomes during the 31-day follow-up include: 1. re-operation; 2. arrhythmia resulting in electrical cardioversion; 3. acute renal failure resulting in dialysis; 4. respiratory failure; 5. infection; 6. surgical site infection; 7. life-threatening, major, or critical-organ bleeding; 8. ileus; 9. myocardial infarction; 10. clinically important atrial fibrillation; 11. symptomatic proximal venous thrombo-embolism; 12. stroke; 13. non-fatal cardiac arrest; 14. clostridium difficile-associated diarrhea; 15. indwelling device inappropriately left in a patient; 16. COVID-19 infection; 17. delirium; 18. surgeon, family physician, or specialist in-person

clinic visit; 19. surgeon, family physician, or specialist virtual clinic visit; 20. sepsis; and 21. acute heart failure.

5. POPULATIONS TO BE ANALYZED

All randomized participants will be included in the treatment groups to which they were randomized, regardless of treatments received or duration of trial participation (i.e., we will follow the intention-to-treat principle).

6. STATISTICAL ANALYSES

6.1 General Methods

Standard methods will be used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. Summaries of continuous variables will include the number of subjects (N), mean, and standard deviation, median, 25th and 75th percentiles. Frequency distributions (N and %) will be given for categorical data.

Primary statistical analyses will be based on unrefuted events. All analyses will be performed in SAS® using version 9.4.

6.1.1 Primary Outcome – Poisson Regression

For the primary analysis, we will use a Poisson regression model that accounts for the clustering by centre, to estimate the 31-day effect of virtual care and RAM technology compared with standard care on the primary outcome of days alive at home.[4-6] In this model, we will adjust for the type of surgery (i.e., cardiac versus non-cardiac) and will also include pre-randomization independent variables known to be associated with acute-hospital care after discharge post surgery (i.e., age, sex, active cancer, requiring assistance with activities of daily living, and the following index hospitalization complications before randomization: cardiac [i.e., myocardial infarction, non-fatal cardiac arrest], bleeding [i.e., life-threatening, major, or critical organ bleeding], venous thromboembolism [i.e., deep vein thrombosis or pulmonary embolism], infection, and sepsis. These variables will be included as long as they do not demonstrate collinearity (i.e., variance inflation factor >2.5). If collinearity is demonstrated, we will remove one of the collinear variables. Based on the model, we will report the corresponding relative risk and 95% confidence interval (CI) for the 31-day effect of virtual care and RAM technology compared with standard care. For the primary outcome, we will use the Mann-Whitney-Wilcoxon test to establish the p value. We will infer statistical significance if the computed 2-sided p-value is less than α=0.05.

6.1.2 Secondary and Tertiary Outcomes: Binary – Poisson Regression

For the binary secondary and tertiary outcomes, we will estimate the effect of virtual care and RAM technology compared with standard care using Poisson regression models that account for the clustering by centre. In these models, we will adjust for the type of surgery (i.e., cardiac versus non-cardiac) and will also evaluate inclusion of the following pre-randomization independent variables: age, sex, active cancer, requiring assistance with activities of daily living, and the following index hospitalization complications before randomization: cardiac (i.e., myocardial infarction, non-fatal cardiac arrest), bleeding (i.e., life-threatening, major, or critical organ bleeding), venous thromboembolism (i.e., deep vein thrombosis or pulmonary embolism),

infection, and sepsis. These variables will be included as long as they do not demonstrate collinearity (i.e., variance inflation factor >2.5). If collinearity is demonstrated, we will remove one of the collinear variables. Based on the models, we will report the corresponding relative risk and 95% CI for the 31-day effect of virtual care and RAM technology compared with standard care. For the secondary outcome of death, we will undertake a Fisher exact test.

6.1.3 Secondary and Tertiary Outcomes: Continuous – Analysis of Co-Variance

For continuous outcomes, we will evaluate treatment effects of virtual care and RAM technology compared with standard care using regression models, that account for the correlation within centres. In these models, we will adjust for the type of surgery (i.e., cardiac versus non-cardiac) and will also evaluate inclusion of pre-randomization independent variables known to be associated with acute-hospital care after discharge post surgery (i.e., age, sex, active cancer, requiring assistance with activities of daily living, and the following index hospitalization complications before randomization: cardiac [i.e., myocardial infarction, non-fatal cardiac arrest], bleeding [i.e., life-threatening, major, or critical organ bleeding], venous thromboembolism [i.e., deep vein thrombosis or pulmonary embolism], infection, and sepsis. These variables will be included as long as they do not demonstrate collinearity (i.e., variance inflation factor >2.5). If collinearity is demonstrated, we will remove one of the collinear variables. Based on the model, we will obtain estimates and their 95% CIs for the independent variables.

6.1.4 Handling Missing Data

All efforts will be made to collect complete data for all patients in this study. Patients will be followed to the study end and will complete all required data collection, regardless of their compliance with study visits. For the primary analysis of the primary outcome, if there is an equal number of patients lost to follow-up in the two randomization groups, we will censor these patients at the time they were lost to follow-up. When modeling the primary outcome, we will use multiple imputation if there is an unequal number of patients lost to follow-up in the two randomization groups or missing covariate data. For secondary or tertiary outcomes, we will follow a similar process to that used for the primary outcome

6.2 Study follow-up time

6.2.1 Missing date information

When an event date is not known, the site investigator will be asked to provide a best estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often does know some information that would indicate the approximate date, such as the first week of a month or at least the date when the patient was last seen or contacted. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be closer to the true date than any produced by an uninformed computer program. This estimated date should be the middle date within the period that the event is known to have occurred. If the event is known to have occurred in the first week of a month, then the date in the middle of that week should be recorded as the estimate. If no information is known, then the date in the middle of the plausible time period should be given, based on the last contact with the patient before the event and the date of contact when information about the event was known.

This method for date estimation has been used in many studies and is recommended by Dubois and Hebert.[7]

6.2.2 Baseline, Time Windows, and Calculated Visits

The day of randomization is day 0 of follow-up and the day after randomization is day 1 of follow-up after randomization, etc. Because patients are followed from the day of randomization (i.e., day 0 of follow-up) until day 30 after randomization, patients have 31 days of follow-up for the main analyses that are the focus of this SAP. Follow-up time will be defined as the date of last contact for an individual, or the date of death if available.

7. EFFICACY ANALYSES

The primary analyses will be based on the intention to treat principle (i.e. participants will be analyzed in the treatment group to which they were randomized) and will include all unrefuted events.

From the regression models, we will report relative risks and 95% CIs. All tests will be two-sided. Unless otherwise stated, all other outcomes will be tested using two-sided tests at the 5% significance level.

8. SUBGROUP ANALYSES

The subgroup analyses will be conducted using tests for interactions in the Poisson model for the primary outcome. We will consider subgroup effects statistically significant if an interaction p value <0.05. All subgroups will be hypothesis generating.

We will perform three subgroup analyses as follows: on patients who underwent cardiac versus non-cardiac surgery; on men versus women; and on patients who did or did not suffer during their index hospitalization before randomization one or more of the following complications: cardiac (i.e., myocardial infarction, non-fatal cardiac arrest), bleeding (i.e., life-threatening, major, or critical organ bleeding), venous thromboembolism (i.e., deep vein thrombosis or pulmonary embolism), infection, and sepsis.

9. SENSITIVITY ANALYSES

For analyses that required imputation of the outcome, we will undertake sensitivity analyses restricted to patients with complete follow-up.

Table 1. Outcome definitions

Outcome	Definition
Days alive at home	Days alive at home are the number of days patients spend at their usual residence – be it a house or apartment, a group home or shelter, a seniors' residence, or a nursing home – or at a community residence of a relative, friend, or acquaintance without, during that day, being admitted to a hospital or visiting an emergency department or urgent-care centre. Thus, patients lose days alive at home if 1. patients go to an emergency department or urgent-care centre; 2. they become inpatients at a hospital or rehabilitation or convalescence-care facility; or 3. they die. More specifically, our approach to calculating days alive at home follows. If a patient visits an emergency department or urgent-care centre anytime between midnight and 23:59 on a given day, they will lose that day as a day alive at home. If a patient visits an emergency department or urgent-care centre anytime between midnight and 23:59 on a given day and they remain in the emergency department or urgent-care centre past midnight into the next day, then they lose 2 day alive at home. If a patient is admitted to the hospital or rehabilitation or convalescence-care facility anytime between midnight and 23:59 on a given day, they will lose that day as a day alive at home. They will continue to lose days alive at home until the day in which they are home and out of an acute-hospital care or a rehabilitation or convalescence-care facility from midnight for an entire day. Patients randomized before hospital discharge do not lose this day alive at home unless after their discharge they die or visit an emergency department or urgent-care centre on the day of their discharge. Patients randomized before hospital discharge will lose this day alive at home if their discharge is ultimately delayed and they do not go home on their day of randomization. Because patients are followed until day 30 after randomization and the day of randomization is day 0, if a patient is discharged home after randomization and remains at home until death on day 2 after randomization (i.e., they survived at home on the day of randomization and day 1 after randomization, but died on the subsequent day) they would be counted as having had 2 day alive at home, and lose 29 of the possible 31 days alive at home.
Hospital re-admission	Patient admission to an acute-care hospital.

Emergency department visit	Patient visit to an emergency department.
Urgent-care centre visit	Patient visit to an urgent-care centre.
Acute-hospital care	Acute-hospital care is a composite outcome of hospital re-admission and emergency department or urgent-care centre visit
Brief acute-hospital care	Acute-hospital care that last <24 hours from the time of arrival to the time of discharge home.
All-cause hospital days	If a patient is admitted to the hospital for any reason anytime between midnight and 23:59 on a given day, this will count as a day in hospital. Study personnel will determine the total number of days in the hospital for any reason. Patients randomized before hospital discharge do not have this day counted as a hospital day unless after their discharge they are re-admitted to the hospital on the day of their discharge. Patients randomized before hospital discharge will have this day counted as a hospital day if their discharge is ultimately delayed and they do not go home on their day of randomization.
COVID-19 infection	For COVID-19 infection, we will accept any laboratory confirmed evidence of COVID-19 infection.
Medication error detection	Medication errors include mistakes in medication prescribing, transcribing, dispensing, administering, or monitoring due to preventable events or actions taken by a patient, caregiver, or healthcare worker. Medication errors include: drug omission (i.e., patient did not take a drug they were supposed to take), drug commission (i.e., patient taking a drug they were not supposed to take), duration error, dosing error, frequency error, route error, and timing error. We will record all drug errors identified and also report whether they resulted in harm. We will use the following definitions for harm: 1. no harm – error that does not cause any clinically appreciable harm to the patient; 2. minor harm – error that leads to event resulting in minor treatment or extra monitoring to ensure significant harm is avoided (e.g., mild symptoms or minimal loss of function; one day of symptoms; laboratory abnormality not requiring emergency department or urgent-care centre visit); 3. moderate harm – error that leads to event requiring treatment or extra monitoring and causes temporary but not permanent harm (e.g., laboratory abnormality, symptoms, or condition requiring emergency department or urgent-care centre visit); 4. severe harm – error that

	leads to event that requires treatment or extra monitoring and results in significant or permanent harm (e.g., permanent disability or loss of function; near-death event [e.g., anaphylaxis, cardiac arrest]; serious laboratory abnormality, symptom, or condition requiring intervention to sustain life or leading to prolonged hospitalization); and 5. death – error leading to loss of life.
Medication error correction	Any medication error that is corrected.
Delirium	For the diagnosis of delirium within 30 days after randomization, any one of the following criteria is required: 1. Patient meets the criteria for ongoing delirium on day 30 at the in-person or telephone 3D-CAM administered on day 30; OR 2. Patient is unable to complete the telephone interview on day 30 because they are too confused. This criterion is significant for an acute decline in their cognition when patients are able to complete telephone interviews at baseline, which is consistent with one of our eligibility criteria; OR 3. Positive history of delirium in the 30 days after randomization as assessed through a telephone interview with a family member/caregiver using the FAM-CAM; OR 4. Positive history of delirium in the 30 days after randomization based on the review of electronic hospital health records. The diagnosis of delirium based on remote assessment (i.e. telephone or videoconference interview) is met when either 1. or 2. is met: 1. Patient able to complete the interview and meeting the delirium criteria as per the Confusion Assessment Method, (i.e., a. acute onset of symptoms OR fluctuating course of symptoms, AND b. inattention AND either c. disorganized thinking or d. altered level of consciousness. 2. Patient unable to complete the interview because too confused. This criterion is applicable when patients are able to complete telephone interviews at baseline, which is consistent with one of our eligibility criteria. In this case, this is significant for an acute decline in their cognitive performance.
Surgeon, family physician, or specialist in-person clinic visit	Patient in-person visit to a surgeon's, family physician's, or specialist's clinic.
Surgeon, family physician, or specialist virtual clinic visit	Patient has a virtual clinical visit with a surgeon, family physician, or specialist.

Sepsis	Our definition of sepsis is based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Sepsis requires a quick Sequential Organ Failure Assessment (qSOFA) Score ≥2 points due to infection. The qSOFA includes the following items and scoring system: 1. altered mental status (1 point); 2. systolic blood pressure ≤100 mm Hg (1 point); and 3. respiratory rate ≥22 breaths per minute (1 point).
Acute heart failure	The definition of acute heart failure requires at least one of the following clinical signs (i.e., elevated jugular venous pressure, respiratory rales or crackles, crepitations, or presence of S3) with at least one of the following: 1. radiographic findings of vascular redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema, OR 2. heart failure treatment with a diuretic and documented clinical improvement.
Death	The definition of death is all cause mortality.
Pain	Pain intensity and related interference with usual daily activities, will be measured via the Brief Pain Inventory-Short Form (BPI-SF). The BPI-SF includes four 11-point numeric rating scales (NRS) of pain intensity, which measure "average", "least", and "worst" pain intensity in the past 24 hours (hrs.), respectively, as well as pain intensity "now" (0= no pain, 10= pain as bad as you can imagine). The BPI-SF interference subscale will also be used, which measures the degree to which pain interferes with general activity, mood, walking, work, relations with others, sleep, and enjoyment of life (NRS for each item; 0=does not interfere, 10=completely interferes). A total interference score is determined by calculating the sum of these 7 items. The BPI-SF has strong psychometric properties with well-established reliability and validity across divergent surgical groups.
Health services utilization-related costs	Data on hospital re-admission, healthcare utilization, and costs of health service utilization will be obtained from the *Institute for Clinical Evaluative Sciences* (ICES) data repository. Administrative databases used to describe the health service utilization include: 1. Registered Persons Database (RPDB) – demographics and vital statistics of all legal residents of Ontario; 2. Discharge Abstract Database – records of inpatient hospitalizations from the Canadian Institute for Health Information (CIHI); 3. Ontario Health Insurance Plan (OHIP) Database – physician billing claims, and the National Ambulatory Care Reporting System – information on emergency department visits from CIHI. In

	addition, to capture data on times spent on the Cloud DX Connected Health mobile application by health providers (e.g., virtual nurses), costs of health providers' time will be captured in the system reporting. Costs of health providers' time on the Cloud DX Connected Health mobile application will be calculated by multiplying the time with unit costs from standard costing sources in Ontario.
Patient-level cost of recovery	The Ambulatory and Home Care Record (AHCR) will be used to comprehensively measure patient-level costs of illness from a societal perspective. This approach gives equal consideration to health system costs and costs borne by patients and unpaid caregivers (e.g., family members, friends). AHCR items can be categorized as publicly financed (e.g., public sector paid resources) or privately financed care (e.g., all out-of-pocket and third-party insurance payments, and time costs incurred by caregiver). Face validity and reliability of the AHCR is well established in multiple groups, including surgical patients.
Re-operation	Re-operation refers to any surgical procedure undertaken for any reason (e.g., wound dehiscence, infection)
Arrhythmia resulting in electrical cardioversion	Any arrhythmia that leads to electrical cardioversion.
Acute renal failure resulting in dialysis	This outcome is defined as acute renal failure that results in dialysis (i.e., use of hemodialysis machine or peritoneal dialysis apparatus) in a patient who was not on chronic dialysis before randomization.
Respiratory failure	Patient intubated or put on bilevel positive airway pressure (BiPAP).
Infection	Infection is defined as a pathologic process caused by the invasion of normally sterile tissue, fluid, or body cavity by pathogenic or potentially pathogenic organisms.
Surgical site infection	Surgical site infection is an infection that occurs within 30 days after surgery and involves the skin, subcutaneous tissue of the incision (superficial incisional), or the deep soft tissue (e.g., fascia, muscle) of the incision (deep incisional).
Life-threatening bleeding	Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope or vasopressor

	therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.
Major bleeding	Major bleeding is defined as bleeding that is not specified under "life- threatening bleeding" and results in at least one of the following: 1. a postoperative hemoglobin ≤ 70 g/L; 2. a transfusion of ≥1 unit of red blood cells; or 3. leads to one of the following interventions: embolization, superficial vascular repair, nasal packing.
Critical-organ bleeding	Critical-organ bleeding is bleeding that is intracranial, intraocular, intraspinal, pericardial, retroperitoneal, or intramuscular with compartment syndrome.
Ileus	Ileus is a physician diagnosis of functional obstruction of the gastrointestinal tract in the absence of an alternative diagnosis that leads to postoperative decreased bowel activity. The definition requires the following criteria: 1. inability to pass flatus or stool for >24 hours; and 2. persistence of one or more of the following signs and symptoms for >24 hours: abdominal distention; diffuse abdominal pain; or nausea or vomiting.
Myocardial infarction	The diagnosis of myocardial infarction requires one of the following criteria: 1. Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following: A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); B. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds; C. new or presumed ECG changes indicative of ischemia (i.e., ST segment elevation [≥ 2 mm in leads V_1, V_2, or V_3 OR ≥ 1 mm in the other leads], ST segment depression [≥ 1 mm], or symmetric inversion of T waves ≥ 1 mm) in at least two contiguous leads; D. new LBBB; or E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging F. identification of intracoronary thrombus on angiography or autopsy 2. Cardiac death, with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were

obtained, or before cardiac biomarker values would be increased.

3. Percutaneous coronary intervention (PCI) related myocardial infarction is defined by elevation of a troponin value (>5 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL) or a rise of a troponin measurement >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

4. Stent thrombosis associated with myocardial infarction when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one of value above the 99th percentile URL.

5. Coronary artery bypass grafting (CABG) related myocardial infarction is defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with a normal baseline troponin value (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

6. For patients who are believed to have suffered a myocardial infarction within 28 days of a MINS event or within 28 days of a prior myocardial infarction, the following criterion for myocardial infarction is required:
   Detection of a rise or fall of a cardiac biomarker (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) and 20% higher than the last troponin measurement related to the preceding event together with evidence of myocardial ischemia with at least one of the following:
   A. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema);

	B. development of pathologic Q waves present in any two contiguous leads that are $\geq$ 30 milliseconds; C. new or presumed new ECG changes indicative of ischemia (i.e., ST segment elevation [$\geq$ 2 mm in leads V_1, V_2, or V_3 OR $\geq$ 1 mm in the other leads], ST segment depression [$\geq$ 1 mm], or symmetric inversion of T waves $\geq$ 1 mm) in at least two contiguous leads; D. new LBBB; or E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging F. identification of intracoronary thrombus on angiography or autopsy
Clinically important atrial fibrillation	The definition of clinically important atrial fibrillation requires the documentation of atrial fibrillation or atrial flutter on a 12 lead electrocardiogram, or confirmed atrial fibrillation or atrial flutter (e.g., rhythm strip) that results in angina, congestive heart failure, symptomatic hypotension, or requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
Symptomatic proximal venous thrombo-embolism	Venous thromboembolism that includes symptomatic pulmonary embolism or symptomatic proximal deep vein thrombosis.
Symptomatic pulmonary embolism	The diagnosis of symptomatic pulmonary embolism requires symptoms (e.g., dyspnea, pleuritic chest pain) and any one of the following: 1. A high probability ventilation/perfusion lung scan; 2. An intraluminal filling defect of segmental or larger artery on a helical CT scan; 3. An intraluminal filling defect on pulmonary angiography; or 4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following: A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan, or B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan
Symptomatic proximal deep venous thrombosis	The diagnosis of symptomatic proximal deep venous thrombosis (DVT) requires: 1. symptoms or signs that suggest DVT (e.g., leg pain or swelling), 2. thrombosis involving the popliteal vein or more proximal veins for leg DVT OR axillary or more proximal veins for arm DVTs Any of the following defines evidence of vein thrombosis:

	A. a persistent intraluminal filling defect on contrast venography (including on computed tomography); B. noncompressibility of one or more venous segments on B mode compression ultrasonography; or C. a clearly defined intraluminal filling defect on doppler imaging in a vein that cannot have compressibility assessed (e.g., iliac, inferior vena cava, subclavian).
Stroke	Stroke is defined as either: 1. a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting ≥24 hours or leading to death; or 2. a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting <24 hours with positive neuroimaging consistent with a stroke.
Non-fatal cardiac arrest	Non-fatal cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation.
Clostridium difficile-associated diarrhea	This outcome requires diarrhea as a symptom with laboratory documentation of Clostridium difficile.
Indwelling device inappropriately left in a patient	An indwelling device (e.g., drain, catheter, pacemaker wire) inappropriately left in patient is defined as an indwelling device inappropriately being left in a bodily organ or passage longer than it was intended.

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APPROVAL

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By signing the below, I designate my approval of the above-named version of the PVC-RAM Trial Statistical Analysis Plan on behalf of all investigators.

Name	**P.J Devereaux**
Role	**Co-Principal Investigator**
Signature	
Date (yyyy/mm/dd)	

Name	**Michael McGillion**
Role	**Co-Principal Investigator**
Signature	
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By signing the below, I designate my approval of the above-named version of the PVC-RAM Trial Statistical Analysis Plan on behalf of PHRI Statistics.

Name	**Yan Yun Liu**
Role	**Blinded Study Statistician**
Signature	
Date (yyyy/mm/dd)	