ONLINE-ONLY SUPPLEMENT 1

PVC-RAM Trial Protocol and amendments

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

Final Protocol v1.0
Dated April 6, 2020

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Protocol Number: 2020.04.06

CLINICAL TRIAL SUMMARY

Title	**P**ost discharge after surgery **V**irtual **C**are with **R**emote **A**utomated **M**onitoring technology (PVC-RAM) Trial
Project Office	PVC-RAM Project Office, Population Health Research Institute Hamilton General Hospital Campus, DBCVSRI 237 Barton Street East, Hamilton, Ontario, Canada L8L 2X2
Study Size	900 patients
Study Design	Multicentre, parallel group, superiority, randomized controlled trial.
Primary Objectives	To determine the effect of virtual care with remote automated monitoring (RAM) technology compared to standard care on the 30-day risk of acute-hospital care (i.e., a composite of hospital re-admission and emergency department or urgent-care centre visit), in adults who have undergone semi-urgent (e.g., oncology), urgent (e.g., hip fracture), or emergency (e.g., ruptured abdominal aortic aneurysm) surgery.
Secondary Objectives	To determine, during the first 30 days, 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. COVID-19 infection; 5. number of days alive and at home; 6. medication error detection; 7. medication error correction; 8. delirium; 9. surgeon, family physician, or specialist in-person clinic visit; 10. surgeon, family physician, or specialist virtual clinic visit; 11. sepsis; 12. acute heart failure; and 13. death. An additional secondary objective is to determine the effect of virtual care with RAM technology on pain at 7, 15, and 30 days after randomization.
Eligibility Criteria	Patients are eligible to participate if they fulfill all of the following criteria: 1. ≥40 years of age; 2. have undergone same-day or inpatient semi-urgent, urgent, or emergency surgery and are being discharged home or are within 24 hours after discharge home, as long as they have not had acute-hospital care since their discharge; and 3. provide informed consent to participate. Patients fulfilling any of the following criteria will be ineligible to participate: 1. underwent same-day surgery and the surgeon or anesthesiologist believe the case reflects a traditional same-day surgery case with a low likelihood of needing acute-hospital care; 2. went to rehabilitation or convalescent care for more than 7 days after undergoing surgery; 3. are unable to communicate with research staff, complete study surveys, or undertake an interview using a tablet computer due to a cognitive, language, visual, or hearing impairment; or 4. reside in an area without cellular network coverage and no home Wi-Fi.
Treatment Regimen	Patients randomized to the PVC-RAM intervention will be taught how to use the cellular modem-enabled tablet computer and RAM technology from Cloud DX. The RAM technology will measure the following biophysical parameters: 1. blood pressure, 2. heart rate, 3. respiratory rate, 4. oxygen saturation, 5. temperature, and 6. weight. Patients will take biophysical measurements with the RAM technology and complete a recovery survey, daily for 30 days, and nurses will review these results daily. Patients will interact with a virtual nurse daily on days 1-15 and every other day from days 16-30. On days without planned virtual visits, nurses will organize unscheduled virtual

	visits if they detect patients' biophysical measurements or recovery survey responses exceed predetermined thresholds or the nurse identifies another reason for concern. During virtual visits, the nurse will discuss any symptoms the patient is experiencing, evaluate their wound and obtain a picture, reinforce principles related to recovery after surgery and the need for physical distancing, and undertake medication review and reconciliation. If the patient's RAM measurements exceed predetermined thresholds, the patient reports specific symptoms (e.g., shortness of breath), a drug error is identified, or the virtual nurse has concerns about the patient's health that they cannot resolve, the virtual nurse will escalate care to a pre-assigned and available physician (i.e., the patient's surgeon or a medical physician). Physicians will add or modify treatments as needed, and if required, they will have the patient come to an outpatient facility for evaluation or management. Via secure video or text messaging, patients will also have access to a virtual nurse at night, for any urgent issues. This mechanism will assure patients have access to a healthcare provider 7 days per week. Patients randomized to standard care will receive post discharge care as per the standard of care at the hospital in which they underwent surgery.
Follow-up	Outcome ascertainment will occur through direct patient follow-up and administrative data obtained from the Institute for Clinical Evaluative Sciences (ICES). Study personnel will actively follow patients until 30 days after randomization, and the primary outcome is the 30-day risk of acute-hospital care. We will evaluate 6-month outcomes through ICES data.

PVC-RAM Protocol v1.0 Approval:

By signing the below, I designate my approval of the above-named version of the PVC-RAM protocol.

Dr. Michael McGillion Principal Investigator Population Health Research Institute	_____ Signature	_____ Date (yyyy-mm-dd)

Dr. PJ Devereaux Principal Investigator Population Health Research Institute	_____ Signature	_____ Date (yyyy-mm-dd)

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1 INTRODUCTION AND RATIONALE

On March 11, 2020, the World Health Organization declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, causing coronavirus disease 2019 (COVID-19), a global pandemic.[1] COVID-19 cases have overwhelmed northern Italy's healthcare system, resulting in the need to ration mechanical ventilation and a high mortality rate.[2] In an attempt to avoid the fate of Italy, many countries, including Canada, have implemented physical distancing.[1,3]

To maximize bed availability for patients with COVID-19, facilitate physical distancing, and to reduce the risk of COVID-19 transmission, physicians are discharging all patients who are eligible and hospitals are cancelling elective surgeries. There remains, however, the need for inpatient semi-urgent (e.g., oncology), urgent (e.g., hip fracture), and emergency (e.g., abdominal aortic aneurysm rupture) surgeries. Patients discharged after undergoing non-elective (i.e., semi-urgent, urgent, or emergency) surgeries are at substantial risk, in the 30 days following surgery, of hospital re-admissions and presentation to emergency departments or urgent-care centres.[4,5] Ensuring adequate hospital, emergency department, and urgent-care centre capacity for patients with COVID-19, and minimizing the risk of COVID-19 transmission, will require innovative interventions designed to reduce surgical patients' subsequent use of acute-hospital care.

There is a strong rationale and encouraging evidence suggesting that virtual care with remote automated monitoring in adults discharged after undergoing inpatient surgery will reduce the 30-day risk of hospital re-admissions and emergency department or urgent-care centre visits.[6] We will undertake the **P**ost discharge after surgery **V**irtual **C**are with **R**emote **A**utomated **M**onitoring technology (PVC-RAM) Trial to inform this issue.

1.1 Primary Research Question

Among adults discharged after non-elective (i.e., semi-urgent, urgent, or emergency) surgery, does virtual care with remote automated monitoring technology reduce the 30-day risk of acute-hospital care (i.e., a composite of hospital re-admission and emergency department or urgent-care centre visit), compared to standard care.

1.2 Need for the PVC-RAM Trial

1.2.1 Patients being discharged from the hospital after inpatient non-elective surgery are at substantial risk of subsequent acute-hospital care

The VISION Study, a prospective cohort study of a representative sample of 40,004 adults ≥45 years of age who underwent inpatient non-cardiac surgery at 28 centres, in 14 countries,[7] demonstrated a 7% incidence of patient re-admission to the hospital within 30 days of surgery. Similarly, a large administrative database study (n=143,232) from the United States demonstrated an overall 30-day incidence of unplanned hospital re-admissions after non-cardiac surgery of 7%.[5] In VISION, a multivariable regression analyses (confidential data) demonstrated that older age, major surgeries (general, neurology, urology/gynecology, thoracic, and vascular), and cancer were associated with an increased risk of hospital re-admission. Moreover, medical complications during the index hospitalization after non-cardiac surgery are strongly associated with an increased risk of subsequent hospital re-admission,[5,8] and non-elective surgeries are strongly associated with an increased risk of perioperative complications.[9-11]

A Canadian Institutes of Health Information study evaluated 2.1 million acute hospitalizations in Canada from April 2010 to April 2011.[4] Patients undergoing inpatient and same-day surgery accounted for 31% of participants. Surgical patients had a 7% unplanned 30-day re-admission rate, and the average cost associated with the re-admission was $9700. Moreover, 19% of the surgical patients presented to an emergency department within 30 days of discharge after their index surgery. Based on these data, it is

estimated that 20-25% of adults being discharged after undergoing non-elective surgery will receive acute-hospital care within a 30-day follow-up period.

In a prospective cohort study of 5158 consecutive patients who underwent cardiac surgery at 10 centres participating in the Cardiothoracic Surgical Trials Network in Canada and the United States, 13% of patients were re-admitted to the hospital within 30 days of discharge.[12] A study of 324,070 Medicare patients in the United States who underwent coronary artery bypass grafting (CABG) surgery had a 22% incidence of emergency department visits within 30 days of discharge after their index hospitalization.[13] Based on these data, it is estimated that at least 25% of patients post hospital discharge after cardiac surgery will receive acute-hospital care within a 30-day follow-up period.

1.2.2 Virtual care with RAM technology holds promise to prevent acute-hospital care

Virtual care encompasses all the ways that healthcare providers remotely interact (e.g., phone, computer) with their patients, and can be a sole healthcare provider (e.g., nurse) or a shared-care approach (e.g., nurse led with escalation to a physician, as needed) mode of care delivery. Virtual care can consist of the following: sharing of patient information (e.g., symptoms, medication review), education (e.g., informing patients about signs of illness), and management (e.g., a recommendation to seek medical attention, physician submitting a drug prescription). Remote automated monitoring (RAM) refers to use of technology to remotely obtain data regarding patients' biophysical parameters (e.g., blood pressure, temperature). Research has evaluated the use of various aspects of virtual care with and without RAM of one or multiple biophysical parameters.

In the non-operative setting, trials of cardiology patients have evaluated the effects of virtual care and RAM technology. A trial of 1437 patients with heart failure randomized patients to standard care or virtual care (i.e., 9 coaching calls over a 6-month period) and RAM.[14] For the RAM aspect of the intervention, patients were asked to submit daily their weight, blood pressure, heart rate, and response to 3 symptom questions. If monitoring results exceeded a predetermined threshold, a nurse telephoned to encourage the patient to contact their health professional. This trial demonstrated no difference in hospital re-admissions between the two study groups; however, adherence to the experimental intervention was suboptimal (i.e., only 55% of patients submitted their biophysical data on >50% of the days), and the trial did not utilize a shared-care strategy that ensured patients received physician prescribed treatment.

In contrast to this trial, a Cochrane systematic review of patients with heart failure demonstrated that non-invasive telemonitoring (i.e., remote monitoring of biophysical parameters and other non-invasive data) reduced heart failure related hospitalizations (8 RCTs; 2148 patients; relative risk, 0.71; 95% CI, 0.60-0.83).[15] This systematic review also reported that structured telephone support reduced heart failure related hospitalizations (16 RCTs; 7030 patients; relative risk, 0.85; 95% CI, 0.77-0.98). An RCT of 128 patients with angina demonstrated that virtual care (i.e., frequent video conferencing with a nurse to assess patients' progress and self-care education) with RAM (i.e., daily transmission of blood pressure and weight) reduced the risk of hospitalization (relative risk reduction 51%; p=0.016), compared to standard care.[16] Collectively these trials provide encouraging evidence that virtual care with RAM technology can prevent hospital admissions in patients with cardiovascular diseases.

In adults discharged after undergoing inpatient surgery, there is a strong rationale supporting the potential for virtual care and RAM technology to reduce the risk of subsequent acute-hospital care. After hospital discharge post surgery, patients typically see a physician only after 2-4 weeks. This limited follow-up can result in delays in recognizing and managing complications, which can lead to re-hospitalization and poor outcomes. The most common causes for re-hospitalization or emergency department visits after surgery are surgical site infection, ileus, bleeding, pain, cardiovascular complications, and dehydration.[5,8,13] Early identification and management of these complications has the potential to reduce acute-hospital care.

A study compared 54 orthopedic surgery patients – who had postoperative home monitoring of blood pressure, heart rate, oxygen saturation, and pain scores 4 times a day for 4 days after discharge with specified alert protocols to a healthcare provider – to 107 orthopedic surgery patients who received standard care after hospital discharge.[6] This observational study reported an 80% relative risk reduction in the composite of hospital re-admission and emergency room visit at 30 days.

1.2.3 Summary

To confront the COVID-19 pandemic, Canadian hospitals need to maximize bed availability for COVID-19 patients and minimize emergency department and urgent-centre visits for non-COVID-19 reasons. Displacing non-urgent care is probably the right decision for society; however, hospitals also have an obligation to treat non-COVID-19 patients with urgent and emergency conditions. As a result, we will continue to provide surgery to patients for non-elective indications, and post discharge after non-elective surgery, patients are at high risk of needing subsequent acute-hospital care. There is a strong rationale and promising data that suggests among adults discharged after undergoing non-elective surgery that virtual care, based on a shared-care approach (e.g., nurse led with escalation to a physician, as needed), with RAM technology can reduce the need for subsequent acute-hospital care. We will undertake the PVC-RAM trial to directly inform this issue.

2 PLAN OF INVESTIGATION

2.1 Trial Objectives

2.1.1 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 the 30-day risk of acute-hospital care.

2.1.2 Secondary objectives

To determine, during the first 30 days, 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. COVID-19 infection; 5. number of days alive and at home; 6. medication error detection; 7. medication error correction; 8. delirium; 9. surgeon, family physician, or specialist in-person clinic visit; 10. surgeon, family physician, or specialist virtual clinic visit; 11. sepsis; 12. acute heart failure; and 13. death. An additional secondary objective is to determine the effect of virtual care with RAM technology on pain at 7, 15, and 30 days after randomization, measured via the Brief Pain Inventory-Short Form.

2.1.3 Tertiary objectives

To determine, during the first 30 days, 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. arrythmia 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; and 16. clostridium difficile-associated diarrhea.

To determine the 6-month effect of virtual care with RAM technology on the following tertiary outcomes: 1. acute-hospital care; 2. COVID-19 infection; 3. surgeon, family physician, or specialist in-person clinic visit; and 4. surgeon, family physician, or specialist virtual clinic visit.

2.1.4 Economic Analysis

A separate protocol will be written outlining a full economic analysis.

2.2 Trial Design

The PVC-RAM trial is a multicentre RCT of 900 patients being discharged from the hospital after non-elective surgery. 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.

2.3 Centres

The Juravinski Hospital and Cancer Centre, the Hamilton General Hospital, and St. Joseph's Healthcare in Hamilton and the London Health Sciences Centre in London, Ontario will participate in this trial. Other centres may also join the trial.

2.4 Sample Size

Table 1 reports the trial power based on a 2-sided α=0.05, control group event rates of 20% and 25%, and relative risks of 0.60 and 0.65. We will recruit 900 patients; this will provide 91% and 96% power if the control group event rate is 20% and 25%, respectively, assuming a relative risk of 0.60. We will have 84% power if the relative risk is 0.70, assuming a control group event rate of 25%.

2.5 Eligibility Criteria

2.5.1 Inclusion Criteria

Patients are eligible if they:

1. are ≥40 years of age;
2. have undergone same-day or inpatient semi-urgent, urgent, or emergency surgery and are being discharged home or are within 24 hours after discharge home, as long as they have not had acute-hospital care since their discharge; and
3. provide informed consent to participate.

2.5.2 Exclusion Criteria

Patients are ineligible if they:

1. underwent same-day surgery and the surgeon or anesthesiologist believe the case reflects a traditional same-day surgery case with a low likelihood of needing acute-hospital care;
2. went to rehabilitation or convalescent care for more than 7 days after undergoing surgery;
3. are unable to communicate with research staff, complete study surveys, or undertake an interview using a tablet computer due to a cognitive, language, visual, or hearing impairment; or
4. reside in an area without cellular network coverage and no home Wi-Fi.

2.6 Patient Recruitment and Informed Consent

Study personnel will utilize efficient recruitment strategies that we developed in prior perioperative trials.[17,18] These include efficient approaches to identify eligible patients through screening: daily surgical list in the operating room, surgical wards, and intensive care units. Centres will also ask clinicians working in anesthesiology, surgery, and medicine to page the study personnel regarding all patients who require non-elective surgery and were admitted through the emergency room or are an inpatient. Research personnel will approach all eligible patients to obtain informed consent.

2.7 Randomization

Randomization will occur when a patient is deemed eligible, pending hospital discharge after surgery, and written informed consent is obtained. Research personnel will randomize patients via an Interactive Web Randomization System. This system is a 24-hour computerized randomization internet system maintained by the coordinating centre at the Population Health Research Institute (PHRI), which is part of Hamilton Health Sciences and McMaster University in Hamilton, Ontario, Canada.

The randomization process will use block randomization stratified by centre and type of surgery (i.e., cardiac versus non-cardiac). We will use randomly varying block sizes, and study personnel and investigators will not know the block sizes. We will randomize patients in a 1:1 fashion to receive virtual care with RAM technology versus standard care.

2.8 Minimizing Bias

Our randomization procedure ensures concealment. Outcome ascertainment will occur through direct patient follow-up and administrative data obtained from the Institute for Clinical Evaluative Sciences. Outcome adjudicators (expert physicians), blind to treatment allocation, will adjudicate the following outcomes: 1. delirium; 2. sepsis; and 3. acute heart failure. All statistical analyses involving these outcomes will use these adjudicated decisions. We will undertake analyses according to the intention-to-treat principle. We will utilize the same mechanisms for ensuring patient follow-up used in our large international perioperative trials (e.g., the POISE Trial randomized 8351 patients and achieved 99.8% follow-up).[17]

2.9 Trial Intervention

Patients will be randomized to 30 days of virtual care with RAM technology or standard care. In the standard-care group, patients will receive their post hospital discharge management as per the standard of care at the hospital in which they underwent surgery.

2.9.1 Virtual care and RAM intervention

Research staff will teach patients randomized to the virtual care with RAM how to use the cellular modem-enabled tablet computer and RAM technology from Cloud DX, Figure 1. This RAM technology will measure the following biophysical parameters: blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, and weight. Patients will take biophysical measurements with the RAM technology and complete a recovery survey, daily for 30 days, and nurses will review these results daily. Patients will interact with a virtual nurse daily on days 1-15 and every other day from days 16-30. On days without planned virtual visits, nurses will organize unscheduled virtual visits if they detect patients' biophysical measurements or recovery survey responses exceed predetermined thresholds or the nurse identifies another reason for concern.

During virtual visits, the nurse will discuss any symptoms the patient is experiencing, evaluate their wound and obtain a picture, reinforce principles related to recovery after surgery and the need for physical distancing, and undertake medication review and reconciliation. If patient's RAM measurements exceed predetermined thresholds, the patient reports specific symptoms (e.g., shortness of breath), a drug error is identified, or the virtual nurse has concerns about a patient's health that they cannot resolve, the virtual nurse will escalate care to a pre-assigned and available physician (i.e., the patient's surgeon or a medical physician). Physicians will add or modify treatments as indicated and, if required, have them come to an outpatient facility for evaluation or management. Patients will also have access to a virtual nurse at night for any urgent issues, via secure video or text messaging. This mechanism will assure patients have access to a healthcare provider 7 days per week.

2.9.2 Cloud DX's technology

The primary interface for the virtual care intervention is the Cloud DX Connected Health mobile application, which is embedded in a Samsung Android tablet computer equipped with a camera to facilitate patient and healthcare provider video-based communication. To ensure cybersecurity and patient privacy, the Samsung tablet supports cellular and Wi-Fi communications through Health Insurance Probability and Accountability Act (HIPAA)-compliant cloud infrastructure. Bell will provide the cellular data plans. The Connected Health mobile application was designed by Cloud DX for use by patients of varying ages, including seniors. The application features simple menus for scheduling tasks (e.g. video visits with a virtual nurse), measuring biophysical parameters, completing the recovery survey, and educational material.

The Cloud DX RAM technology consists of a group of easy-to-use, Bluetooth-enabled, Health Canada-licensed, biophysical parameters monitoring devices, which will be paired with the pre-programmed Samsung tablet computer. This RAM technology contains the Cloud DX Pulsewave PAD-1A wrist-based blood pressure monitor, which derives measurements for blood pressure, pulse rate, and respiration rate. Patients will also receive a Cloud DX wireless pulse oximeter and wireless weight scale for measuring blood oxygen saturation and body weight. A wireless digital thermometer will also capture core body temperature. These biophysical parameters will upload automatically to the Samsung tablet, except for temperature, which must be entered manually. These Cloud DX monitors are certified according to International Standards Organization (ISO) Quality Management Standards, and have achieved perfect high patient usability and recommendation scores.

2.9.3 Patients obtaining Cloud DX technology, monitoring schedule, and training

Around the time of randomization, patients will receive the Samsung tablet computer and the RAM technology, instructions on how to use these devices, and their 30-day monitoring schedule. This schedule outlines the frequency and timing of daily monitoring of biophysical parameters, recovery survey, and virtual nurse video visits. The Connected Health mobile application will be prepopulated with this 30-day program and will guide patients through the daily requirements with interactive prompts. Study personnel will provide patients with a 30-minute checklist-oriented rehearsal of all Connected Health mobile application features and usage of the RAM technology. Study personnel will also invite and answer any questions.

2.9.4 Obtaining measurements of patients' biophysical parameters and recovery survey

Based on a schedule developed by a virtual nurse, the tablet will prompt patients to measure their biophysical parameters. The frequency of daily biophysical measurements will be 3 times a day for the first 15 days, and then twice a day from day 16 until 30 days after randomization. Weight will be measured daily in the morning before breakfast. Measurement of biophysical parameters can be adjusted according to a patient's acuity and tolerance, based on the virtual nurse's judgement or directions from a physician. Patients will record at least one full set of biophysical parameters each day of the study. The tablet will prompt patients daily to complete the recovery survey. The recovery survey consists of questions related to infection, bleeding, pain, dehydration, ileus, and cardiovascular and respiratory complications.

2.9.5 Virtual nurse triage priority of patients, daily patient virtual visits, and escalation of care

RAM measurements (apart from temperature, which is entered manually) are uploaded automatically to the Android tablet and can be viewed by the virtual nurse within 1 to 3 minutes. When a RAM measurement or survey result crosses any one of a set of pre-determined thresholds, the Connected Health mobile application will send real-time notifications to the virtual nurse. The virtual nurse then texts patients using the secure messaging feature on the Samsung tablet, to arrange a virtual visit; timing of visit will depend on the severity of the abnormality. The clinical dashboard on the Connected Health mobile application will facilitate remote patient management, which will automatically list patients

according to a triage priority order based on the severity of changes in RAM biophysical measurements or recovery survey responses.

Through the Connected Health mobile application, the virtual nurse will: 1. view and interpret patients' biophysical parameters and recovery survey responses; 2. conduct video visits with the patients, discuss any symptoms patients are experiencing, evaluate surgical wounds and obtain pictures, and reinforce principles related to recovery after surgery and the need for physical distancing; 3. undertake medication review and reconciliation on days 1, 8, 15, 22, and 30 after randomization; 4. intervene as needed; 5. escalate care to a pre-assigned and available physician (i.e., the patient's surgeon or a medical physician) when a predetermined threshold is surpassed or the virtual nurse has concerns about the patient's health that they cannot resolve; and 6. document their observations and interventions. Physicians will add or modify treatments as they deem appropriate and, if required, they have the patient come to an outpatient facility for evaluation or management.

2.10 Risk to the Safety of Participants

Patients randomized to the virtual care and RAM technology intervention will be at very low risk of serious harm related to the intervention. No studies of such interventions have reported a serious adverse event related to the intervention. We are using Health-Canada approved RAM technology.

2.11 Trial Outcomes

2.11.1 Primary Outcome

The primary outcome is the 30-day risk of acute-hospital care (i.e., a composite of hospital re-admission and emergency department or urgent-care centre visit).

2.11.2 Secondary Outcomes

Secondary outcomes during the first 30 days after randomization include: 1. hospital re-admission; 2. emergency department visit; 3. urgent-care centre visit; 4. COVID-19 infection; 5. number of days alive and at home; 6. medication error detection; 7. medication error correction; 8. delirium; 9. surgeon, family physician, or specialist in-person clinic visit; 10. surgeon, family physician, or specialist virtual clinic visit; 11. sepsis; 12. acute heart failure; and 13. death. An additional secondary outcome is pain, assessed at 7, 15, and 30 days after randomization. Outcome definitions are reported in the Supplemental Appendix.

2.11.3 Tertiary Outcomes

Tertiary outcomes during the first 30 days after randomization include: 1. health services utilization-related costs; 2. patient-level cost of recovery; 3. re-operation; 4. arrythmia 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; and 16. clostridium difficile-associated diarrhea. Additional tertiary outcome during the first 6 months after randomization include: 1. acute-hospital care; 2. COVID-19 infection; 3. surgeon, family physician, or specialist in-person clinic visit; and 4. surgeon, family physician, or specialist virtual clinic visit.

2.12 Follow-up

Through the Institute for Clinical Evaluative Sciences, we will collect data on the following outcomes: 1. hospital re-admission; 2. emergency department visit; 3. urgent-care centre visit; 4. COVID-19 infection; 5. re-operation; 6. surgeon, family physician, or specialist clinic visit; and 7. health services utilization-related costs. For patients in the virtual care and RAM group, the virtual nurse will collect data

on the following outcomes: 1. medication error detection; 2. medication error corrections; and 3. the Brief Pain Inventory-Short Form (BPI-SF).

Study personnel will contact all study patients 31 days after randomization and collect data on the following outcomes: 1. number of days alive and at home; 2. delirium; 3. sepsis; 4. acute heart failure; 5. death; 6. patient-level cost of recovery; 7. arrythmia resulting in electrical cardioversion; 8. acute renal failure resulting in dialysis; 9. respiratory failure; 10. infection; 11. surgical site infection; 12. life-threatening, major, or critical-organ bleeding; 13. ileus; 14. myocardial infarction; 15. clinically important atrial fibrillation; 16. symptomatic proximal venous thrombo-embolism; 17. stroke; 18. non-fatal cardiac arrest; and 19. clostridium difficile-associated diarrhea. Study personnel will contact patients in the standard-care group on days 7, 15, and 30 after randomization and collect data on the following outcomes: 1. medication error detection; 2. medication error corrections; and 3. the BPI-SF.

2.13 Statistical Analyses

Following the intention-to-treat principle, we will analyze patients in the treatment groups to which they were randomized. Any patients lost to follow-up will be censored at the time they are lost. The Operations Committee will create a separate statistical analysis plan that the statistical analyses will follow. The statistical analysis plan will be developed and finalized before any investigator is unblinded.

2.13.1 Main analyses

For the primary analysis, we will use Cox proportional hazards model to estimate the 30-day effect of virtual care and RAM technology compared with standard care on the primary outcome of acute-hospital care, with stratification by centre and type of surgery. We will present the time-to-the first occurrence of one of the components of the primary outcome using the Kaplan-Meier estimator. We will calculate the hazard ratio (HR), corresponding 95% confidence intervals (CI) and associated P values. We will infer statistical significance if the computed 2-sided p-value is less than α=0.05.

For the binary secondary and tertiary outcomes, we will use the same statistical approach as per the primary outcome. For continuous outcomes, we will evaluate treatment effects using analysis of co-variance (ANOVA).

2.13.2 Interim Analyses

Two interim analyses based on the primary outcome will occur when 50% and 75% of the patients have been followed for 30 days. The Data Monitoring Committee (DMC) will employ the modified Haybittle-Peto rule of 4 standard deviations (SDs) (α = 0.0001) for the first planned interim analysis and 3 SDs (α = 0.00047) for the second planned interim analysis. For a finding of the treatment to be considered significant, these predefined boundaries will have to be exceeded in at least 2 consecutive analyses, 2 or more months apart. The α-level for the final analysis will remain the conventional α = 0.05 given the infrequent interim analyses, their extremely low α-levels, and the requirement for confirmation with subsequent analyses.

At any time during the trial, if safety concerns arise the DMC chairperson will assemble a formal meeting of the full committee. The DMC will make their recommendations to the Project Office Operations Committee after considering all the available data and any external data from relevant studies. If a recommendation for termination is being considered, the DMC will invite the Project Office Operations Committee to explore all possibilities before a decision is made. A detailed charter will be developed and govern the activities of the DMC. The DMC will have members with expertise in clinical trials, perioperative medicine, and biostatistics.

3 TRIAL MANAGEMENT

3.1 Arrangements for the Day-to-Day Management of the Trial

Figure 2 illustrates the organizational structure of the PVC-RAM Trial. The PHRI Project Office is the coordinating centre for this trial and is responsible for the development of the protocol, development of the randomization scheme, trial database, data consistency checks, data analyses, coordination of the trial centres, and conducting the trial. The Co-Principal Investigators, Project Officer, Program Manager, and Research Coordinator are responsible for the activities of the Project Office. No statistician with knowledge of the randomization code will participate in the management or coordination of the PVC-RAM.

3.2 Site Principal Investigators

All participating centres will have a site Principal Investigator (PI), and this individual is responsible for ensuring compliance with respect to the intervention, visit schedule, and procedures required by the protocol. The site PI will ensure the provision of all information requested in the Case Report Forms (CRFs) in an accurate and timely manner according to instructions provided. The site PI will maintain patient confidentiality with respect of all information accumulated in the course of the trial, other than that information to be disclosed by law.

4 ENSURING DATA QUALITY

The Data Management Plan will outline the procedures to ensure data quality and will include the following: 1. all research personnel will undergo a training session before trial commencement to ensure consistency in trial procedures including data collection and reporting; 2. all centres will have a detailed trial Manual of Operations that will outline each step of the protocol; 3. the Project Office personnel will review detailed monthly reports on screening, enrollment, patient follow-up, data transmission, thoroughness, and completeness of data collection, and event rates, and they will rapidly address any identified issues; 4. the programmer will create internal validity and range checks using iDataFax which will identify any errors or omissions and notify the sender and Project Office of any such issues; 5. the Project Office will undertake multi-level data validation of the trial Case Report Forms; and 6. the Project Office will send investigators regular quality control reports.

5 ETHICAL CONSIDERATIONS

This trial will be conducted in compliance with the protocol, principles laid down in the Declaration of Helsinki, Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH), and all applicable laws and regulations of Canada. Before study initiation, the site PI must have written and dated approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the protocol and consent form. Amendments to the protocol will require IRB/IEC approval.

All patient information will be stored in a high security computer system and kept strictly confidential. Subject confidentiality will be further ensured by utilizing subjects' identification code numbers to correspond to treatment data in the computerized files. Patients' medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited. Medical information may be given to patients' personal physicians or to other appropriate medical personnel responsible for the patients' welfare. Data generated as a result of the trial are to be available for inspection on request by the participating physicians, IRB/IEC, study monitors, and competent authorities.

6 IMPORTANCE OF TRIAL

Canadian hospitals need to maximize bed availability for COVID-19 patients and minimize emergency department and urgent-centre visits for non-COVID-19 reasons. Hospitals also have an obligation to treat non-COVID-19 patients with urgent or emergency conditions. As a result, the participating hospitals will continue to provide surgery to patients for non-elective indications. Post discharge after non-elective surgery, these patients are at high risk of needing subsequent acute-hospital care. There is a strong rationale and promising data that suggests among adults discharged after undergoing inpatient non-elective surgery that virtual care with RAM technology can reduce the need for subsequent acute-hospital care. The PVC-RAM trial will answer an important question that will inform how to manage surgical patients after discharge in the setting of a pandemic.

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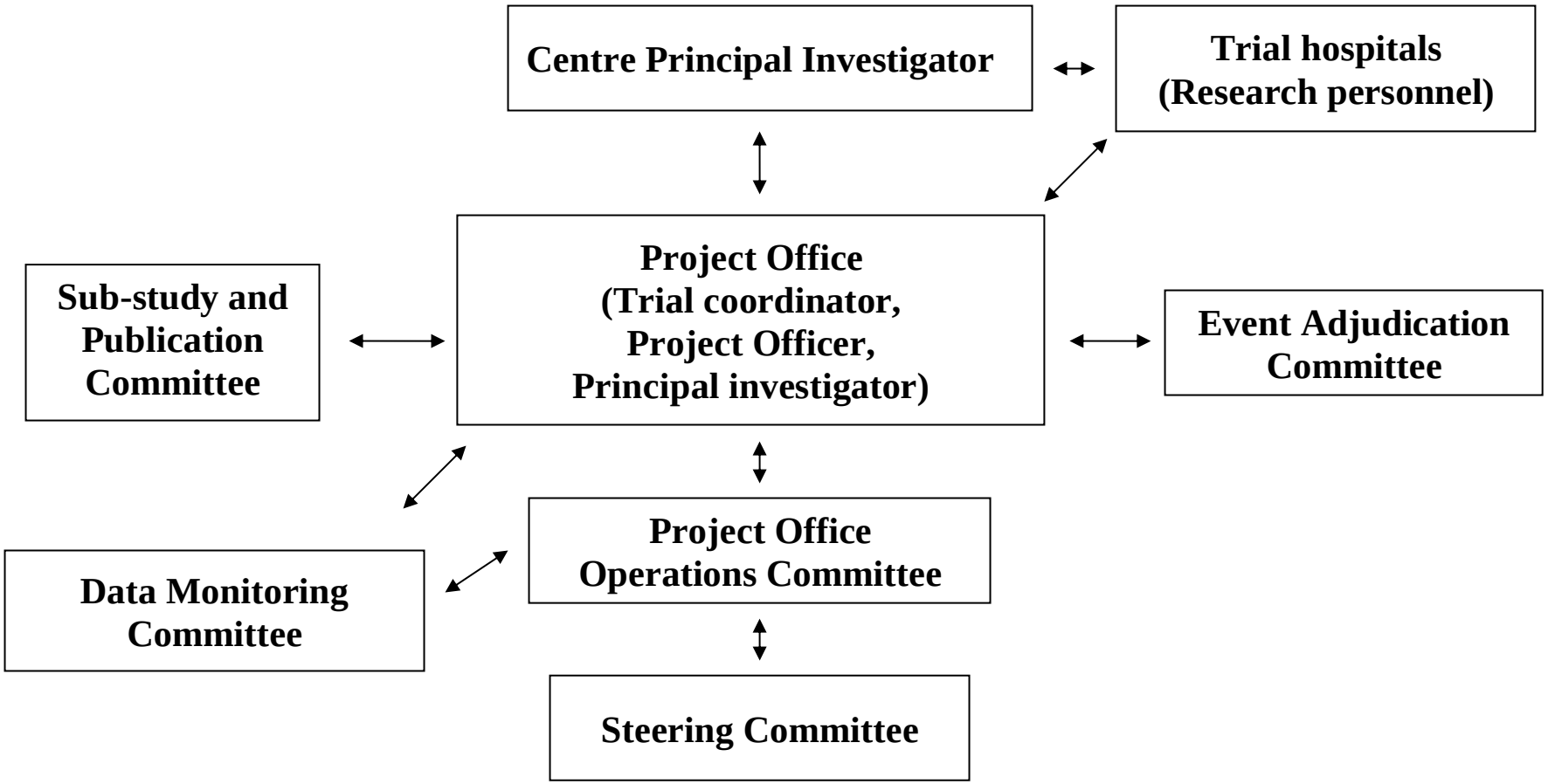
8 APPENDIX 1: Tables and Figures

TABLE 1. Power for detecting various relative risks using 2-sided α=0.05, with 450 subjects per arm, and various event rates in the control arm

Control group event rate	Experimental group event rate	Relative risk	Power
25%	15%	0.60	96%
25%	16%	0.65	90%
20%	12%	0.60	91%
20%	13%	0.65	81%

Figure 1. Cloud DX Connected Health kit

FIGURE 2. PVC-RAM organizational structure



9 APPENDIX 2: Outcome Definitions

Outcome	Definition
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.
COVID-19 infection	For COVID-19 infection, we will accept any laboratory confirmed evidence of COVID-19 infection.
Number of days alive and at home	The number of days the patient is alive and at their home.
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	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

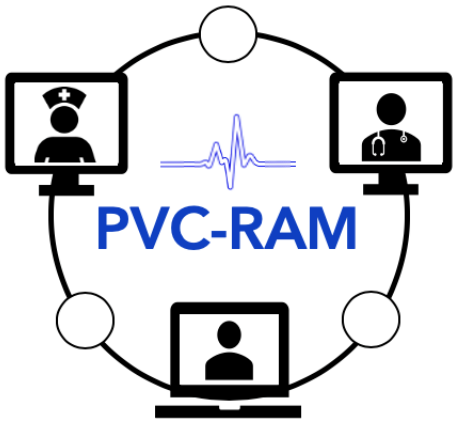
	symptoms OR fluctuating course of symptoms, AND b. inattention AND either c. disorganized thinking or d. altered level of consciousness. 2. Patient unable to complete the interview because too confused. This criterion is applicable when patients are able to complete telephone interviews at baseline, 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).[19] 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).[20] 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.[21,22] 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)
Arrythmia resulting in electrical cardioversion	Any arrythmia 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 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 >24h (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 documented new graft or new native coronary artery occlusion, 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 of any duration on an electrocardiogram or rhythm strip, which 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	Nonfatal 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.



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

Protocol Change Summary

Documentation of revisions made to **Protocol v1.0 2020-04-06**
that became **Protocol v2.0 2020-04-12**

Sponsor and Study Coordinating Group:
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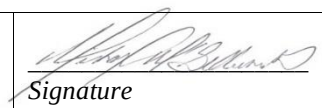
Dr. Michael McGillion Principal Investigator Population Health Research Institute	 *Signature*	2020-05-14 *Date (YYYY-MM-DD)*

Dr. P.J. Devereaux Principal Investigator Population Health Research Institute	 *Signature*	2020-05-14 *Date (YYYY-MM-DD)*

1. RATIONALE FOR CHANGES BETWEEN PROTOCOL V1.0 AND V2.0

1. 1. We have updated our power table and now report hazard ratios because our primary analysis will be a time-to-event analysis. We have also added the absolute risk reductions to this table, which reports the numerical impact on our primary outcome (acute-hospital care).

2. We have clarified that patients will only be randomized when the most responsible physician has decided to discharge the patient home and there is no change to surgeons' standard of care regarding post-discharge management as a result of this trial.

2. DESCRIPTION OF CHANGES BETWEEN v1.0 and v2.0

Page 9/25
THE FOLLOWING TEXT IS MODIFIED:

2.4 Sample Size

Table 1 reports the trial power based on a 2-sided α=0.05, control group event rates of 20% and 25%, and hazard ratios of 0.60, 0.65, 0.70, and 0.75~~relative risks of 0.60 and 0.65~~. We will recruit 900 patients; this will provide 95~~1~~% and 98~~6~~% power if the control group event rate is 20% and 25%, respectively, assuming a hazard ratio of 0.65~~relative risk of 0.60~~. We will have 87~~4~~% power if the ~~relative risk~~hazard ratio is 0.70, assuming a control group event rate of 20~~5~~%.

2.6 Patient Recruitment and Informed Consent

Study personnel will utilize efficient recruitment strategies that we developed in prior perioperative trials.[17,18] These include efficient approaches to identify eligible patients through screening: daily surgical list in the operating room, surgical wards, and intensive care units. Centres will also ask clinicians working in anesthesiology, surgery, and medicine to page the study personnel regarding all patients who ~~require~~ have undergone non-elective surgery and were admitted through the emergency room or are an inpatient. Research personnel will approach all eligible patients after surgery to obtain written informed consent. Study personnel can obtain consent via the telephone, if the patient has already been discharged home and they are within 24 hours of discharge.

Page 10/25
THE FOLLOWING TEXT IS ADDED:

2.7 Randomization

Randomization will occur when a patient is deemed eligible, pending hospital discharge after surgery, and written informed consent is obtained. Patients will only be randomized after the most responsible physician has decided to discharge the patient home. Although our goal is to try and randomize patients before hospital discharge, some patients may be discharge before study personnel can consent and randomize the patient. If an eligible patient is discharged before randomization was possible, study personnel can consent and randomize patients until 24 hours after discharge home, as long as they have not had acute-hospital care since their discharge.

Research personnel will randomize patients via an Interactive Web Randomization System. This system is a 24-hour computerized randomization internet system maintained by the coordinating centre at the Population Health Research Institute (PHRI), which is part of Hamilton Health Sciences and McMaster University in Hamilton, Ontario, Canada.

The randomization process will use block randomization stratified by centre and type of surgery (i.e., cardiac versus non-cardiac). We will use randomly varying block sizes, and study personnel and investigators will not know the block sizes. We will randomize patients in a 1:1 fashion to receive virtual care with RAM technology versus standard care.

2.9 Trial Intervention

Patients will be randomized to 30 days of virtual care with RAM technology or standard care. In the standard-care group, patients will receive their post hospital discharge management as per the standard of care at the hospital in which they underwent surgery. No changes to surgeons' standard of care regarding post discharge management will occur for patients randomized to the standard-care group, as a result of the trial.

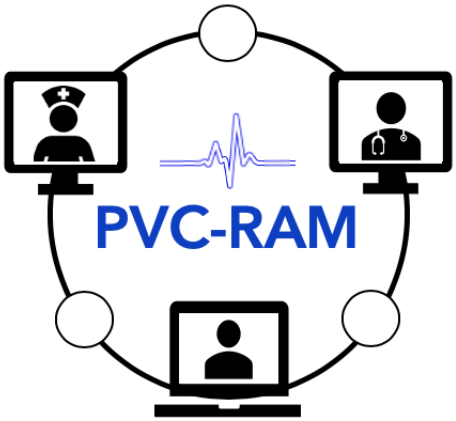
Page 17/25
THE FOLLOWING TEXT IS MODIFIED:

8 APPENDIX 1: Tables and Figures

TABLE 1. Power for detecting various ~~relative risks~~hazard ratios using 2-sided α=0.05, with 450 subjects per arm, and various event rates in the control arm

~~Control group event rate~~	~~Experimental group event rate~~	~~Relative risk~~	~~Power~~
~~25%~~	~~15%~~	~~0.60~~	~~96%~~
~~25%~~	~~16%~~	~~0.65~~	~~90%~~
~~20%~~	~~12%~~	~~0.60~~	~~91%~~
~~20%~~	~~13%~~	~~0.65~~	~~81%~~

Control group event rate	Experimental group event rate	Absolute risk reduction	Hazard ratio	Power
25%	16%	9%	0.60	99%
25%	17%	8%	0.65	98%
25%	18%	7%	0.70	92%
25%	19%	6%	0.75	79%
20%	13%	7%	0.60	99%
20%	14%	6%	0.65	95%
20%	15%	5%	0.70	87%
20%	16%	4%	0.75	71%



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

Protocol Change Summary

Documentation of revisions made to **Protocol v2.0 2020-04-12**
that became **Protocol v3.0 2020-05-14**

Sponsor and Study Coordinating Group:
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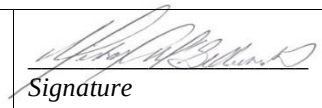
SIGNATURES

Dr. Michael McGillion Principal Investigator Population Health Research Institute	 *Signature*	2020-05-14 *Date (YYYY-MM-DD)*

Dr. P.J. Devereaux Principal Investigator Population Health Research Institute	 *Signature*	2020-05-14 *Date (YYYY-MM-DD)*

1. RATIONALE FOR CHANGES BETWEEN PROTOCOL V2.0 AND V3.0

1. We changed our primary outcome from acute-hospital care (i.e., a composite of hospital re-admission and emergency department or urgent-care centre visit) to a prior secondary outcome of number of days alive and at home. Moreover, we abbreviated this outcome to days alive at home.

We made this change because discussions within our group made us recognize the following limitations of having acute-hospital care as our primary outcome. This dichotomous outcome will miss repeat acute-hospital care visits. If there is differential in the severity of illness, which impacts the length of hospital stay between the two randomized groups, this will also be missed. Finally, there is risk of a competing outcomes problem. It is possible that monitored patients will be identified to have a substantial problem (e.g., profound bradycardia and low blood pressure) that the patient is not aware, and as a result of the monitoring technology, the patient is brought to the hospital for appropriate management (e.g., complete heart block). It is possible this goes unrecognized in a similar patient in the control group who then dies at home. This would then create a competing outcomes problem.

Days alive at home overcomes all of these problems. As such we have moved this secondary outcome to the primary outcome position and have moved acute-hospital care to become a secondary outcome.

2. We added the outcome brief acute-hospital care (i.e., a composite outcome of hospital re-admission and emergency department or urgent-care centre visit lasting <24 hours from the time of arrival to the time of discharge home). Some patients will develop complications after surgery that will lead to appropriate acute-hospital care (e.g., complete heart block), and most of these conditions are likely to require ≥24 hours of care. Some patients will seek acute-hospital care that could have been managed without acute-hospital care. Most of these conditions are likely to require <24 hours of acute-hospital care.

3. We have clarified that the follow-up is until 30 days after randomization throughout the document. We have also clarified the following regarding follow-up. The day of randomization is day 0 of follow-up and the day after randomization is day 1of 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 surgery, patients have 31 days of follow-up.

4. Because centres from outside of Ontario have joined the trial and the Institute of Clinical Evaluation Sciences does not collect data on these patients, we have added that we will obtain administrative data from the Canadian Institute of Health Information for patients enrolled outside of Ontario.

5. In the Section on the Need for the PVC-RAM Trial, we have added data on the risk of death after non-cardiac and cardiac surgery.

6. We have added additional centres who will participate in the trial.

7. We have modified the sample size section based on our new primary outcome.

8. We have modified the statistical analyses section based on our new primary outcome.

9. We have expanded the number of events that will undergo outcome adjudication because we believed this will minimize any potential risk of bias.

2. DESCRIPTION OF CHANGES BETWEEN v2.0 and v3.0

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THE FOLLOWING TEXT IS MODIFIED:

1 INTRODUCTION AND RATIONALE

To maximize bed availability for patients with COVID-19, facilitate physical distancing, and to reduce the risk of COVID-19 transmission, physicians are discharging all patients who are eligible and hospitals are cancelling elective surgeries. There remains, however, the need for inpatient semi-urgent (e.g., oncology), urgent (e.g., hip fracture), and emergency (e.g., abdominal aortic aneurysm rupture) surgeries. Patients discharged after undergoing non-elective (i.e., semi-urgent, urgent, or emergency) surgeries are at substantial risk, in the 30 days following surgery, of hospital re-admissions, ~~and~~ presentation to emergency departments or urgent-care centres, and death.[4,5] Ensuring adequate hospital, emergency department, and urgent-care centre capacity for patients with COVID-19, and minimizing the risk of COVID-19 transmission, will require innovative interventions designed to increase~~reduce~~ surgical patients' days alive at home~~subsequent use of acute-hospital care~~.

There is a strong rationale and encouraging evidence suggesting that virtual care with remote automated monitoring in adults discharged after undergoing inpatient surgery will increase days alive at home during the ~~reduce the~~ first 30 ~~-~~days after randomization~~ risk of hospital re-admissions and emergency department or urgent-care centre visits~~.[6] We will undertake the **P**ost discharge after surgery **V**irtual **C**are with **R**emote **A**utomated **M**onitoring technology (PVC-RAM) Trial to inform this issue.

1.1 Primary Research Question

Among adults discharged after non-elective (i.e., semi-urgent, urgent, or emergency) surgery, does virtual care with remote automated monitoring technology increase days alive at home during the first ~~reduce the~~ 30 ~~-~~ days after randomization~~risk of acute-hospital care (i.e., a composite of hospital re-admission and emergency department or urgent-care centre visit)~~, compared to standard care.

1.1.1 Patients being discharged from the hospital after inpatient non-elective surgery are at substantial risk of subsequent acute-hospital care and mortality

The VISION Study, a prospective cohort study of a representative sample of 40,004 adults ≥45 years of age who underwent inpatient non-cardiac surgery at 28 centres, in 14 countries,[7] demonstrated a 7% incidence of patient re-admission to the hospital within 30 days of surgery. VISION also demonstrated that 1.8% of patients died within 30 days of non-cardiac surgery and that 29% of deaths occurred after hospital discharge.[7] Similarly, a large administrative database study (n=143,232) from the United States demonstrated an overall 30-day incidence of unplanned hospital re-admissions after non-cardiac surgery of 7%.[5]

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THE FOLLOWING TEXT IS MODIFIED:

1.1.2 Patients being discharged from the hospital after inpatient non-elective surgery are at substantial risk of subsequent acute-hospital care and mortality

In a prospective cohort study of 5158 consecutive patients who underwent cardiac surgery at 10 centres participating in the Cardiothoracic Surgical Trials Network in Canada and the United States, 13% of patients were re-admitted to the hospital within 30 days of discharge.[12] A study of 324,070 Medicare patients in the United States who underwent coronary artery bypass grafting (CABG) surgery had a 22% incidence of emergency department visits within 30 days of discharge after their index hospitalization.[13]

Based on these data, it is estimated that at least 25% of patients post hospital discharge after cardiac surgery will receive acute-hospital care within a 30-day follow-up period. In the VISION Cardiac Surgery Study, a prospective prospective cohort study of a representative sample of 13,575 adults ≥18 years of age who underwent cardiac surgery at 24 hospitals in 12 countries, 2.2% of patients died within 30-days after surgery and 16% of the deaths occurred after patients were discharged from the hospital (confidential unpublished data).

1.1.3 Virtual care with RAM technology holds promise to increase days alive at home~~prevent acute-hospital care~~

2 In adults discharged after undergoing inpatient surgery, there is a strong rationale supporting the potential for virtual care and RAM technology to increase days alive at home~~reduce the risk of subsequent acute-hospital care~~. After hospital discharge post surgery, patients typically see a physician only after 2-4 weeks. This limited follow-up can result in delays in recognizing and managing complications, which can lead to re-hospitalization and poor outcomes including death. The most common causes for re-hospitalization or emergency department visits after surgery are surgical site infection, ileus, bleeding, pain, cardiovascular complications, and dehydration.[5,8,13] Early identification and management of these complications has the potential to increase days alive at home~~reduce acute-hospital care~~.

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THE FOLLOWING TEXT IS MODIFIED:

1.2.3 Summary

As a result, we will continue to provide surgery to patients for non-elective indications, and post discharge after non-elective surgery, patients are at high risk of needing subsequent acute-hospital care and death. There is a strong rationale and promising data that suggests among adults discharged after undergoing non-elective surgery that virtual care, based on a shared-care approach (e.g., nurse led with escalation to a physician, as needed), with RAM technology can increase days alive at home~~reduce the need for subsequent acute-hospital care~~. We will undertake the PVC-RAM trial to directly inform this issue.

2.1.1 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 the first ~~the~~ 30 ~~-~~days after randomization ~~risk of acute-hospital care~~.

2.1.2 Secondary objectives

To determine, during the first 30 days after randomization, 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. COVID-19 infection; ~~5. number of days alive and at home; 6~~7. medication error detection; 8~~7~~. medication error correction; 9~~8~~. delirium; 10~~9~~. surgeon, family physician, or specialist in-person clinic visit; 11~~0~~. surgeon, family physician, or specialist virtual clinic visit; 12~~1~~. sepsis; 13~~2~~. acute heart failure; and 14~~3~~. death. An additional secondary objective is to determine the effect of virtual care with RAM technology on pain at 7, 15, and 30 days after randomization, measured via the Brief Pain Inventory-Short Form.

2.1.3 Tertiary objectives

To determine, during the first 30 days after randomization, 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;

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THE FOLLOWING TEXT IS MODIFIED:

2.2 Trial Design

The PVC-RAM trial is a multicentre RCT of 900 patients being discharged from the hospital after non-elective surgery. 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*.

2.3 Centres

The Juravinski Hospital and Cancer Centre, the Hamilton General Hospital, and St. Joseph's Healthcare in Hamilton, and the University Hospital and Victoria Hospital in London, London Health Sciences Centre in Londonand, the Kingston General Hospital in Kingston, and the University of Alberta Hospital in Edmonton Ontario will participate in this trial. Other centres may also join the trial.

2.4 Sample Size

Table 1 reports the trial power based on a 2-sided α=0.05 and a sample size of 450 patients in each treatment group. , control group We expect patients in the control group to have on average 29.34 days alive at home. If on average virtual care with RAM results in 29.55, 29.58, or 29.61 days alive at home,event rates of 20% and 25%, and hazard ratios of 0.60, 0.65, 0.70, and 0.75. Wwe will recruit 900 patients; this will haveprovide 9581%, and 8798%, and 92% power if the control group event rate is 20% and 25%, respectively, assuming a hazard ratio of 0.65. We will have 87% power if the patients in the control group have on average 29.49 days alive at homehazard ratio is 0.70, assuming no average virtual care with RAM results in 29.69 days alive at homea control group event rate of 20%.

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THE FOLLOWING TEXT IS MODIFIED:

2.8 Minimizing Bias

Our randomization procedure ensures concealment. 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*. Outcome adjudicators (expert physicians), blind to treatment allocation, will adjudicate the following outcomes: 1. days alive at home; 2. delirium; 32. sepsis; and 34. acute heart failure; 5. myocardial infarction; 6. stroke; 7. non-fatal cardiac arrest; 8. clinically important atrial fibrillation; 9. symptomatic pulmonary embolism; 10. symptomatic proximal deep venous thrombosis; 11. bleeding; and 12. ileus. All statistical analyses involving these outcomes will use these adjudicated decisions. We will undertake analyses according to the intention-to-treat principle. We will utilize the same mechanisms for ensuring patient follow-up used in our large international perioperative trials (e.g., the POISE Trial randomized 8351 patients and achieved 99.8% follow-up).[17]

Page 11/27
THE FOLLOWING TEXT IS MODIFIED:

2.9.1 Virtual care and RAM intervention

Research staff will teach patients randomized to the virtual care with RAM how to use the cellular modem-enabled tablet computer and RAM technology from Cloud DX, Figure 1. This RAM technology will measure the following biophysical parameters: blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, and weight. Patients will take biophysical measurements with the RAM technology and complete a recovery survey, daily for 30 days, and nurses will review these results daily. Patients will interact with a virtual nurse daily on days 1-15 after randomization and every other day from days 16-30. On days without planned virtual visits, nurses will organize unscheduled virtual visits if they detect patients' biophysical measurements or recovery survey responses exceed predetermined thresholds or the nurse identifies another reason for concern.

Page 12/27
THE FOLLOWING TEXT IS MODIFIED:

2.11.1 Primary Outcome

The primary outcome is days alive at home during the first 30 days after randomization~~the 30-day risk of acute-hospital care (i.e., a composite of hospital re-admission and emergency department or urgent-care centre visit)~~.

2.11.2 Secondary Outcomes

Secondary outcomes during the first 30 days after randomization include: 1. hospital re-admission; 2. emergency department visit; 3. urgent-care centre visit; 4. acute-hospital care; 5. brief acute-hospital care; 6. COVID-19 infection; ~~5. number of days alive and at home; 6~~7. medication error detection; ~~7~~8. medication error correction; ~~8~~9. delirium; ~~9~~10. surgeon, family physician, or specialist in-person clinic visit; 11~~0~~. surgeon, family physician, or specialist virtual clinic visit; 12~~1~~. sepsis; 12~~2~~3. acute heart failure; and 14~~3~~. death. An additional secondary outcome is pain, assessed at 7, 15, and 30 days after randomization. Outcome definitions are reported in the Supplemental Appendix.

Page 13/27
THE FOLLOWING TEXT IS MODIFIED:

2.12 Follow-up

The day of randomization is day 0 of follow-up and the day after randomization is day 1of 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 surgery, patients have 31 days of follow-up. Study personnel will contact all study patients 31 days after randomization and collect data on the following outcomes: 1. ~~number of~~ days alive ~~and~~ at home; 2. delirium; 3. sepsis; 4. acute heart failure; 5. death; 6. patient-level cost of recovery; 7. arrythmia resulting in electrical cardioversion; 8. acute renal failure resulting in dialysis; 9. respiratory failure; 10. infection; 11. surgical site infection; 12. life-threatening, major, or critical-organ bleeding; 13. ileus; 14. myocardial infarction; 15. clinically important atrial fibrillation; 16. symptomatic proximal venous thrombo-embolism; 17. stroke; 18. non-fatal cardiac arrest; and 19. clostridium difficile-associated diarrhea. Study personnel will contact patients in the standard-care group and collect data on the following outcomes: 1. BPI-SF on days 7, 15, and 30 after randomization; and 2. medication error detection and medication error corrections on day 31~~0~~ after randomization.

2.13 Statistical Analyses

Following the intention-to-treat principle, we will analyze patients in the treatment groups to which they were randomized. ~~Any patients lost to follow-up will be censored at the time they are lost.~~ The Operations Committee will create a separate statistical analysis plan that the statistical analyses will follow. The statistical analysis plan will be developed and finalized before any investigator is unblinded.

Page 14/27
THE FOLLOWING TEXT IS MODIFIED:

2.13.1 Main analyses

For the primary analysis, we will use Poisson regression ~~Cox proportional hazards model~~ to estimate the 30-day effect of virtual care and RAM technology compared with standard care on the primary outcome of days alive at home~~acute hospital care~~, with stratification by centre and type of surgery. For the primary outcome, we will use the Mann-Whitney-Wilcoxon test to establish the p value.~~We will present the time-to-the first occurrence of one of the components of the primary outcome using the Kaplan-Meier estimator. We will calculate the hazard ratio (HR), corresponding 95% confidence intervals (CI) and associated P values.~~ We will infer statistical significance if the computed 2-sided p-value is less than α=0.05.

For the binary secondary and tertiary outcomes, we will compare the effect of virtual care and RAM technology based on a Chi-squared test, and we will report the corresponding relative risk reductions or increases and 95% CIs. ~~use the same statistical approach as per the primary outcome.~~ For continuous outcomes, we will evaluate treatment effects using analysis of co-variance (ANOVA).

Page 15/27
THE FOLLOWING TEXT IS MODIFIED:

6 IMPORTANCE OF TRIAL

Canadian hospitals need to maximize bed availability for COVID-19 patients and minimize emergency department and urgent-centre visits for non-COVID-19 reasons. Hospitals also have an obligation to treat non-COVID-19 patients with urgent or emergency conditions. As a result, the participating hospitals will continue to provide surgery to patients for non-elective indications. Post discharge after non-elective surgery, these patients are at high risk of needing subsequent acute-hospital care and mortality. There is a strong rationale and promising data that suggests among adults discharged after undergoing inpatient non-elective surgery that virtual care with RAM technology can increase days alive at home~~reduce the need for subsequent acute-hospital care~~. The PVC-RAM trial will answer an important question that will inform how to manage surgical patients after discharge in the setting of a pandemic.

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THE FOLLOWING TEXT IS MODIFIED:

8 APPENDIX 1: Tables and Figures

Table 1. Power ~~for detecting various hazard ratios~~ using 2-sided α=0.05, with 450 subjects per arm~~, and various event rates in the control arm~~

Control group Days alive at home	Virtual Care with RAM Days alive at home	Power
29.34	29.55	81%
29.34	29.58	87%
29.34	29.61	92%
29.49	29.67	81%
29.49	29.69~~7%~~	87%

~~Control group event rate~~	~~Experimental group event rate~~	~~Absolute risk reduction~~	~~Hazard ratio~~	~~Power~~
~~25%~~	~~16%~~	~~9%~~	~~0.60~~	~~99%~~
~~25%~~	~~17%~~	~~8%~~	~~0.65~~	~~98%~~
~~25%~~	~~18%~~	~~7%~~	~~0.70~~	~~92%~~
~~25%~~	~~19%~~	~~6%~~	~~0.75~~	~~79%~~
~~20%~~	~~13%~~	~~7%~~	~~0.60~~	~~99%~~
~~20%~~	~~14%~~	~~6%~~	~~0.65~~	~~95%~~
~~20%~~	~~15%~~	~~5%~~	~~0.70~~	~~87%~~
~~20%~~	~~16%~~	~~4%~~	~~0.75~~	~~71%~~

Page 21/27
THE FOLLOWING TEXT IS ADDED:

9 APPENDIX 2: 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. 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.
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.

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THE FOLLOWING TEXT IS REMOVED:

~~Number of days alive and at home~~	~~The number of days the patient is alive and at their home.~~

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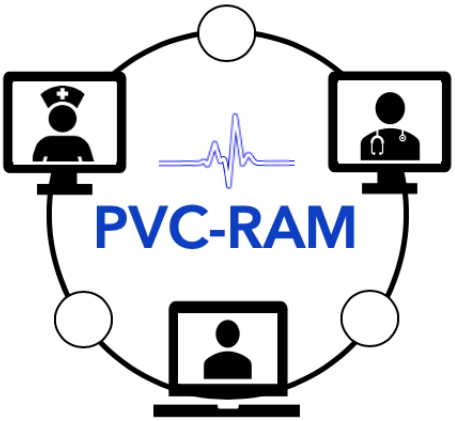
THE FOLLOWING TEXT IS MODIFIED:

Clinically important atrial fibrillation	The definition of clinically important atrial fibrillation requires the documentation of atrial fibrillation or atrial flutter on a 12 lead ~~of any duration on an~~ electrocardiogram, or confirmed atrial fibrillation or atrial flutter (e.g., rhythm strip)~~, which~~ that results in angina, congestive heart failure, symptomatic hypotension, or requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.



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

Protocol Change Summary

Documentation of revisions made to **Protocol v3.0 2020-05-14**
that became **Protocol v4.0 2020-07-22**

Sponsor and Study Coordinating Group:
PVC-RAM Project Office
Population Health Research Institute
Hamilton General Hospital Campus, DBCVSRI
237 Barton Street East
Hamilton, Ontario, Canada L8L 2X2

Principal Investigators:
Dr. Michael McGillion RN, PhD & Dr. PJ Devereaux, MD, PhD, FRCPC
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DBCVSRI, 237 Barton Street East
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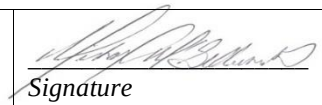
SIGNATURES

Dr. Michael McGillion Principal Investigator Population Health Research Institute	 *Signature*	2020-07-22 *Date (YYYY-MM-DD)*

Dr. P.J. Devereaux Principal Investigator Population Health Research Institute	 *Signature*	2020-07-22 *Date (YYYY-MM-DD)*

1. RATIONALE FOR CHANGES BETWEEN PROTOCOL V3.0 AND V4.0

1. Page 8, 2.1.2 Secondary Objectives Section. We have added all-cause hospital days and pain at 6 months as secondary objectives because these outcomes will help provide insights into the effects of the intervention.

2. Page 8, 2.1.3 Tertiary Objectives Section. We have added indwelling device inappropriately left in a patient within 30 days, the secondary outcomes and health services utilization-related costs within 6 months as tertiary objectives because these outcomes will help provide insights into the effects of the intervention.

3. Page 9, Sample Size Section. We have corrected the data in this section which was based upon 30 days of follow-up, when it should have been based upon 31 days.

4. Page 10, Virtual Care and RAM Intervention Section. We have clarified that patients have access to a healthcare provider 24-hours a day.

5. Page 12, Secondary Outcomes Section. We have added all-cause hospital days and pain at 6 months as secondary outcomes because these outcomes will help provide insights into the effects of the intervention.

6. Page 13, Tertiary Outcomes Section. We have added indwelling device inappropriately left in a patient within 30 days, the secondary outcomes and health services utilization-related costs within 6 months as tertiary outcomes because these outcomes will help provide insights into the effects of the intervention.

7. Page 13, Follow-up Section. We have reordered this section to put the clinical follow-up first and have added all the clinical outcomes for which study personnel will collect data.

8. Page 13, Main Analyses Section. We have clarified that the effect is based on 31-days of follow-up for the main outcome. To keep the analytic approach consistent (i.e., adjusted analyses) we will also evaluate the binary secondary and tertiary outcomes using modified Poisson regression. We have corrected an error for the continuous outcomes that should have stated that we will use ANCOVA and not ANOVA.

9. Page 14, Interim Analyses Section. We have clarified that the analyses will occur when patients have been followed for 30 days "after randomization." Also, we have corrected an error that the second interim analysis will use the rule of 3.5 SDs. The p value was right but the 3SD was an error and should have been 3.5 SDs.

10. Page 18, Appendix 1: Table 1. Power using 2-sided α=0.05, with 450 subjects per arm. We have corrected the data in this table, which was based upon 30 days of follow-up, when it should have been based upon 31 days.

11. Page 21, Appendix 2, Outcome Definitions. We have added text to clarify the calculation of days alive at home, the definition of all-cause hospital days, have added vasopressor therapy to life-threatening bleeding, updated the definition of MI after CABG surgery to make consistent with the 4th universal definition of MI, and added the definition for indwelling device inappropriately left in a patient.

2. DESCRIPTION OF CHANGES BETWEEN v3.0 and v4.0

Page 2/28
THE FOLLOWING TEXT IS MODIFIED:

Secondary Objectives	To determine, during the first 30 days after randomization, 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. COVID-19 infection; 87. medication error detection; 98. medication error correction; 109. delirium; 110. surgeon, family physician, or specialist in-person clinic visit; 121. surgeon, family physician, or specialist virtual clinic visit; 132. sepsis; 143. acute heart failure; and 154. death. An additional secondary objective is to determine the effect of virtual care with RAM technology on pain at 7, 15, and 30 days and 6 months after randomization.

Page 3/28
THE FOLLOWING TEXT IS MODIFIED:

Follow-up	Outcome ascertainment will occur through direct patient follow-up and administrative data obtained from the Institute for Clinical Evaluative Sciences (ICES) and the Canadian Institute of Health Information (CIHI). Study personnel will contact and assess patients for the 30-day primary, secondary, and tertiary outcomes and 6-month outcomes. We will also evaluate ~~6 month~~ outcomes up to 6 months after randomization through ICES and CIHI data.

Page 8/28
THE FOLLOWING TEXT IS MODIFIED:

2.1.2 Secondary objectives

To determine, during the first 30 days after randomization, 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. COVID-19 infection; ~~7~~8. medication error detection; ~~8~~9. medication error correction; 10~~9~~. delirium; 11~~0~~. surgeon, family physician, or specialist in-person clinic visit; 12~~1~~. surgeon, family physician, or specialist virtual clinic visit; 13~~2~~. sepsis; 14~~3~~. acute heart failure; and 15~~4~~. death. An additional secondary objective is to determine the effect of virtual care with RAM technology on pain at 7, 15, and 30 days and 6 months after randomization, measured via the Brief Pain Inventory-Short Form.

2.1.3 Tertiary objectives

To determine, during the first 30 days after randomization, 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. arrythmia 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; ~~and~~ 16. clostridium difficile-associated diarrhea; and 17. indwelling device inappropriately left in a patient.

To determine the 6-month effect of virtual care with RAM technology on the following tertiary outcomes: 1. the secondary outcomes; and 2. health services utilization-related costs~~acute-hospital care; 2. COVID-19 infection; 3. surgeon, family physician, or specialist in-person clinic visit; and 4. surgeon, family physician, or specialist virtual clinic visit~~.

Page 9/28
THE FOLLOWING TEXT IS MODIFIED:

2.3 Centres

The Juravinski Hospital and Cancer Centre, the Hamilton General Hospital, and St. Joseph's Healthcare in Hamilton, the University Hospital and Victoria Hospital in London, and the Kingston General Hospital in Kingston, the Ottawa Hospital in Ottawa, and the University of Alberta Hospital in Edmonton will participate in this trial. Other centres may also join the trial.

2.4 Sample Size

Table 1 reports the trial power based on a 2-sided α=0.05 and a sample size of 450 patients in each treatment group. We expect patients in the control group to have on average 29.6034 days alive at home. If on average virtual care with RAM results in 29.8155, 29.58, or 29.61 days alive at home, we will have 8991%, 87%, and 92% power, respectively. We will have 87% power if the patients in the control group have on average 29.49 days alive at home, assuming no average virtual care with RAM results in 29.69 days alive at home. For other possible estimates of days alive at home in the control group (i.e., 29.40, 29.50, 29.60), for absolute increases of 0.21 to 0.30 days alive at home in the intervention group, we have 89%-99% power.

Page 10/28
THE FOLLOWING TEXT WAS ADDED:

2.9.1 Virtual care and RAM intervention

During virtual visits, the nurse will discuss any symptoms the patient is experiencing, evaluate their wound and obtain a picture, reinforce principles related to recovery after surgery and the need for physical distancing, and undertake medication review and reconciliation. If patient's RAM measurements exceed predetermined thresholds, the patient reports specific symptoms (e.g., shortness of breath), a drug error is identified, or the virtual nurse has concerns about a patient's health that they cannot resolve, the virtual nurse will escalate care to a pre-assigned and available physician (i.e., the patient's surgeon or a medical physician). Physicians will add or modify treatments as indicated and, if required, have them come to an outpatient facility for evaluation or management. Patients will also have access to a virtual nurse at night for any urgent issues, via secure video or text messaging. This mechanism will assure patients have access to a healthcare provider 24-hours a day, 7 days per week.

Page 12/28
THE FOLLOWING TEXT IS MODIFIED:

2.11.2 Secondary Outcomes

Secondary outcomes during the first 30 days after randomization 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. COVID-19 infection; ~~7~~8. medication error detection; ~~8~~9. medication error correction; ~~9~~10. delirium; 1~~0~~1. surgeon, family physician, or specialist in-person clinic visit; 1~~1~~2.

surgeon, family physician, or specialist virtual clinic visit; 132. sepsis; 143. acute heart failure; and 154. death. An additional secondary outcome is pain, assessed at days 7, 15, and 30 and 6 monthsdays after randomization. Outcome definitions are reported in the Supplemental Appendix.

Page 13/28
THE FOLLOWING TEXT IS MODIFIED:

2.11.3 Tertiary Outcomes

Tertiary outcomes during the first 30 days after randomization include: 1. health services utilization-related costs; 2. patient-level cost of recovery; 3. re-operation; 4. arrythmia 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; and 16. clostridium difficile-associated diarrhea; and 17. indwelling device inappropriately left in a patient. Additional tertiary outcome during the first 6 months after randomization include: 1. the secondary outcomes; and 2. health services utilization-related costsacute-hospital care; 2. COVID-19 infection; 3. surgeon, family physician, or specialist in-person clinic visit; and 4. surgeon, family physician, or specialist virtual clinic visit.

2.12 Follow-up

Through the *Institute for Clinical Evaluative Sciences, we will collect data on the following outcomes: 1.* hospital re-admission; 2. emergency department visit; 3. urgent-care centre visit; 4. COVID-19 infection; 5. re-operation; 6. surgeon, family physician, or specialist clinic visit; and 7. health services utilization-related costs. For patients in the virtual care and RAM group, the virtual nurse will collect data on the following outcomes: 1. medication error detection; 2. medication error corrections; and 3. the Brief Pain Inventory-Short Form (BPI-SF).

The day of randomization is day 0 of follow-up and the day after randomization is day 1of 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 randomizationsurgery, patients have 31 days of follow-up. Study personnel will contact all study patients 31 days and 6 months after randomization and collect data on the following outcomes: 1. days alive at home; 2. hospital re-admission; 3. emergency department visit; 4. urgent-care centre visit; 5. all-cause hospital days; 6. delirium; 73. sepsis; 84. acute heart failure; 95. death; 106. patient-level cost of recovery; 117. arrythmia resulting in electrical cardioversion; 128. acute renal failure resulting in dialysis; 139. respiratory failure; 140. infection; 151. surgical site infection; 162. life-threatening, major, or critical-organ bleeding; 173. ileus; 184. myocardial infarction; 195. clinically important atrial fibrillation; 1016. symptomatic proximal venous thrombo-embolism; 2117. stroke; 2118. non-fatal cardiac arrest; and 1923. clostridium difficile-associated diarrhea; and 24. indwelling device inappropriately left in a patient. Study personnel will contact patients in the standard-care group and collect data on the following outcomes: 1. Brief Pain Inventory-Short Form (BPI-SF) on days 7, 15, and 30 and 6 months after randomization; and 2. medication error detection and medication error corrections on day 31 after randomization.

Through the *Institute for Clinical Evaluative Sciences, we will collect data on the following outcomes: 1.* hospital re-admission; 2. emergency department visit; 3. urgent-care centre visit; 4. COVID-19 infection; 5. re-operation; 6. surgeon, family physician, or specialist clinic visit; and 7. health services utilization-related costs. For patients in the virtual care and RAM group, the virtual nurse will collect data on the following outcomes: 1. medication error detection; 2. medication error corrections; and 3. the Brief Pain Inventory-Short Form (BPI-SF until day 30 after randomization). Through the *Institute for Clinical Evaluative Sciences and the Canadian Institute of Health Information, we will collect data on the following outcomes up to 6 months after randomization: 1. acute-hospital care* 2. COVID-19 infection; 3. re-

operation; 4. surgeon, family physician, or specialist clinic visit; and 5. health services utilization-related costs.

2.13.1 Main analyses

For the primary analysis, we will use Poisson regression to estimate the 310-day effect of virtual care and RAM technology compared with standard care on the primary outcome of days alive at home, with stratification by centre and type of surgery. 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.

For the binary secondary and tertiary outcomes, we will compare the effect of virtual care and RAM technology using modified Poisson regression~~based on a Chi-squared test~~,[19] and we will report the corresponding relative risk reductions or increases and 95% CIs. For continuous outcomes, we will evaluate treatment effects using the regression approach to fitting the analysis of co-variance (ANCOVA) models, so we can obtain estimates and their 95% CIs for the independent variables.

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THE FOLLOWING TEXT IS MODIFIED:

2.13.2 Interim Analyses

Two interim analyses based on the primary outcome will occur when 50% and 75% of the patients have been followed for 30 days after randomization. The Data Monitoring Committee (DMC) will employ the modified Haybittle-Peto rule of 4 standard deviations (SDs) (α = 0.0001) for the first planned interim analysis and 3.5 SDs (α = 0.00047) for the second planned interim analysis. For a finding of the treatment to be considered significant, these predefined boundaries will have to be exceeded in at least 2 consecutive analyses, 2 or more months apart. The α-level for the final analysis will remain the conventional α = 0.05 given the infrequent interim analyses, their extremely low α-levels, and the requirement for confirmation with subsequent analyses.

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THE FOLLOWING TEXT IS MODIFIED:

8 APPENDIX 1: Tables and Figures

Table 1. Power using 2-sided α=0.05, with 450 subjects per arm

~~Control group Days alive at home~~	~~Virtual Care with RAM Days alive at home~~	~~Power~~
~~29.34~~	~~29.55~~	~~81%~~
~~29.34~~	~~29.58~~	~~87%~~
~~29.34~~	~~29.61~~	~~92%~~
~~29.49~~	~~29.67~~	~~81%~~
~~29.49~~	~~29.69~~	~~87%~~

Control group Days alive at home	Virtual Care with RAM Days alive at home	Power
29.40	29.61	89%
29.40	29.69	99%
29.50	29.71	89%
29.50	29.80	99%
29.60	29.81	89%
29.60	29.90	99%

Page 21/28
THE FOLLOWING TEXT IS ADDED:

9 APPENDIX 2: 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.

Page 22/28
THE FOLLOWING TEXT IS ADDED:

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.

Page 25/28
THE FOLLOWING TEXT IS ADDED:

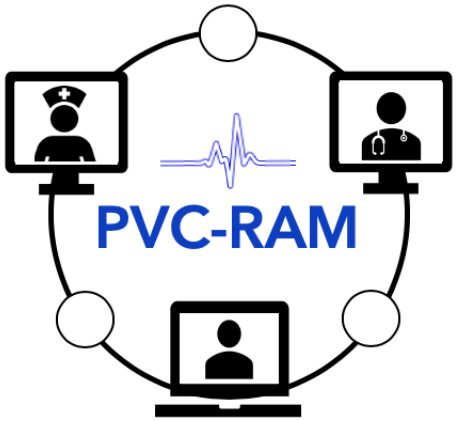
Life-threatening bleeding	Life-threatening bleeding is bleeding that is fatal, or leads to: significant hypotension that requires inotrope or vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.

Page 26/28
THE FOLLOWING TEXT IS MODIFIED:

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, ~~documented new graft or new native coronary artery occlusion~~, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Page 28/28
THE FOLLOWING TEXT IS ADDED:

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.



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

Protocol Change Summary

Documentation of revisions made to **Protocol v4.0 2020-07-22**
that became **Protocol v5.0 2020-09-12**

Sponsor and Study Coordinating Group:
PVC-RAM Project Office
Population Health Research Institute
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237 Barton Street East
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Principal Investigators:
Dr. Michael McGillion RN, PhD & Dr. PJ Devereaux, MD, PhD, FRCPC
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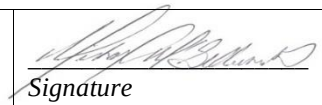
SIGNATURES

Dr. Michael McGillion Principal Investigator Population Health Research Institute	 *Signature*	2020-09-12 *Date (YYYY-MM-DD)*

Dr. P.J. Devereaux Principal Investigator Population Health Research Institute	 *Signature*	2020-09-12 *Date (YYYY-MM-DD)*

1. RATIONALE FOR CHANGES BETWEEN PROTOCOL V3.0 AND V4.0

1. Page 8, 2.1.2 Secondary Objectives Section. We have removed COVID-19 infection; delirium; surgeon, family physician, or specialist in-person clinic visit; surgeon, family physician, or specialist virtual clinic visit; sepsis; and acute heart failure as secondary objectives. We decided to restrict the secondary objectives to components of the primary outcome and outcomes that our intervention had the most potential to affect.

2. Page 8, 2.1.3 Tertiary Objectives Section. We have added COVID-19 infection; delirium; surgeon, family physician, or specialist in-person clinic visit; surgeon, family physician, or specialist virtual clinic visit; sepsis; and acute heart failure as tertiary objectives. These outcomes remain important, but we believe they are better included as tertiary as opposed to secondary outcomes. We also corrected the spelling of arrhythmia in this section. Previously
COVID-19 infection; delirium; surgeon, family physician, or specialist in-person clinic visit; surgeon, family physician, or specialist virtual clinic visit; sepsis; and acute heart failure were evaluated as a tertiary outcome at 6 months as they were secondary outcomes. To allow evaluation of these outcomes that are no longer secondary outcomes at 6 months, we added them to the 6-month tertiary outcomes.

3. Page 13, Secondary Outcomes Section. We have made the changes discussed in point 1 above in this section.

4. Page 13, Tertiary Outcomes Section. We have made the changes discussed in point 2 above in this section.

5. Page 23, Delirium definition. We have updated the primary definition for delirium. Missed in the previous protocol version due to a copy/paste error.

2. DESCRIPTION OF CHANGES BETWEEN v4.0 and v5.0

Page 2/28
THE FOLLOWING TEXT IS MODIFIED:

Secondary Objectives	To determine, during the first 30 days after randomization, 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. ~~COVID-19 infection; 8.~~ medication error detection; 98. medication error correction; ~~10. delirium; 11. surgeon, family physician, or specialist in-person clinic visit; 12. surgeon, family physician, or specialist virtual clinic visit; 13. sepsis; 14. acute heart failure;~~ and ~~15~~9. death. An additional secondary objective is to determine the effect of virtual care with RAM technology on pain at 7, 15, and 30 days and 6 months after randomization.

Page 8/28

THE FOLLOWING TEXT IS MODIFIED:

2.1.2 Secondary objectives

To determine, during the first 30 days after randomization, 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. ~~COVID-19 infection; 8.~~ medication error detection; ~~9~~8. medication error correction; ~~10. delirium; 11. surgeon, family physician, or specialist in-person clinic visit; 12. surgeon, family physician, or specialist virtual clinic visit; 13. sepsis; 14. acute heart failure;~~ and ~~15~~9. death. An additional secondary objective is to determine the effect of virtual care with RAM technology on pain at 7, 15, and 30 days and 6 months after randomization, measured via the Brief Pain Inventory-Short Form.

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THE FOLLOWING TEXT IS MODIFIED:

clostridium difficile-associated diarrhea; ~~and~~ 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; ~~and~~ 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.

Page 13/28

THE FOLLOWING TEXT IS MODIFIED:

2.11.2 Secondary Outcomes

Secondary outcomes during the first 30 days after randomization 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. ~~COVID-19 infection; 8.~~ medication error detection; ~~9~~8. medication error correction; ~~10. delirium; 11. surgeon, family physician, or specialist in-person clinic visit; 12. surgeon, family physician, or specialist virtual clinic visit; 13. sepsis; 14. acute heart failure;~~ and ~~15~~9. death. An additional secondary outcome is pain, assessed at days 7, 15, and 30 and 6 months after randomization. Outcome definitions are reported in the Supplemental Appendix.

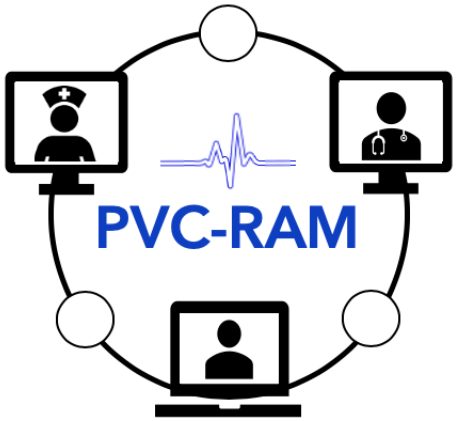
2.11.3 Tertiary Outcomes

Tertiary outcomes during the first 30 days after randomization include: 1. health services utilization-related costs; 2. patient-level cost of recovery; 3. re-operation; 4. arrythmia 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; ~~and~~ 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. Additional tertiary outcome during the first 6 months after randomization include: 1. the secondary outcomes; ~~and~~ 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.

Page 23/28

THE FOLLOWING TEXT IS ADDED:

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.



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

Final Protocol v5.0
Dated Sept 12, 2020

Sponsor and Study Coordinating Group:
PVC-RAM Project Office
Population Health Research Institute
Hamilton General Hospital Campus, DBCVSRI
237 Barton Street East
Hamilton, Ontario, Canada L8L 2X2

Principal Investigators:
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Protocol Number: 2020.09.12
Trial registration: NCT04344665

CLINICAL TRIAL SUMMARY

Title	**P**ost discharge after surgery **V**irtual **C**are with **R**emote **A**utomated **M**onitoring technology (PVC-RAM) Trial
Project Office	PVC-RAM Project Office, Population Health Research Institute Hamilton General Hospital Campus, DBCVSRI 237 Barton Street East, Hamilton, Ontario, Canada L8L 2X2
Study Size	900 patients
Study Design	Multicentre, parallel group, superiority, randomized controlled trial.
Primary Objectives	To determine the effect of virtual care with remote automated monitoring (RAM) technology compared to standard care on days alive at home during the 30-day follow-up after randomization, in adults who have undergone semi-urgent (e.g., oncology), urgent (e.g., hip fracture), or emergency (e.g., ruptured abdominal aortic aneurysm) surgery.
Secondary Objectives	To determine, during the first 30 days after randomization, 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. An additional secondary objective is to determine the effect of virtual care with RAM technology on pain at 7, 15, and 30 days and 6 months after randomization.
Eligibility Criteria	Patients are eligible to participate if they fulfill all of the following criteria: 1. ≥40 years of age; 2. have undergone same-day or inpatient semi-urgent, urgent, or emergency surgery and are being discharged home or are within 24 hours after discharge home, as long as they have not had acute-hospital care since their discharge; and 3. provide informed consent to participate. Patients fulfilling any of the following criteria will be ineligible to participate: 1. underwent same-day surgery and the surgeon or anesthesiologist believe the case reflects a traditional same-day surgery case with a low likelihood of needing acute-hospital care; 2. went to rehabilitation or convalescent care for more than 7 days after undergoing surgery; 3. are unable to communicate with research staff, complete study surveys, or undertake an interview using a tablet computer due to a cognitive, language, visual, or hearing impairment; or 4. reside in an area without cellular network coverage and no home Wi-Fi.
Treatment Regimen	Patients randomized to the PVC-RAM intervention will be taught how to use the cellular modem-enabled tablet computer and RAM technology from Cloud DX. The RAM technology will measure the following biophysical parameters: 1. blood pressure, 2. heart rate, 3. respiratory rate, 4. oxygen saturation, 5. temperature, and 6. weight. Patients will take biophysical measurements with the RAM technology and complete a recovery survey, daily for 30 days after randomization, and nurses will review these results daily. Patients will interact with a virtual nurse daily on days 1-15 and every other day from days 16-30 after randomization. On days without planned virtual visits,

	nurses will organize unscheduled virtual visits if they detect patients' biophysical measurements or recovery survey responses exceed predetermined thresholds or the nurse identifies another reason for concern. During virtual visits, the nurse will discuss any symptoms the patient is experiencing, evaluate their wound and obtain a picture, reinforce principles related to recovery after surgery and the need for physical distancing, and undertake medication review and reconciliation. If the patient's RAM measurements exceed predetermined thresholds, the patient reports specific symptoms (e.g., shortness of breath), a drug error is identified, or the virtual nurse has concerns about the patient's health that they cannot resolve, the virtual nurse will escalate care to a pre-assigned and available physician (i.e., the patient's surgeon or a medical physician). Physicians will add or modify treatments as needed, and if required, they will have the patient come to an outpatient facility for evaluation or management. Via secure video or text messaging, patients will also have access to a virtual nurse at night, for any urgent issues. This mechanism will assure patients have access to a healthcare provider 7 days per week. Patients randomized to standard care will receive post discharge care as per the standard of care at the hospital in which they underwent surgery.
Follow-up	Outcome ascertainment will occur through direct patient follow-up and administrative data obtained from the Institute for Clinical Evaluative Sciences (ICES) and the Canadian Institute of Health Information (CIHI). Study personnel will contact and assess patients for the 30-day primary, secondary, and tertiary outcomes and 6-month outcomes. We will also evaluate outcomes up to 6 months after randomization through ICES and CIHI data.

PVC-RAM Protocol v5.0 Approval:

By signing the below, I designate my approval of the above-named version of the PVC-RAM protocol.

Dr. Michael McGillion Principal Investigator Population Health Research Institute	_____ Signature	___2020-07-22___ Date (yyyy-mm-dd)

Dr. PJ Devereaux Principal Investigator Population Health Research Institute	_____ Signature	__2020-07-22____ Date (yyyy-mm-dd)

Contents

7 INTRODUCTION AND RATIONALE

On March 11, 2020, the World Health Organization declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, causing coronavirus disease 2019 (COVID-19), a global pandemic.[1] COVID-19 cases have overwhelmed northern Italy's healthcare system, resulting in the need to ration mechanical ventilation and a high mortality rate.[2] In an attempt to avoid the fate of Italy, many countries, including Canada, have implemented physical distancing.[1,3]

To maximize bed availability for patients with COVID-19, facilitate physical distancing, and to reduce the risk of COVID-19 transmission, physicians are discharging all patients who are eligible and hospitals are cancelling elective surgeries. There remains, however, the need for inpatient semi-urgent (e.g., oncology), urgent (e.g., hip fracture), and emergency (e.g., abdominal aortic aneurysm rupture) surgeries. Patients discharged after undergoing non-elective (i.e., semi-urgent, urgent, or emergency) surgeries are at substantial risk, in the 30 days following surgery, of hospital re-admissions, presentation to emergency departments or urgent-care centres, and death.[4,5] Ensuring adequate hospital, emergency department, and urgent-care centre capacity for patients with COVID-19, and minimizing the risk of COVID-19 transmission, will require innovative interventions designed to increase surgical patients' days alive at home.

There is a strong rationale and encouraging evidence suggesting that virtual care with remote automated monitoring in adults discharged after undergoing inpatient surgery will increase days alive at home during the first 30 days after randomization.[6] We will undertake the **P**ost discharge after surgery **V**irtual **C**are with **R**emote **A**utomated **M**onitoring technology (PVC-RAM) Trial to inform this issue.

7.1 Primary Research Question

Among adults discharged after non-elective (i.e., semi-urgent, urgent, or emergency) surgery, does virtual care with remote automated monitoring technology increase days alive at home during the first 30 days after randomization, compared to standard care.

7.2 Need for the PVC-RAM Trial

7.2.1 Patients being discharged from the hospital after inpatient non-elective surgery are at substantial risk of subsequent acute-hospital care and mortality

The VISION Study, a prospective cohort study of a representative sample of 40,004 adults ≥45 years of age who underwent inpatient non-cardiac surgery at 28 centres, in 14 countries,[7] demonstrated a 7% incidence of patient re-admission to the hospital within 30 days of surgery. VISION also demonstrated that 1.8% of patients died within 30 days of non-cardiac surgery and that 29% of deaths occurred after hospital discharge.[7] Similarly, a large administrative database study (n=143,232) from the United States demonstrated an overall 30-day incidence of unplanned hospital re-admissions after non-cardiac surgery of 7%.[5] In VISION, a multivariable regression analyses (confidential data) demonstrated that older age, major surgeries (general, neurology, urology/gynecology, thoracic, and vascular), and cancer were associated with an increased risk of hospital re-admission. Moreover, medical complications during the index hospitalization after non-cardiac surgery are strongly associated with an increased risk of subsequent hospital re-admission,[5,8] and non-elective surgeries are strongly associated with an increased risk of perioperative complications.[9-11]

A Canadian Institutes of Health Information study evaluated 2.1 million acute hospitalizations in Canada from April 2010 to April 2011.[4] Patients undergoing inpatient and same-day surgery accounted for 31% of participants. Surgical patients had a 7% unplanned 30-day re-admission rate, and the average cost associated with the re-admission was $9700. Moreover, 19% of the surgical patients presented to an emergency department within 30 days of discharge after their index surgery. Based on these data, it is

estimated that 20-25% of adults being discharged after undergoing non-elective surgery will receive acute-hospital care within a 30-day follow-up period.

In a prospective cohort study of 5158 consecutive patients who underwent cardiac surgery at 10 centres participating in the Cardiothoracic Surgical Trials Network in Canada and the United States, 13% of patients were re-admitted to the hospital within 30 days of discharge.[12] A study of 324,070 Medicare patients in the United States who underwent coronary artery bypass grafting (CABG) surgery had a 22% incidence of emergency department visits within 30 days of discharge after their index hospitalization.[13] Based on these data, it is estimated that at least 25% of patients post hospital discharge after cardiac surgery will receive acute-hospital care within a 30-day follow-up period. In the VISION Cardiac Surgery Study, a prospective prospective cohort study of a representative sample of 13,575 adults ≥18 years of age who underwent cardiac surgery at 24 hospitals in 12 countries, 2.2% of patients died within 30-days after surgery and 16% of the deaths occurred after patients were discharged from the hospital (confidential unpublished data).

7.2.2 Virtual care with RAM technology holds promise to increase days alive at home

Virtual care encompasses all the ways that healthcare providers remotely interact (e.g., phone, computer) with their patients, and can be a sole healthcare provider (e.g., nurse) or a shared-care approach (e.g., nurse led with escalation to a physician, as needed) mode of care delivery. Virtual care can consist of the following: sharing of patient information (e.g., symptoms, medication review), education (e.g., informing patients about signs of illness), and management (e.g., a recommendation to seek medical attention, physician submitting a drug prescription). Remote automated monitoring (RAM) refers to use of technology to remotely obtain data regarding patients' biophysical parameters (e.g., blood pressure, temperature). Research has evaluated the use of various aspects of virtual care with and without RAM of one or multiple biophysical parameters.

In the non-operative setting, trials of cardiology patients have evaluated the effects of virtual care and RAM technology. A trial of 1437 patients with heart failure randomized patients to standard care or virtual care (i.e., 9 coaching calls over a 6-month period) and RAM.[14] For the RAM aspect of the intervention, patients were asked to submit daily their weight, blood pressure, heart rate, and response to 3 symptom questions. If monitoring results exceeded a predetermined threshold, a nurse telephoned to encourage the patient to contact their health professional. This trial demonstrated no difference in hospital re-admissions between the two study groups; however, adherence to the experimental intervention was suboptimal (i.e., only 55% of patients submitted their biophysical data on >50% of the days), and the trial did not utilize a shared-care strategy that ensured patients received physician prescribed treatment.

In contrast to this trial, a Cochrane systematic review of patients with heart failure demonstrated that non-invasive telemonitoring (i.e., remote monitoring of biophysical parameters and other non-invasive data) reduced heart failure related hospitalizations (8 RCTs; 2148 patients; relative risk, 0.71; 95% CI, 0.60-0.83).[15] This systematic review also reported that structured telephone support reduced heart failure related hospitalizations (16 RCTs; 7030 patients; relative risk, 0.85; 95% CI, 0.77-0.98). An RCT of 128 patients with angina demonstrated that virtual care (i.e., frequent video conferencing with a nurse to assess patients' progress and self-care education) with RAM (i.e., daily transmission of blood pressure and weight) reduced the risk of hospitalization (relative risk reduction 51%; p=0.016), compared to standard care.[16] Collectively these trials provide encouraging evidence that virtual care with RAM technology can prevent hospital admissions in patients with cardiovascular diseases.

In adults discharged after undergoing inpatient surgery, there is a strong rationale supporting the potential for virtual care and RAM technology to increase days alive at home. After hospital discharge post surgery, patients typically see a physician only after 2-4 weeks. This limited follow-up can result in delays in recognizing and managing complications, which can lead to re-hospitalization and poor outcomes including death. The most common causes for re-hospitalization or emergency department

visits after surgery are surgical site infection, ileus, bleeding, pain, cardiovascular complications, and dehydration.[5,8,13] Early identification and management of these complications has the potential to increase days alive at home.

A study compared 54 orthopedic surgery patients – who had postoperative home monitoring of blood pressure, heart rate, oxygen saturation, and pain scores 4 times a day for 4 days after discharge with specified alert protocols to a healthcare provider – to 107 orthopedic surgery patients who received standard care after hospital discharge.[6] This observational study reported an 80% relative risk reduction in the composite of hospital re-admission and emergency room visit at 30 days.

7.2.3 Summary

To confront the COVID-19 pandemic, Canadian hospitals need to maximize bed availability for COVID-19 patients and minimize emergency department and urgent-centre visits for non-COVID-19 reasons. Displacing non-urgent care is probably the right decision for society; however, hospitals also have an obligation to treat non-COVID-19 patients with urgent and emergency conditions. As a result, we will continue to provide surgery to patients for non-elective indications, and post discharge after non-elective surgery, patients are at high risk of needing subsequent acute-hospital care and death. There is a strong rationale and promising data that suggests among adults discharged after undergoing non-elective surgery that virtual care, based on a shared-care approach (e.g., nurse led with escalation to a physician, as needed), with RAM technology can increase days alive at home. We will undertake the PVC-RAM trial to directly inform this issue.

8 PLAN OF INVESTIGATION

8.1 Trial Objectives

8.1.1 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 the first 30 days after randomization.

8.1.2 Secondary objectives

To determine, during the first 30 days after randomization, 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. An additional secondary objective is to determine the effect of virtual care with RAM technology on pain at 7, 15, and 30 days and 6 months after randomization, measured via the Brief Pain Inventory-Short Form.

8.1.3 Tertiary objectives

To determine, during the first 30 days after randomization, 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.

8.1.4 Economic Analysis

A separate protocol will be written outlining a full economic analysis.

8.2 Trial Design

The PVC-RAM trial is a multicentre RCT of 900 patients being discharged from the hospital after non-elective surgery. 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.

8.3 Centres

The Juravinski Hospital and Cancer Centre, the Hamilton General Hospital, and St. Joseph's Healthcare in Hamilton, the University Hospital and Victoria Hospital in London, and the Kingston General Hospital in Kingston, the Ottawa Hospital in Ottawa, and the University of Alberta Hospital in Edmonton will participate in this trial. Other centres may also join the trial.

8.4 Sample Size

Table 1 reports the trial power based on a 2-sided α=0.05 and a sample size of 450 patients in each treatment group. We expect patients in the control group to have on average 29.60 days alive at home. If on average virtual care with RAM results in 29.81 days alive at home, we will have 89% power. For other possible estimates of days alive at home in the control group (i.e., 29.40, 29.50, 29.60) for absolute increases of 0.21 to 0.30 days alive at home in the intervention group, we have 89%-99% power.

8.5 Eligibility Criteria

8.5.1 Inclusion Criteria

Patients are eligible if they:

4. are ≥40 years of age;
5. have undergone same-day or inpatient semi-urgent, urgent, or emergency surgery and are being discharged home or are within 24 hours after discharge home, as long as they have not had acute-hospital care since their discharge; and
6. provide informed consent to participate.

8.5.2 Exclusion Criteria

Patients are ineligible if they:

5. underwent same-day surgery and the surgeon or anesthesiologist believe the case reflects a traditional same-day surgery case with a low likelihood of needing acute-hospital care;
6. went to rehabilitation or convalescent care for more than 7 days after undergoing surgery;
7. are unable to communicate with research staff, complete study surveys, or undertake an interview using a tablet computer due to a cognitive, language, visual, or hearing impairment; or

8. reside in an area without cellular network coverage and no home Wi-Fi.

8.6 Patient Recruitment and Informed Consent

Study personnel will utilize efficient recruitment strategies that we developed in prior perioperative trials.[17,18] These include efficient approaches to identify eligible patients through screening: daily surgical list in the operating room, surgical wards, and intensive care units. Centres will also ask clinicians working in anesthesiology, surgery, and medicine to page the study personnel regarding all patients who have undergone non-elective surgery and were admitted through the emergency room or are an inpatient. Research personnel will approach all eligible patients after surgery to obtain written informed consent. Study personnel can obtain consent via the telephone, if the patient has already been discharged home and they are within 24 hours of discharge.

8.7 Randomization

Randomization will occur when a patient is deemed eligible, pending hospital discharge after surgery, and informed consent is obtained. Patients will only be randomized after the most responsible physician has decided to discharge the patient home. Although our goal is to try and randomize patients before hospital discharge, some patients may be discharge before study personnel can consent and randomize the patient. If an eligible patient is discharged before randomization was possible, study personnel can consent and randomize patients until 24 hours after discharge home, as long as they have not had acute-hospital care since their discharge.

Research personnel will randomize patients via an Interactive Web Randomization System. This system is a 24-hour computerized randomization internet system maintained by the coordinating centre at the Population Health Research Institute (PHRI), which is part of Hamilton Health Sciences and McMaster University in Hamilton, Ontario, Canada.

The randomization process will use block randomization stratified by centre and type of surgery (i.e., cardiac versus non-cardiac). We will use randomly varying block sizes, and study personnel and investigators will not know the block sizes. We will randomize patients in a 1:1 fashion to receive virtual care with RAM technology versus standard care.

8.8 Minimizing Bias

Our randomization procedure ensures concealment. 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. Outcome adjudicators (expert physicians), blind to treatment allocation, will adjudicate the following outcomes: 1. days alive at home; 2. delirium; 3. sepsis; 4. acute heart failure; 5. myocardial infarction; 6. stroke; 7. non-fatal cardiac arrest; 8. clinically important atrial fibrillation; 9. symptomatic pulmonary embolism; 10. symptomatic proximal deep venous thrombosis; 11. bleeding; and 12. ileus. All statistical analyses involving these outcomes will use these adjudicated decisions. We will undertake analyses according to the intention-to-treat principle. We will utilize the same mechanisms for ensuring patient follow-up used in our large international perioperative trials (e.g., the POISE Trial randomized 8351 patients and achieved 99.8% follow-up).[17]

8.9 Trial Intervention

Patients will be randomized to 30 days of virtual care with RAM technology or standard care. In the standard-care group, patients will receive their post hospital discharge management as per the standard of care at the hospital in which they underwent surgery. No changes to surgeons' standard of care regarding post discharge management will occur for patients randomized to the standard-care group, as a result of the trial.

8.9.1 Virtual care and RAM intervention

Research staff will teach patients randomized to the virtual care with RAM how to use the cellular modem-enabled tablet computer and RAM technology from Cloud DX, Figure 1. This RAM technology will measure the following biophysical parameters: blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, and weight. Patients will take biophysical measurements with the RAM technology and complete a recovery survey, daily for 30 days, and nurses will review these results daily. Patients will interact with a virtual nurse daily on days 1-15 after randomization and every other day from days 16-30. On days without planned virtual visits, nurses will organize unscheduled virtual visits if they detect patients' biophysical measurements or recovery survey responses exceed predetermined thresholds or the nurse identifies another reason for concern.

During virtual visits, the nurse will discuss any symptoms the patient is experiencing, evaluate their wound and obtain a picture, reinforce principles related to recovery after surgery and the need for physical distancing, and undertake medication review and reconciliation. If patient's RAM measurements exceed predetermined thresholds, the patient reports specific symptoms (e.g., shortness of breath), a drug error is identified, or the virtual nurse has concerns about a patient's health that they cannot resolve, the virtual nurse will escalate care to a pre-assigned and available physician (i.e., the patient's surgeon or a medical physician). Physicians will add or modify treatments as indicated and, if required, have them come to an outpatient facility for evaluation or management. Patients will also have access to a virtual nurse at night for any urgent issues, via secure video or text messaging. This mechanism will assure patients have access to a healthcare provider 24-hours a day, 7 days per week.

8.9.2 Cloud DX's technology

The primary interface for the virtual care intervention is the Cloud DX Connected Health mobile application, which is embedded in a Samsung Android tablet computer equipped with a camera to facilitate patient and healthcare provider video-based communication. To ensure cybersecurity and patient privacy, the Samsung tablet supports cellular and Wi-Fi communications through Health Insurance Probability and Accountability Act (HIPAA)-compliant cloud infrastructure. Bell will provide the cellular data plans. The Connected Health mobile application was designed by Cloud DX for use by patients of varying ages, including seniors. The application features simple menus for scheduling tasks (e.g. video visits with a virtual nurse), measuring biophysical parameters, completing the recovery survey, and educational material.

The Cloud DX RAM technology consists of a group of easy-to-use, Bluetooth-enabled, Health Canada-licensed, biophysical parameters monitoring devices, which will be paired with the pre-programmed Samsung tablet computer. This RAM technology contains the Cloud DX Pulsewave PAD-1A wrist-based blood pressure monitor, which derives measurements for blood pressure, pulse rate, and respiration rate. Patients will also receive a Cloud DX wireless pulse oximeter and wireless weight scale for measuring blood oxygen saturation and body weight. A wireless digital thermometer will also capture core body temperature. These biophysical parameters will upload automatically to the Samsung tablet, except for temperature, which must be entered manually. These Cloud DX monitors are certified according to International Standards Organization (ISO) Quality Management Standards, and have achieved perfect high patient usability and recommendation scores.

8.9.3 Patients obtaining Cloud DX technology, monitoring schedule, and training

Around the time of randomization, patients will receive the Samsung tablet computer and the RAM technology, instructions on how to use these devices, and their 30-day monitoring schedule. This schedule outlines the frequency and timing of daily monitoring of biophysical parameters, recovery survey, and virtual nurse video visits. The Connected Health mobile application will be prepopulated with this 30-day program and will guide patients through the daily requirements with interactive prompts. Study personnel will provide patients with a 30-minute checklist-oriented rehearsal of all Connected

Health mobile application features and usage of the RAM technology. Study personnel will also invite and answer any questions.

8.9.4 Obtaining measurements of patients' biophysical parameters and recovery survey

Based on a schedule developed by a virtual nurse, the tablet will prompt patients to measure their biophysical parameters. The frequency of daily biophysical measurements will be 3 times a day for the first 15 days, and then twice a day from day 16 until 30 days after randomization. Weight will be measured daily in the morning before breakfast. Measurement of biophysical parameters can be adjusted according to a patient's acuity and tolerance, based on the virtual nurse's judgement or directions from a physician. Patients will record at least one full set of biophysical parameters each day of the study. The tablet will prompt patients daily to complete the recovery survey. The recovery survey consists of questions related to infection, bleeding, pain, dehydration, ileus, and cardiovascular and respiratory complications.

8.9.5 Virtual nurse triage priority of patients, daily patient virtual visits, and escalation of care

RAM measurements (apart from temperature, which is entered manually) are uploaded automatically to the Android tablet and can be viewed by the virtual nurse within 1 to 3 minutes. When a RAM measurement or survey result crosses any one of a set of pre-determined thresholds, the Connected Health mobile application will send real-time notifications to the virtual nurse. The virtual nurse then texts patients using the secure messaging feature on the Samsung tablet, to arrange a virtual visit; timing of visit will depend on the severity of the abnormality. The clinical dashboard on the Connected Health mobile application will facilitate remote patient management, which will automatically list patients according to a triage priority order based on the severity of changes in RAM biophysical measurements or recovery survey responses.

Through the Connected Health mobile application, the virtual nurse will: 1. view and interpret patients' biophysical parameters and recovery survey responses; 2. conduct video visits with the patients, discuss any symptoms patients are experiencing, evaluate surgical wounds and obtain pictures, and reinforce principles related to recovery after surgery and the need for physical distancing; 3. undertake medication review and reconciliation on days 1, 8, 15, 22, and 30 after randomization; 4. intervene as needed; 5. escalate care to a pre-assigned and available physician (i.e., the patient's surgeon or a medical physician) when a predetermined threshold is surpassed or the virtual nurse has concerns about the patient's health that they cannot resolve; and 6. document their observations and interventions. Physicians will add or modify treatments as they deem appropriate and, if required, they have the patient come to an outpatient facility for evaluation or management.

8.10 Risk to the Safety of Participants

Patients randomized to the virtual care and RAM technology intervention will be at very low risk of serious harm related to the intervention. No studies of such interventions have reported a serious adverse event related to the intervention. We are using Health-Canada approved RAM technology.

8.11 Trial Outcomes

8.11.1 Primary Outcome

The primary outcome is days alive at home during the first 30 days after randomization.

8.11.2 Secondary Outcomes

Secondary outcomes during the first 30 days after randomization 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 and 6 months after randomization. Outcome definitions are reported in the Supplemental Appendix.

8.11.3 Tertiary Outcomes

Tertiary outcomes during the first 30 days after randomization include: 1. health services utilization-related costs; 2. patient-level cost of recovery; 3. re-operation; 4. arrythmia 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. Additional tertiary outcome during the first 6 months after randomization include: 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.

8.12 Follow-up

The day of randomization is day 0 of follow-up and the day after randomization is day 1of 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. Study personnel will contact all study patients 31 days and 6 months after randomization and collect data on the following outcomes: 1. days alive at home; 2. hospital re-admission; 3. emergency department visit; 4. urgent-care centre visit; 5. all-cause hospital days; 6. delirium; 7. sepsis; 8. acute heart failure; 9. death; 10. patient-level cost of recovery; 11. arrythmia resulting in electrical cardioversion; 12. acute renal failure resulting in dialysis; 13. respiratory failure; 14. infection; 15. surgical site infection; 16. life-threatening, major, or critical-organ bleeding; 17. ileus; 18. myocardial infarction; 19. clinically important atrial fibrillation; 10. symptomatic proximal venous thrombo-embolism; 21. stroke; 21. non-fatal cardiac arrest; 23. clostridium difficile-associated diarrhea; and 24. indwelling device inappropriately left in a patient. Study personnel will contact patients in the standard-care group and collect data on the following outcomes: 1. Brief Pain Inventory-Short Form (BPI-SF) on days 7, 15, and 30 and 6 months after randomization; and 2. medication error detection and medication error corrections on day 31 after randomization.

For patients in the virtual care and RAM group, the virtual nurse will collect data on the following outcomes: 1. medication error detection; 2. medication error corrections; and 3. the BPI-SF until day 30 after randomization. Through the Institute for Clinical Evaluative Sciences and the Canadian Institute of Health Information, we will collect data on the following outcomes up to 6 months after randomization: 1. acute-hospital care 2. COVID-19 infection; 3. re-operation; 4. surgeon, family physician, or specialist clinic visit; and 5. health services utilization-related costs.

8.13 Statistical Analyses

Following the intention-to-treat principle, we will analyze patients in the treatment groups to which they were randomized. The Operations Committee will create a separate statistical analysis plan that the statistical analyses will follow. The statistical analysis plan will be developed and finalized before any investigator is unblinded.

8.13.1 Main analyses

For the primary analysis, we will use Poisson regression 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, with stratification by centre and type of surgery. 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.

For the binary secondary and tertiary outcomes, we will compare the effect of virtual care and RAM technology using modified Poisson regression,[19] and we will report the corresponding relative risk reductions or increases and 95% CIs. For continuous outcomes, we will evaluate treatment effects using the regression approach to fitting the analysis of co-variance (ANCOVA) models, so we can obtain estimates and their 95% CIs for the independent variables.

8.13.2 Interim Analyses

Two interim analyses based on the primary outcome will occur when 50% and 75% of the patients have been followed for 30 days after randomization. The Data Monitoring Committee (DMC) will employ the modified Haybittle-Peto rule of 4 standard deviations (SDs) ($\alpha = 0.0001$) for the first planned interim analysis and 3.5 SDs ($\alpha = 0.00047$) for the second planned interim analysis. For a finding of the treatment to be considered significant, these predefined boundaries will have to be exceeded in at least 2 consecutive analyses, 2 or more months apart. The α-level for the final analysis will remain the conventional $\alpha = 0.05$ given the infrequent interim analyses, their extremely low α-levels, and the requirement for confirmation with subsequent analyses.

At any time during the trial, if safety concerns arise the DMC chairperson will assemble a formal meeting of the full committee. The DMC will make their recommendations to the Project Office Operations Committee after considering all the available data and any external data from relevant studies. If a recommendation for termination is being considered, the DMC will invite the Project Office Operations Committee to explore all possibilities before a decision is made. A detailed charter will be developed and govern the activities of the DMC. The DMC will have members with expertise in clinical trials, perioperative medicine, and biostatistics.

9 TRIAL MANAGEMENT

9.1 Arrangements for the Day-to-Day Management of the Trial

Figure 2 illustrates the organizational structure of the PVC-RAM Trial. The PHRI Project Office is the coordinating centre for this trial and is responsible for the development of the protocol, development of the randomization scheme, trial database, data consistency checks, data analyses, coordination of the trial centres, and conducting the trial. The Co-Principal Investigators, Project Officer, Program Manager, and Research Coordinator are responsible for the activities of the Project Office. No statistician with knowledge of the randomization code will participate in the management or coordination of the PVC-RAM.

9.2 Site Principal Investigators

All participating centres will have a site Principal Investigator (PI), and this individual is responsible for ensuring compliance with respect to the intervention, visit schedule, and procedures required by the protocol. The site PI will ensure the provision of all information requested in the Case Report Forms (CRFs) in an accurate and timely manner according to instructions provided. The site PI will maintain patient confidentiality with respect of all information accumulated in the course of the trial, other than that information to be disclosed by law.

10 ENSURING DATA QUALITY

The Data Management Plan will outline the procedures to ensure data quality and will include the following: 1. all research personnel will undergo a training session before trial commencement to ensure

consistency in trial procedures including data collection and reporting; 2. all centres will have a detailed trial Manual of Operations that will outline each step of the protocol; 3. the Project Office personnel will review detailed monthly reports on screening, enrollment, patient follow-up, data transmission, thoroughness, and completeness of data collection, and event rates, and they will rapidly address any identified issues; 4. the programmer will create internal validity and range checks using iDataFax which will identify any errors or omissions and notify the sender and Project Office of any such issues; 5. the Project Office will undertake multi-level data validation of the trial Case Report Forms; and 6. the Project Office will send investigators regular quality control reports.

11 ETHICAL CONSIDERATIONS

This trial will be conducted in compliance with the protocol, principles laid down in the Declaration of Helsinki, Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH), and all applicable laws and regulations of Canada. Before study initiation, the site PI must have written and dated approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the protocol and consent form. Amendments to the protocol will require IRB/IEC approval.

All patient information will be stored in a high security computer system and kept strictly confidential. Subject confidentiality will be further ensured by utilizing subjects' identification code numbers to correspond to treatment data in the computerized files. Patients' medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited. Medical information may be given to patients' personal physicians or to other appropriate medical personnel responsible for the patients' welfare. Data generated as a result of the trial are to be available for inspection on request by the participating physicians, IRB/IEC, study monitors, and competent authorities.

12 IMPORTANCE OF TRIAL

Canadian hospitals need to maximize bed availability for COVID-19 patients and minimize emergency department and urgent-centre visits for non-COVID-19 reasons. Hospitals also have an obligation to treat non-COVID-19 patients with urgent or emergency conditions. As a result, the participating hospitals will continue to provide surgery to patients for non-elective indications. Post discharge after non-elective surgery, these patients are at high risk of needing subsequent acute-hospital care and mortality. There is a strong rationale and promising data that suggests among adults discharged after undergoing inpatient non-elective surgery that virtual care with RAM technology can increase days alive at home. The PVC-RAM trial will answer an important question that will inform how to manage surgical patients after discharge in the setting of a pandemic.

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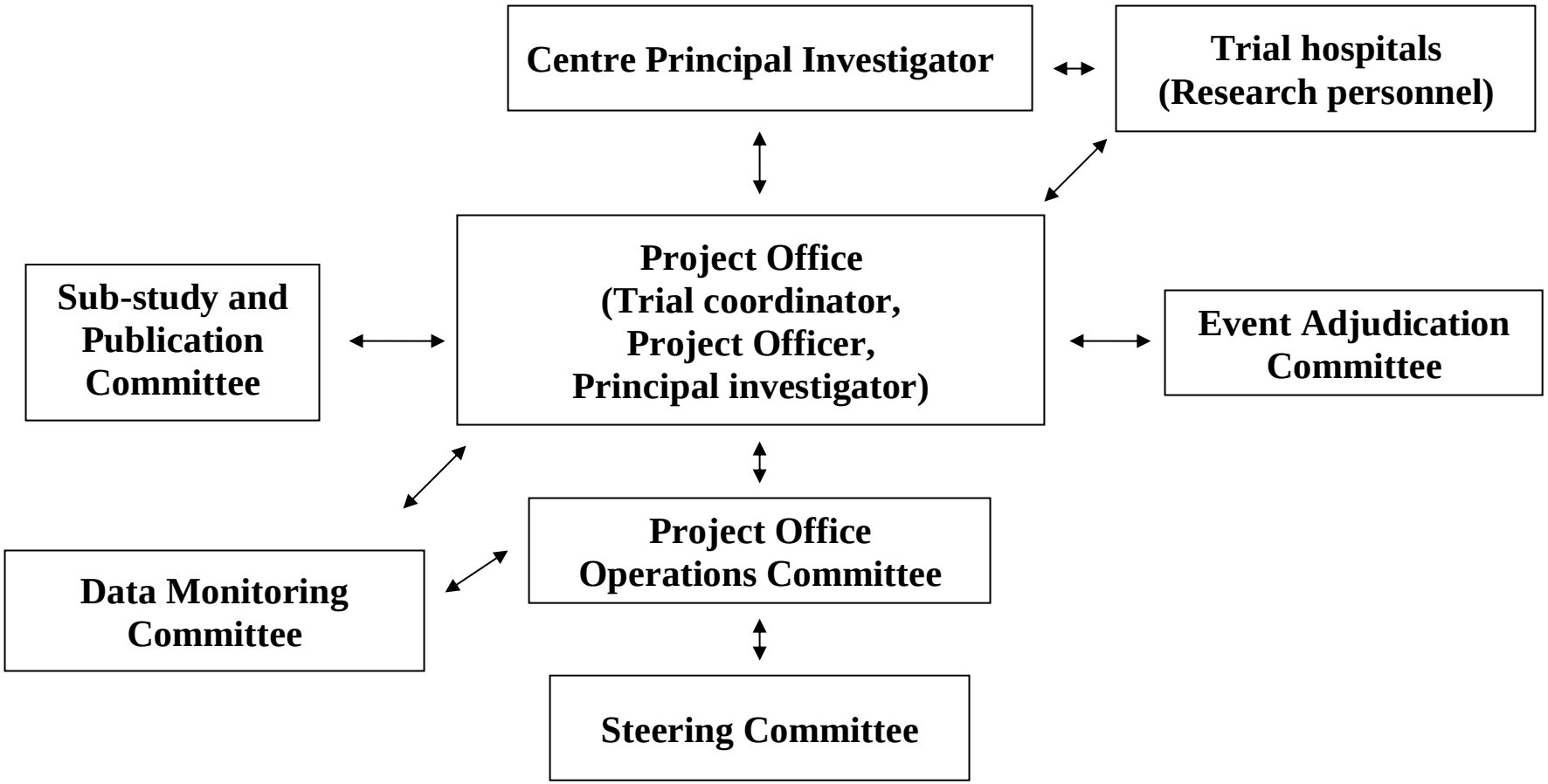
14 APPENDIX 1: Tables and Figures

Table 1. Power using 2-sided α=0.05, with 450 subjects per arm

Control group Days alive at home	Virtual Care with RAM Days alive at home	Power
29.40	29.61	89%
29.40	29.69	99%
29.50	29.71	89%
29.50	29.80	99%
29.60	29.81	89%
29.60	29.90	99%

Figure 1. Cloud DX Connected Health kit

FIGURE 2. PVC-RAM organizational structure



15 APPENDIX 2: 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).[20] 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).[21] 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.[22,23] 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)
Arrythmia resulting in electrical cardioversion	Any arrythmia 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 $\leq$ 70 g/L; 2. a transfusion of $\geq$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 >24h (abdominal distention; diffuse abdominal pain; or nausea or vomiting.
Myocardial infarction	The diagnosis of myocardial infarction requires one of the following criteria: 7. 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: G. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); H. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds; I. 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; J. new LBBB; or K. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging L. identification of intracoronary thrombus on angiography or autopsy 8. 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. 9. 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. 10. 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. 11. 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. 12. 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: G. ischemic signs or symptoms (i.e., chest, arm, neck, or jaw discomfort; shortness of breath, pulmonary edema); H. development of pathologic Q waves present in any two contiguous leads that are $\geq$ 30 milliseconds; I. 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; J. new LBBB; or K. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging L. 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: 5. A high probability ventilation/perfusion lung scan; 6. An intraluminal filling defect of segmental or larger artery on a helical CT scan; 7. An intraluminal filling defect on pulmonary angiography; or 8. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following: B. 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: 3. symptoms or signs that suggest DVT (e.g., leg pain or swelling), 4. 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: D. a persistent intraluminal filling defect on contrast venography (including on computed tomography); E. noncompressibility of one or more venous segments on B mode compression ultrasonography; or F. 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	Nonfatal 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.