Effect of Post discharge after surgery Virtual Care with Remote Automated Monitoring technology versus standard care: The PVC-RAM-1 randomised controlled trial

Journal:	*BMJ*
Manuscript ID	BMJ-2021-064099.R1
Article Type:	Research
Date Submitted by the Author:	16-Jul-2021
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Keywords:	Perioperative Medicine, Remote Automated Monitoring, Virtual care, Non-elective surgery, Acute Hospital Care, Randomized Controlled Trial

Fiona Godlee, MD
Editor in Chief, BMJ

Dear Dr. Godlee:

We are submitting the Effect of Post discharge after surgery Virtual Care with Remote Automated Monitoring technology versus standard care: The PVC-RAM randomised controlled trial, for consideration of publication in the BMJ.

Virtual delivery of care and remote automated monitoring (RAM) has garnered the attention of healthcare providers and funders during the COVID-19 pandemic. There has been substantial investment and great promise. We designed PVC-RAM to evaluate the impact of virtual care with RAM in patients being discharge from the hospital after non-elective surgery, during the COVID-19 pandemic.

Virtual care and RAM are at real risk of failing to improve outcomes without adequate attention to how we organize and deliver it, and rigorous trials like PVC-RAM are essential to learning how to use virtual care and RAM to their potential. We demonstrate that these interventions can be of meaningful benefit to patients when these technologies are used by teams of healthcare providers in processes that are intentional in detecting and responding to patient problems, and are followed with high fidelity.

During the COVID-19 pandemic, when patients presumably would wish to avoid post-discharge acute-hospital care, in the standard-care group that more than 1 in 4 patients sought acute-hospital care. We also demonstrated that 30% of patients had drug errors and each patient with a drug error had a mean of 2 drug errors. These are just two of the points highlight the magnitude of the problem in transitional care to home after non-elective surgery.

Although our trial occurred during the COVID-19 pandemic, the insights from our trial are likely also relevant in non-pandemic settings. We believe our trial results will be of interest to your readers.

As per the instructions to authors, we recommend consideration of the following individuals as potential reviewers of our paper.

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Thank you for considering our submission.

Sincerely,

P.J. Devereaux, MD, PhD Michael McGillion, RN, PhD

Effect of Post discharge after surgery Virtual Care with Remote Automated Monitoring-1 technology versus standard care: The PVC-RAM-1 randomised controlled trial

PVC-RAM-1 Investigators

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ABSTRACT

Objective: To determine among adults discharged after non-elective surgery if virtual care with remote automated monitoring (RAM) technology versus standard care increases days alive at home, during the COVID-19 pandemic.

Design: PVC-RAM-1 was a multicentre randomised controlled trial. Patients, healthcare providers, and data collectors were aware of patients' group allocations. Outcome adjudicators were blinded to group allocation.

Setting: 8 Canadian centres.

Participants: 905 adults being discharged from hospital after non-elective surgery were randomised, and 903 (99.8%) completed the 30-day follow-up. Patients who resided in areas without cellular coverage were excluded.

Intervention: Patients in the experimental group received a tablet computer and RAM technology, which measured blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, and weight. For 30 days, patients took daily biophysical measurements and wound photographs and interacted with nurses virtually. In the standard-care group, patients received post-hospital discharge management according to their centre's usual care.

Main Outcomes and Measures: The primary outcome was days alive at home. The 12 secondary outcomes included: acute-hospital care, detection and correction of medication errors, and pain at 7, 15, and 30 days after randomisation.

Results: All 905 randomised patients (mean age 63.1 years) were analysed in the groups to which they were randomised. Days alive at home were 29.7 days in the virtual-care and 29.5 days in the standard-care groups; relative risk, 1.01 (95% CI, 0.99-1.02). Acute-hospital care occurred in 99 patients (22.0%) and 124 patients (27.3%) in the virtual-care and standard-care

groups, respectively (relative risk, 0.80; 95% CI, 0.64-1.01). More patients in the virtual-care group compared to the standard-care group had a medication error detected (134 patients [29.7%] versus 25 patients [5.5%]; absolute difference, 24.2%; 95% CI, 19.5-28.9) and a medication error corrected (absolute difference 24.4%; 95% CI, 19.9-28.9). Fewer patients in the virtual care group compared to the standard-care group reported pain at 7, 15, and 30 days after randomisation (absolute differences of 13.9% [95% CI, 7.4-20.4]; 11.9%, [5.1-18.7]; and 9.6% [2.9-16.3], respectively). Beneficial effects proved substantially larger in centres with a higher rate of care escalation.

Conclusion and Relevance: Virtual care with RAM shows promise in improving both outcomes important to patients and to optimal health system function.

Trial Registration: NCT04344665.

INTRODUCTION

At the start of the Coronavirus Disease 2019 (COVID-19) pandemic, many hospitals canceled elective surgery; however, the need for semi-urgent (e.g., oncology), urgent (e.g., hip fracture), and emergent (e.g., abdominal aortic aneurysm rupture) surgeries remained. Patients discharged after these non-elective surgeries frequently utilise acute-hospital care (i.e., hospital re-admission, emergency department visit, or urgent-care centre visit) in the 30 days following discharge.[1,2] As hospitals struggle with COVID-19 and in many cases resume elective surgeries, there is the need to reduce surgical patients' post-discharge use of acute-hospital care to ensure hospital capacity and facilitate management of the backlog of individuals waiting for elective surgeries.

Virtual care encompasses all the ways that healthcare providers remotely interact (e.g., telephone, computer) with their patients. Remote automated monitoring (RAM) refers to use of technology to remotely obtain data regarding patients' biophysical parameters (e.g., blood pressure). A strong rationale and preliminary evidence suggest that virtual care and RAM will decrease acute-hospital care, in adults discharged after surgery.[3]

Virtual delivery of care and RAM has garnered the attention of healthcare providers and funders during the COVID-19 pandemic.[4] There has been substantial investment and great promise; however, there is the need for robust data.[5] We undertook the Post discharge after surgery Virtual Care with Remote Automated Monitoring-1 technology (PVC-RAM-1) Trial to address the following question: among adults discharged after non-elective surgery, does virtual care with RAM increase days alive at home during the first 30 days after randomisation, compared to standard care?

METHODS

Design, Ethics, Structure

We undertook this investigator-initiated, randomised, controlled trial at 8 centres in Canada. Online-only Supplement 1 presents the trial protocol and online-only Supplement 2 the statistical analysis plan. We have reported details of the trial design and methods,[6] and PVC-RAM-1 was registered at ClinicalTrials.gov, NCT04344665. Before commencing recruitment, centres obtained ethics approval. Study personnel recruited patients from April 23, 2020 until July 25, 2020. Online-only Supplement 3 presents the trial investigators, coordinating centre, and committees.

The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of PVC-RAM-1. The funders of the trial had no role in data collection, data analyses, data interpretation, or writing of the manuscript. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication.

Patient Population

Eligible patients were ≥40 years of age, had undergone inpatient non-elective surgery and the most responsible physician had decided to discharge the patient home or patients were within 24 hours after discharge home without having obtained acute-hospital care since discharge, and provided informed consent to participate. Patients who underwent same-day, non-elective surgery were eligible if the attending surgeon or anesthesiologist believed the patient would normally have received inpatient surgery but received same-day surgery because of the COVID-19 pandemic.

We excluded patients who: 1. were discharged to rehabilitation or convalescent care for >7 days; 2. were 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 3. resided in an area without cellular coverage.

Randomisation and Blinding

Randomisation occurred after the most responsible physician decided to discharge the patient home. Research personnel randomised patients in a 1:1 fashion to receive virtual care with RAM or standard care, via a 24-hour Interactive Web Randomisation System, using block randomisation stratified by centre and type of surgery (i.e., cardiac versus non-cardiac). We used randomly varying block sizes; study personnel and investigators were unaware of the block sizes. Due to the nature of the intervention and follow-up procedures, patients, healthcare providers, and data collectors were aware of patients' group allocations. Outcome adjudicators were blind to group allocation.

Interventions

Research personnel taught patients allocated to virtual care and RAM how to use the cellular tablet and RAM technology from Cloud DX, Figure 1, Supplement 3. The RAM technology measured the following biophysical parameters: blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, and weight. Daily for 30 days, patients took biophysical measurements and completed a recovery survey; nurses reviewed these results, Appendix 1, Supplement 3.

Patients interacted daily with a nurse virtually via the tablet on days 1-15 and every other day from days 16-30 after randomisation. On days without planned virtual visits, if patients' biophysical measurements or recovery survey responses exceeded predetermined thresholds or nurses identified another reason for concern, nurses organised unscheduled virtual visits.

During virtual visits, nurses discussed patients' symptoms, evaluated participants' wounds and obtained pictures, reinforced principles of recovery after surgery and the need for physical distancing, and undertook medication review and reconciliation on days 1, 8, 15, 22, and 30 after randomisation. Nurses escalated care to pre-assigned physicians (i.e., perioperative physicians or surgeons) if patients' RAM measurements exceeded predetermined thresholds (Appendix 2, Supplement 3), patients reported specific concerning symptoms (e.g., syncope), they identified drug errors, or they had concerns about patients' health that required a physician's attention. Physicians could interact with patients virtually via the tablet, and they added or modified treatments as appropriate. In the virtual-care group, patients had access to a nurse or physician 24 hours a day, 7 days per week. Appendix 3, Supplement 3 reports further details regarding how nurses and physicians delivered virtual care and how devices were returned.

In the standard-care group, patients received post-hospital management per the usual care at the hospital in which they underwent surgery. PVC-RAM-1 did not change the surgeons' usual care regarding post-discharge management for patients in the standard-care group. Canada has a universal public payment system that covers the cost of hospital and physician services, which alleviates cost as a barrier to these services post-discharge after surgery. In Canada, standard care for most patients after non-elective surgery would include seeing a healthcare provider within 30 days of hospital discharge. Prior to this visit, the onus is on the patient to

connect with their surgeon should questions arise related to the appropriate use of medications or symptoms or signs of potential complications.

Outcomes and Follow-up

Very shortly after trial commencement, we recognised the potential for a competing-outcomes issue between death and acute-hospital care, Appendix 4, Supplement 3. We therefore changed the primary outcome from acute-hospital care to days alive at home during the first 30 days after randomisation. Secondary and tertiary outcomes and all outcome definitions are reported in Appendix 5 and 6, Supplement 3, respectively. We hypothesized that we would detect more medication errors and corrections in the virtual-care group compared to the standard-care group, and a priori stated we would interpret this as an improvement in care.

The day of randomisation was day 0 of follow-up, and the day after randomisation was day 1 of follow-up after randomisation, etc. Because patients were followed from the day of randomisation until day 30 after randomisation, patients had 31 days of follow-up. Appendix 7, Supplement 3 presents the follow-up process.

Patient and public involvement

A panel of four patient partners reviewed the daily symptom survey for clarity and perceived ease of use. Given rules on social distancing and limitations to in-person meetings, all feedback was provided via email. Patients were not involved in the trial design or analyses and did not contribute to the paper.

Sample Size

PVC-RAM-1 was designed to randomise 900 patients, Appendix 8, Supplement 3. This sample size provided ≥89% power if the virtual-care with RAM group had ≥29.81 days alive at home, assuming patients in the control group would have on average 29.60 days alive at home, out of 31 potential days (2-sided α=0.05).

Statistical Analyses

The Data Monitoring Committee (DMC) reviewed the data at two time points, and recommended continuation of the trial. This included a safety review when the first 100 patients completed 31-days of follow-up, and the first interim efficacy review when 50% of patients completed 31 days of follow-up. The DMC used the modified Haybittle-Peto rule of 4 standard deviations (SDs) (α = 0.00006) for the first efficacy interim analysis. The second interim analysis was scheduled to occur when 75% of the patients had completed 31 days of follow-up but did not occur because the last 25% of participants were recruited before the first 75% of participants completed 31 days of follow-up.

The Operations Committee wrote and finalised the statistical analysis plan before analyses were undertaken or any investigator was unblinded to the trial results. Patients were analysed in the groups to which they were randomised, regardless of compliance. Patients lost to follow-up without having had the outcome of interest were censored on the last day their outcome status was known.

We used modified Poisson regression with robust variance estimator accounting for clustering by study centre, to estimate the 31-day effect of virtual care and RAM compared with standard care on the primary outcome of days alive at home.[7] In this model, we adjusted for the type of surgery (i.e., cardiac versus non-cardiac) and pre-randomisation variables known to be

associated with acute-hospital care after discharge post-surgery, Appendix 9, Supplement 3. Treatment effects were also assessed in pre-specified subgroups using tests for interactions in the modified Poisson regression models; interaction p values inform whether subgroup effects are likely due to chance.

As per the primary outcome, for the secondary and tertiary outcomes we compared the effect of virtual care and RAM using modified Poisson regression. We designated a computed 2-sided p-value <0.05 as statistically significant. All analyses were performed in SAS®, version 9.4.

RESULTS

PVC-RAM-1 randomised 905 patients, 451 to virtual care and RAM and 454 to standard care. Follow-up was complete for 903 patients (99.8%), Figure 1. The baseline characteristics and details of surgery were similar between groups, Table 1. Participants' mean age was 63.1 years, 54.7% were men, 55.8% had hypertension, and 34.1% had active cancer. Participants underwent non-cardiac surgery (80.9%) and cardiac surgery (19.7%); a few patients underwent both types. Participants underwent semi-urgent (56.8%), urgent (35.4%), and emergent (7.8%) surgeries. Table 1, Supplement 3 reports the subtypes of surgery patients underwent, which proved similar between groups.

Table 2, Supplement 3 presents, among patients in the virtual-care group, compliance with virtual visits, wound photos, and use of RAM. Forty-one patients (9.2%) permanently discontinued using the tablet and RAM technology before completing 30 days of the intervention. Usual post-discharge follow-up was consistent for both trial groups: an in-person

or virtual follow-up visit with a non-study surgeon, family physician, or specialist occurred in 76.9% of patients in the standard-care group and 77.2% of patients in the virtual-care group.

Table 2 reports the primary and secondary outcomes. The primary outcome (days alive at home) was 29.7 days in the virtual-care and 29.5 days in the standard-care groups; relative risk, 1.01 (95% CI, 0.99-1.02). Acute-hospital care occurred in 99 patients (22.0%) randomised to virtual care and 124 patients (27.3%) randomised to standard care (relative risk, 0.80; 95% CI, 0.64-1.01).

Of the 12 prespecified secondary outcomes, 5 demonstrated statistically significant results, Table 2. More patients in the virtual-care group compared to the standard-care group had a medication error detected (absolute difference, 24.2%; 95% CI, 19.5-28.9) and a medication error correction (absolute difference 24.4%; 95% CI, 19.9-28.9). Fewer patients in the virtual-care group compared to the standard-care group had pain at 7, 15, and 30 days after randomisation (absolute differences of 13.9% [95% CI, 7.4-20.4]; 11.9%, [95% CI, 5.1-18.7]; and 9.6% [95% CI, 2.9-16.3], respectively).

Among the 29.7% of patients in the virtual-care group who had a drug error detected, there were 286 drug errors (i.e., each patient with a drug error had a mean of 2.1 drug errors), and among the 5.5% of patients in the standard-care group who had a drug error detected, there were 44 drug errors (i.e., each patient with a drug error had a mean of 1.8 drug errors), Table 3, Supplement 3. Drug omission was the most common medication error. Detection of drug omission was more common in the virtual-care group (82 patients [18.2%]) compared to the standard-care group (16 patients [3.5%]); absolute difference 14.7% (95% CI, 10.7-18.6); among these patients with drug omissions, there were 173 versus 28 drug omission errors, respectively. More patients in the virtual-care group compared to the standard-care group had a physician or

nurse correct their drug error (102 patients [22.6%] versus 6 patients [1.3%]); absolute difference, 21.3% (95% CI, 17.3-25.3); among these patients, 173 versus 9 drug errors were corrected by a physician or nurse, respectively.

Table 4, Supplement 3 reports the most responsible person for drug errors and the reason for drug errors. Patients were responsible for 77.6% of the drug errors, and the most common reasons for their drug errors included an intentional decision (46.1%), mistake (22.7%), forgot (11.3%), and financial barrier (8.6%). Physicians and nurses were responsible for 18.5% of the drug errors, and the most common reasons for their drug errors included failure to communicate clear instructions on what medications should and should not be taken at home (54.1%), failure to write a prescription for a new medication (34.4%), and failure to write a prescription to discontinue a medication (6.6%). Pharmacists were responsible for 3.6% of the drug errors and this was always due to a failure to provide the medication as prescribed.

Compared to patients in the standard-care group, patients in the virtual-care group had less moderate to severe pain while laying down and while moving at 15 and 30 days after randomisation, Table 5, Supplement 3. Patients in the virtual-care group also reported lower moderate to severe pain-related interference scores at 7 and 30 days after randomisation, compared to patients in the standard-care group. Acetaminophen was the pain medication for which relative usage between patients in the virtual-care group versus the standard-care group changed over time (i.e., usage before the index hospitalisation, at hospital discharge after surgery, and at 30-days after randomisation), Table 6, Supplement 3. More patients randomised to virtual care than standard care were taking acetaminophen at 30 days after randomisation (absolute difference 25.2%; 95% CI, 18.8-31.6).

Most tertiary outcomes at 30 days after randomisation were uncommon, Table 7, Supplement 3. Virtual care did not significantly affect any tertiary outcome. In the prespecified subgroup analyses for the primary outcome at 30 days after randomisation, the effects did not differ across the subgroups, Figure 2, Supplement 3.

In the virtual-care group, centres varied in the frequency with which nurses escalated care to a physician, Table 8, Supplement 3. We undertook post hoc analyses that evaluated results across the centres that had the highest (89.3% of patients had escalation of care), intermediate (54.5%), and lowest escalation of care (34.1%), Table 3. In the virtual-care group, the total number of escalations and the mean escalations per patient, respectively, was 758 and 4.3 in the highest escalation centres, 227 and 1.2 in the intermediate escalation centres, and 56 and 0.7 in the lowest escalation centres. The total number and the mean escalations per patient varied in the virtual-care group for various triggers across centres. For example, the mean escalations per patient for a biophysical parameter trigger was 1.6, 0.4, and 0.1 in the highest, intermediate, and lowest escalation of care centres, respectively.

Most escalations of care were to a perioperative physician, occurring in the highest escalation centres 747 times, in the intermediate escalation centres 200 times, and in the lowest escalation centres 43 times. The results of the escalation of care varied across centres. For example, the mean change in medication per patient in the virtual-care group was 1.3 in the highest, 0.7 in the intermediate, and 0.3 in the lowest escalation of care centres.

The subgroup analyses based on centres with the highest, intermediate, and lowest escalation of care for acute-hospital care, brief acute-hospital care, emergency department visit, and hospital re-admission, demonstrated interaction p values of 0.05, 0.06, 0.03, and 0.54, respectively, Figure 2. These analyses suggested patients in the highest escalation centres had a

lower risk of acute-hospital care (relative risk, 0.56; 95% CI, 0.38-0.82), brief acute-hospital care (relative risk, 0.47; 95% CI, 0.27-0.80), and emergency department visit (relative risk, 0.54; 95% CI, 0.37-0.81) with virtual care compared to standard care.

Table 9, Supplement 3 reports the effects of virtual care with RAM on tertiary 6-month outcomes. There was no impact on days alive at home at 6 months.

DISCUSSION

Statement of Principal Findings

Virtual care and RAM did not meaningfully increase days alive at home. Virtual care and RAM did, however, result in significantly more patients having a medication error detected and corrected. In addition, fewer patients in the virtual-care group had pain at 7, 15, and 30 days after randomisation, compared to patients in the standard-care group. Post hoc analyses suggested that virtual care and RAM reduced the risk of acute-hospital care, brief acute-hospital care, and emergency department visit, compared to standard care in centres with high escalation of care but not in centres with lower levels of escalation.

Our Trial in Relation to Other Studies

An observational study of 20 patients discharged after esophagectomy demonstrated patients' use of virtual care with RAM after discharge was feasible and well received by all patients.[8] 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.[3] This observational study

reported an 80% relative risk reduction in the composite of hospital re-admission and emergency room visit at 30 days. A systematic review that evaluated virtual care in the recovery of surgical patients after hospital discharge demonstrated that investigators have thus far conducted only small observational studies with a high-risk of bias; the 3 randomized controlled trials (RCTs) included a total of only 153 patients.[9] Although the findings of this review require cautious interpretation, the studies suggest the acceptability of virtual care by patients and physicians, the potential to save patients time and money related to avoiding travel to clinics and missing work, and providing hospital clinic space for new patients. Among eligible patients for PVC-RAM-1, approximately 18% refused to participate, and 18% of surgeons did not agree to have patients participate. Moreover, only 9% of patients permanently discontinued using virtual care and RAM before completing the trial. Although our study demonstrated that the majority of patients and surgeons were agreeable to the trial and compliant with the intervention, further research is needed to establish what barriers exist for patients and surgeons regarding virtual care with RAM after surgery and participation in clinical trials.

Interpretation

We changed our primary outcome to days alive at home because of a case that identified the potential for death to be a competing-outcomes problem with our original primary outcome, acute-hospital care. With only 3 deaths in each treatment group, relevant competing outcomes proved inconsequential. Virtual care and RAM did not significantly affect days alive at home, but raised the possibility of a reduction in acute-hospital care (22.0% in the virtual-care group versus 27.3% in the standard-care group; relative risk, 0.80; 95% CI, 0.64-1.01), brief acute-hospital care (13.7% versus 18.1%, relative risk, 0.75; 95% CI, 0.56-1.02), hospital re-admission

(9.5% versus 12.8%; relative risk, 0.77; 95% CI, 0.53-1.11), and emergency department visit (19.7% versus 24.4%; relative risk, 0.81; 95% CI, 0.64-1.04). During the COVID-19 pandemic, when patients presumably would wish to avoid post-discharge acute-hospital care,[10] our finding in the standard-care group that more than 1 in 4 patients sought acute-hospital care highlights the magnitude of the problem. Although our trial occurred during the COVID-19 pandemic, the insights from our trial are likely also relevant in non-pandemic settings.

Drug errors after hospital discharge post-surgery proved common (i.e., 29.7% of virtual-care patients and these patients had a mean of 2.1 drug errors). Virtual care demonstrated large absolute benefits in detecting (24.2%) and correcting medication errors (24.4%). Detection and correction of drug errors have the potential to improve both short and long-term health. Virtual care also demonstrated substantial absolute benefits in reducing pain, moderate to severe pain, including with movement, and moderate to severe pain-related interference scores, compared to standard care. Patients are likely to consider these absolute differences important.[11] Our finding that demonstrated a substantial increase in acetaminophen usage at 30-days after randomisation in the virtual-care group (i.e., absolute difference 25.2%), suggests that healthcare providers can, through virtual care, increase the use of this well tolerated drug and substantially improve pain after hospital discharge following surgery.

It is only credible to expect virtual care with RAM to impact outcomes if these interventions identify problems and lead to changes in management. Across centres in the virtual-care group, there were marked variations in the following: the proportions of patients for whom nurses escalated care to a physician, the number of escalations, the frequency in which biophysical parameters and onset or change in signs or symptoms triggered escalation of care, and the result of the escalation of care (e.g., change in medications). In post hoc analyses, the

patients in the highest escalation of care centres demonstrated virtual care and RAM had a lower risk of acute-hospital care (relative risk, 0.56; 95% CI, 0.38-0.82), brief acute-hospital care (relative risk, 0.47; 95% CI, 0.27-0.80), and emergency department visit (relative risk, 0.54; 95% CI, 0.37-0.81), compared to standard care.

Although we established predetermined thresholds for biophysical measurement in which nurses were to escalate care to a physician, nurses or physicians could adjust the frequency of biophysical measurements and parameters for alerts. Moreover, nurses decided if they had concerns about patients' health that required a physician's attention. These results suggest virtual care and RAM can have substantial effects on lowering the risk of acute-hospital care, brief acute-hospital care, and emergency department visits, if compliance with predetermined biophysical thresholds is rigorous, escalation of care to a physician is frequent, and physicians then appropriately modify care.

Our study provides proof of concept that virtual care with RAM can improve outcomes after discharge following non-elective surgery. Further trials are needed to improve the efficiency (e.g., not all patients need to interact with a nurse on days 1-15 and every other day from days 16-30 after hospital discharge) and cost effectiveness of virtual care with RAM in this setting.

Centres in high-income countries could implement our virtual care with RAM intervention. Key issues for centres to consider before implementing our intervention include: ensuring an adequate supply of dedicated and committed nurses and physicians to ensure 24 hours a day patient support; procuring reliable and reusable virtual care and RAM technology (e.g., the Cloud DX technology we used in this study); establishing if the patient population resides in areas with cellular coverage; and ensuring adequate funding. Although some may

question whether virtual care with RAM is viable in patients being discharged after surgery in low-income countries, given that the dominant cost of this intervention is personnel costs, which are often more affordable in lower-income countries, and that many low-income countries have extensive cellular coverage, it is possible that low-income countries could leapfrog past high-income countries in the use of this technology. More research, including research in low-income countries, is needed to inform the potential and cost effectiveness of virtual care with RAM in patients being discharged after surgery.

Strengths and Limitations

PVC-RAM-1 randomised 905 patients in 8 centres and obtained follow-up on 99.8% of participants. Among patients in the virtual-care group, escalation of care varied substantially across centres. Our post hoc analyses suggest that this variation may have influenced the results. Patients were aware of their treatment allocation and this may have impacted the reporting of pain. We did, however, demonstrate increased usage of appropriate pain medications, reductions in moderate to severe pain, and reductions in moderate to severe pain-related interference scores in the virtual-care group, supporting the results that demonstrated a reduced burden of pain with virtual care. If physicians and patients knew immediately after surgery that patients were randomised to receive virtual care with RAM after discharge, this knowledge could have facilitated earlier hospital discharges, compared to patients randomised to standard care. Because we randomised patients after the most responsible physician had decided to discharge the patient home, we were not able to inform this issue. We did not ascertain if patients viewed days alive at home as an important outcome. We do not have documentation on how the usual standards of care (e.g., discharge protocols) changed at participating centres during the COVID-

19 pandemic. Although baseline variables, including the subtypes of surgery, appear balanced between the two treatment groups, we cannot exclude the possibility of a baseline imbalance of prognosis in this moderate-sized RCT. We did not assess the impact of the intervention on quality of life.

Conclusions

Virtual care and RAM did not significantly affect days alive at home but increased detection and correction of drug errors and reduced pain. In post hoc analyses of centres with high escalation of care that commonly led to changes in medical management, virtual-care and RAM reduced the risk of acute-hospital care, brief acute-hospital care, and emergency department visits.

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MHM, JP, FKB, MM, MJ, AA, MML, CO, MB, SO, PSR, AP, HY, SOL, VT, GMH, MM, DC, VH, JL, RM, SIB, RA, TS, GHG, PG, MG, RN, AJF, MN, KL, KM, SC, SH, LD, BL, CJLM, EHS, JV, SMP, DD, ADP, MS, DCW, SH, JH, RMM, DT, HS, CMS, NP, DRP, HY, EP, AL, JP, HM, HS, MW, JS, EPBC, and PJD planned the conceptualisation and the design of the study

and the protocol. All members of the writing committee contributed to critical revisions of the current manuscript and approved the manuscript for submission.

FUNDING: This trial is supported by the following grants: Roche Innovation Challenge Application Grant; McMaster COVID-19 Research Fund Grant; The Research Institute of St. Joseph's Healthcare Hamilton Grant; COVID-19 Innovation funding grant from the Ottawa Hospital Academic Medical Association (TOHAMO); and Queen's University Department of Anaesthesiology Award and Department of Medicine Research Award to help fund the trial at Kingston Health Sciences. This trial received in-kind support to cover the salaries of the virtual nurses from the Hamilton Health Sciences, Kingston Health Sciences, London Health Sciences, St. Joseph's Healthcare Hamilton, the Ottawa Hospital, and the University of Alberta Hospital. MHM holds the Heart and Stroke Foundation/Michael G. DeGroote Endowed Chair in Cardiovascular Nursing. CO and SO received internship funding from Mitacs Accelerate to support work on the PVC-RAM-1 Trial. FKB and MM hold McMaster University Department of Medicine Career Research Awards. DC holds a McMaster University Department of Medicine Mid-Career Research Award. PJD holds the McMaster University / Hamilton Health Sciences Chair in Perioperative Care and a Tier 1 Canada Research Chair in Perioperative Medicine.

DISCLAIMER: The members of the writing committee are solely responsible for the trial design, conduct, management, analyses, data interpretation, writing of this paper, and decision to submit this paper for publication.

COMPETING INTERESTS: CloudDX undertook training sessions for virtual nurses and perioperative physicians and surgeons regarding how to use their technology. DC received consultation fees from Servier, Canada, outside of the current work. EPBC has received grants from Roche and Bayer. PJD has received grants from Philips' Healthcare.

Data Sharing Statement: The Population Health Research Institute (PHRI) is the sponsor of this trial. The PHRI believes the dissemination of clinical research results is vital and sharing of data is important. PHRI prioritises access to data analyses to researchers who have worked on the trial for a significant duration, have played substantial roles, and have participated in raising the funds to conduct the trial. PHRI balances the length of the research study, and the intellectual and financial investments that made it possible with the need to allow wider access to the data collected. Data will be disclosed only upon request and approval of the proposed use of the data by a Review Committee. Data are available to the journal for evaluation of reported analyses. Regarding the ICES data, while data sharing agreements prohibit ICES from making the data set publicly available, access can be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS.

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Figure 1. Patient flow chart

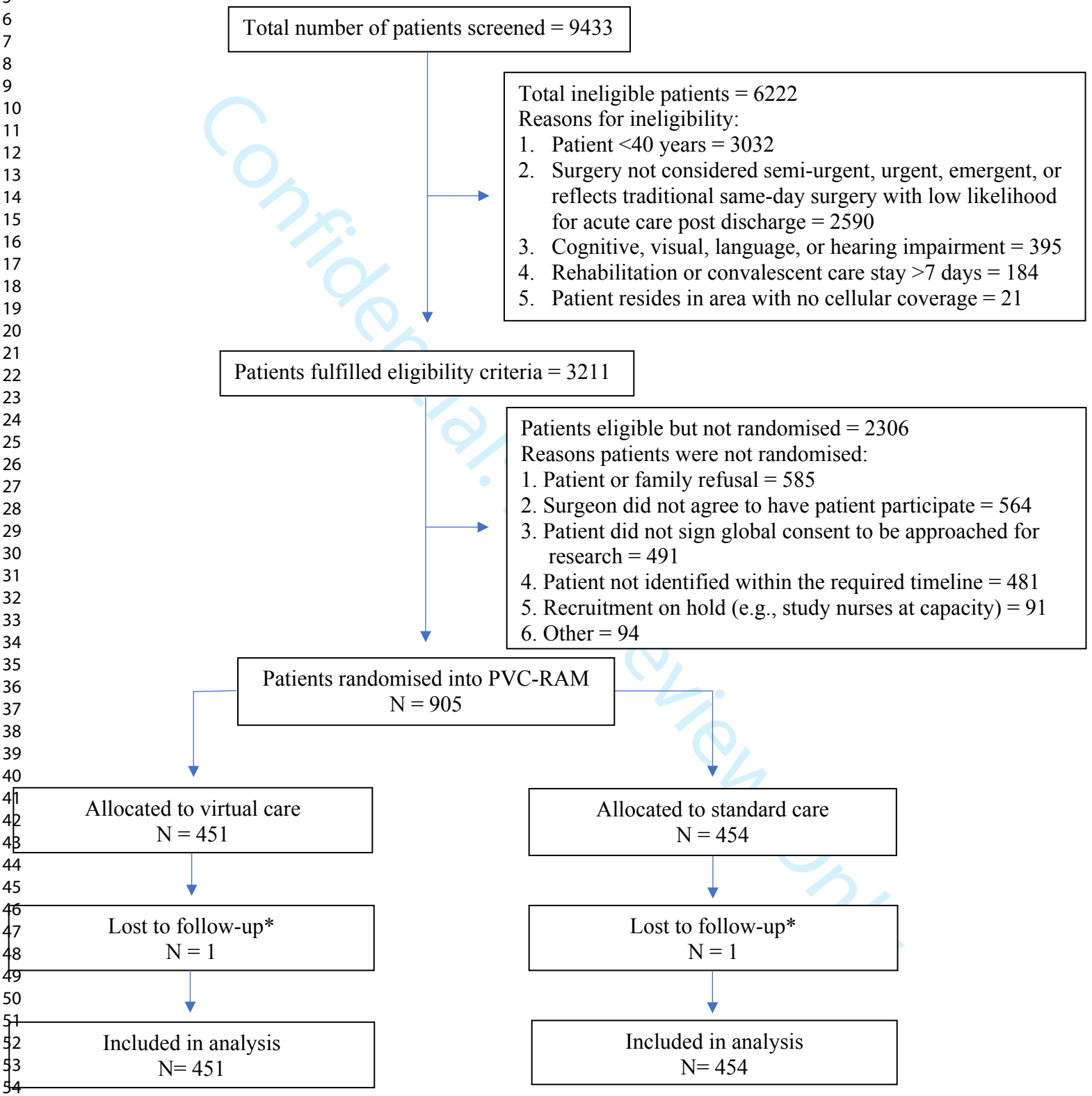

Figure 2. Panel A: Subgroup analysis based on centres' escalation of care for 31-day outcome of acute-hospital care

	Virtual care Count/Total (%)	Standard care Count/Total (%)	Relative Risk (95% CI)	P value for Interaction
Overall results	**99/451 (22.0)**	**124/454 (27.3)**	**0.80 (0.64-1.01)**	**0.05**
Subgroups				
Centre				
Centres with highest escalation of care (Centres 1, 2, and 4)	32/177 (18.1)	58/180 (32.2)	0.56 (0.38-0.82)	
Centres with intermediate escalation of care (Centres 3, 6, and 7)	50/189 (26.5)	50/187 (26.7)	0.99 (0.71-1.38)	
Centres with the lowest escalation of care (Centres 5 and 8)	17/85 (20.0)	16/87 (18.4)	1.08 (0.59-2.01)	

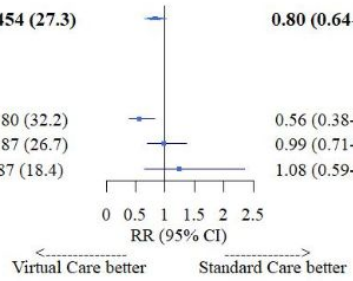

Figure 2. Panel B: Subgroup analysis based on centres' escalation of care for 31-day outcome of brief acute hospital care

	Virtual care Count/Total (%)	Standard care Count/Total (%)	Relative Risk (95% CI)	P value for Interaction
Overall results	**62/451 (13.7)**	**82/454 (18.1)**	**0.76 (0.56-1.03)**	**0.06**
Subgroups				
Centre				
Centres with highest escalation of care (Centres 1, 2, and 4)	17/177 (9.6)	37/180 (20.6)	0.47 (0.27-0.80)	
Centres with intermediate escalation of care (Centres 3, 6, and 7)	36/189 (19.0)	35/187 (18.7)	1.02 (0.67-1.55)	
Centres with the lowest escalation of care (Centres 5 and 8)	9/85 (10.6)	10/87 (11.5)	0.92 (0.39-2.15)	

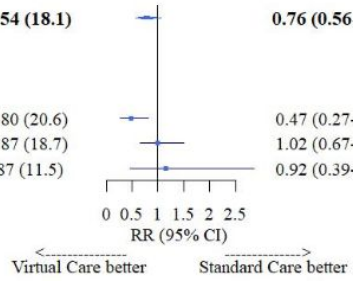

Figure 2. Panel C: Subgroup analysis based on centres' escalation of care for 31-day outcome of emergency department visit

	Virtual care Count/Total (%)	Standard care Count/Total (%)	Relative Risk (95% CI)	P value for Interaction
Overall results	**89/451 (19.7)**	**111/454 (24.4)**	**0.81 (0.63-1.03)**	**0.03**
Subgroups				
Centre				
Centres with highest escalation of care (Centres 1, 2, and 4)	30/177 (16.9)	56/180 (31.1)	0.54 (0.37-0.81)	
Centres with intermediate escalation of care (Centres 3, 6, and 7)	43/189 (22.8)	39/187 (20.9)	1.09 (0.74-1.60)	
Centres with the lowest escalation of care (Centres 5 and 8)	16/85 (18.8)	16/87 (18.4)	1.02 (0.55-1.91)	

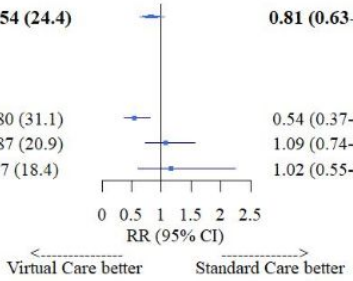

Figure 2. Panel D: Subgroup analysis based on centres' escalation of care for 31-day outcome of hospital re-admission

	Virtual care Count/Total (%)	Standard care Count/Total (%)	Relative Risk (95% CI)	P value for Interaction
Overall results	**43/451 (9.5)**	**58/454 (12.8)**	**0.75 (0.51-1.08)**	**0.54**
Subgroups				
Centre				
Centres with highest escalation of care (Centres 1, 2, and 4)	17/177 (9.6)	28/180 (15.6)	0.62 (0.35-1.09)	
Centres with intermediate escalation of care (Centres 3, 6, and 7)	18/189 (9.5)	23/187 (12.3)	0.77 (0.43-1.39)	
Centres with the lowest escalation of care (Centres 5 and 8)	8/85 (9.4)	7/87 (8.0)	1.17 (0.44-3.08)	

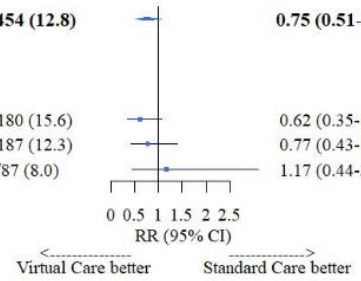

Figure Legend.

Figure 1. Patient flow chart

* 2 patients withdrew from follow-up. The data from these participants are included in the analysis and censored at the time of last follow-up, as per the statistical analysis plan.

Figure 2. Panel A: Subgroup analysis based on centres' escalation of care for 31-day outcome of acute hospital care

Figure 2. Panel B: Subgroup analysis based on centres' escalation of care for 31-day outcome of brief acute hospital care

Figure 2. Panel C: Subgroup analysis based on centres' escalation of care for 31-day outcome of emergency department visit

Figure 2. Panel D: Subgroup analysis based on centres' escalation of care for 31-day outcome of hospital re-admission

Table 1. Baseline characteristics and surgical details

Characteristics	Virtual-care group (N=451)	Standard-care group (N=454)
Age (years, mean [± SD])	63.2 ± 10.4	62.9 ± 11.2
Sex (men) – no. (%)	259 (57.4)	236 (52.0)
History before randomisation – no. (%)		
hypertension	241 (53.4)	264 (58.1)
active cancer*	153 (33.9)	156 (34.4)
coronary artery disease	100 (22.2)	107 (23.6)
diabetes	98 (21.7)	96 (21.1)
smoked within 28 days before surgery	88 (19.5)	88 (19.4)
obstructive sleep apnea	74 (16.4)	75 (16.5)
myocardial infarction	56 (12.4)	60 (13.2)
atrial fibrillation	54 (12.0)	60 (13.2)
chronic pain	52 (11.5)	50 (11.0)
chronic obstructive pulmonary disease	41 (9.1)	39 (8.6)
peripheral arterial disease	22 (4.9)	32 (7.0)
stroke	22 (4.9)	17 (3.7)
congestive heart failure	20 (4.4)	17 (3.7)
transient ischemic attack	18 (4.0)	15 (3.3)
deep venous thrombosis	11 (2.4)	8 (1.8)
pulmonary embolism	10 (2.2)	9 (2.0)
needing assistance with activities of daily living	9 (2.0)	7 (1.5)
COVID-19 infection	0 (0)	1 (0.2)
Type of surgery† – no. (%)		
Non-cardiac†	366 (81.2)	366 (80.6)
general	146 (32.4)	130 (28.6)
urology/gynecology	81 (18.0)	91 (20.0)
orthopedic	62 (13.7)	68 (15.0)
neurosurgery	30 (6.7)	31 (6.8)
vascular	22 (4.8)	25 (5.5)
thoracic	23 (5.1)	17 (3.7)
plastic	10 (2.2)	6 (1.3)
other	10 (2.2)	15 (3.3)
Cardiac†	89 (19.7)	89 (19.6)
coronary artery bypass grafting	69 (15.3)	75 (16.5)
valve	28 (6.2)	19 (4.2)
aortic	12 (2.7)	6 (1.3)
other	12 (2.7)	13 (2.9)
Timing of surgery – no. (%)		
semi-urgent	241 (53.4)	273 (60.1)
urgent	178 (39.5)	142 (31.3)
emergent	32 (7.1)	39 (8.6)

Same-day surgery – no. (%)	28 (6.2)	42 (9.3)
Surgical approach† – no. (%)		
open	341 (75.6)	338 (74.4)
minimally invasive	63 (14.0)	68 (15.0)
endoscopic/endovascular	76 (16.9)	71 (15.6)
Anesthesia† – no. (%)		
general	435 (96.5)	436 (96.0)
neuraxial	53 (11.8)	64 (14.1)
regional block	22 (4.9)	15 (3.3)
local	10 (2.2)	11 (2.4)
New diagnoses from initiation of surgery until randomisation – no. (%)		
bleeding	29 (6.4)	29 (6.4)
myocardial injury after non-cardiac surgery	24 (6.6)	18 (4.9)
infection	11 (2.4)	11 (2.4)
delirium	5 (1.1)	4 (0.9)
Laboratory measurements before randomisation		
hemoglobin (g/L, median [IQR])	108 (94-124)	110 (95-124)
creatinine (umol/L, median [IQR])	69 (58-85)	71 (58-88)
Present at time of hospital discharge – no. (%)		
surgical drain	37 (8.2)	19 (4.2)
stoma	22 (4.9)	17 (3.7)
Timing of hospital discharge relative to randomisation		
patients randomised before hospital discharge – no. (%)	358 (79.4)	361 (79.5)
time from randomisation to discharge (days, median [IQR])	0.08 (0.04-0.17)	0.08 (0.04-0.17)
patients randomised within 24 hours after hospital discharge – no. (%)	93 (20.6)	93 (20.5)

IQR = interquartile range; no. = number; SD = standard deviation; % = percentage

* Defined as a patient with a diagnosis of cancer who was receiving or has received active treatment for their cancer (e.g., chemo, radiation, or surgery) within the previous 6 months; however, it does not apply to patients with non-melanoma skin cancers.

† Some patients had more than one type of surgery, surgical approach, or anesthesia. Therefore, sums of subtypes of surgery, surgical approach, and anesthesia surpass total number of patients.

Table 2: Effects of virtual care and remote automated monitoring on the 31-day outcomes

Outcome	Virtual-care group (N=451)	Standard-care group (N=454)	Relative risk* (95% CI)	Absolute difference† % (95% CI)	P Value
Primary outcome – mean (± SD)					
days alive at home	29.7 (3.9)	29.5 (3.8)	1.01 (0.99-1.02)	0.2 (-0.5-0.9) ^	0.53
Secondary outcomes – no. (%)					
acute-hospital care	99 (22.0)	124 (27.3)	0.80 (0.64-1.01)	5.3 (-0.3-10.9)	0.06
brief acute-hospital care	62 (13.7)	82 (18.1)	0.75 (0.56-1.02)	4.4 (-0.4-9.2)	0.07
hospital re-admission	43 (9.5)	58 (12.8)	0.77 (0.53-1.11)	3.3 (-0.8-7.4)	0.16
emergency department visit	89 (19.7)	111 (24.4)	0.81 (0.64-1.04)	4.7 (-0.7-10.1)	0.10
urgent-care centre visit	4 (0.9)	9 (2.0)	NR	1.1 (-0.5-2.7)	0.26
all-cause hospital days (median [IQR])	0 (0-0)	0 (0-0)	0.89 (0.59-1.35)	0.1 (0.0-0.2)^	0.59
death	3 (0.7)	3 (0.7)	NR	0	1.00
detection of medication error	134 (29.7)	25 (5.5)	5.29 (3.52-7.93)	24.2 (19.5-28.9)	<0.001
correction of medication error	128 (28.4)	18 (4.0)	7.01 (4.36-11.52)	24.4 (19.9-28.9)	<0.001
pain at 7 days after randomisation#	227/386 (58.8)	309/425 (72.7)	0.81 (0.73-0.90)	13.9 (7.4-20.4)	<0.001
pain at 15 days after randomisation#	193/402 (48.0)	248/414 (59.9)	0.80 (0.71-0.91)	11.9 (5.1-18.7)	<0.001
pain at 30 days after randomisation#	144/411 (35.0)	184/413 (44.6)	0.80 (0.67-0.94)	9.6 (2.9-16.3)	<0.008

IQR = interquartile range; no. = number; NR = not reported, because there were too few events to produce a stable relative risk estimate based on a modified Poisson regression; SD = standard deviation; % = percentage

* Relative risks and 95% confidence intervals were obtained from Modified Poisson model

† Absolute differences and 95% confidence intervals were calculated from the crude proportions.

^ Absolute rate differences and 95% confidence intervals were determined based on a Normal Approximation to Poisson.

In the virtual care group 85.6%, 89.1%, 91.1% of patients provided pain data at 7, 15, and 30 days after randomisation, respectively.

In the standard-care group 93.6%, 91.2%, 90.9% of patients provided pain data at 7, 15, and 30 days after randomisation, respectively.

Table 3: Nurse escalation of care among patients in virtual-care and remote automated monitoring group*

	All virtual-care patients (n=451)	Virtual-care patients in centres with highest escalation of care (i.e., centres 1, 2, 4) (n=177)	Virtual-care patients in centres with intermediate escalation of care (i.e., centres 3, 6, 7) (n=189)	Virtual-care patients in centres with lowest escalation of care (i.e., centres 5, 8) (n=85)	P value
Patients with escalation of care – no. (%)	290 (64.3)	158 (89.3)	103 (54.5)	29 (34.1)	<0.001
Total number of escalations – no.	1041	758	227	56	
Escalations per patient in virtual-care group – mean	2.3	4.3	1.2	0.7	
Trigger of escalation of care – no.					
onset/change of sign or symptom	481	353	86	42	
biophysical parameter	366	278	78	10	
medication issue	152	98	50	4	
other	42	29	13	0	
Triggers of escalation of care per patient in the virtual-care group – mean					
onset/change of sign or symptom	1.1	2.0	0.5	0.5	
biophysical parameter	0.8	1.6	0.4	0.1	
medication issue	0.3	0.6	0.3	0.1	
other	0.1	0.2	0.1	0	
Escalation of care to study physician† – no.					
perioperative medicine physician	990	747	200	43	
surgeon	55	29	22	4	
Escalation of care to study physician per patient in the virtual-care group – mean					
perioperative medicine physician	2.2	4.2	1.1	0.5	
surgeon	0.1	0.2	0.1	0.1	

Result of escalation of care – no.				
change in medication	385	237	124	24
virtual visit	316	234	61	21
continue to monitor with no immediate action	329	295	31	3
outpatient diagnostic testing‡	79	38	29	12
nurse to educate patient§	73	67	4	2
patient to follow-up with non-study physician	49	35	11	3
other	53	28	16	9
Results of escalation of care per patient in the virtual-care group – mean				
change in medication	0.9	1.3	0.7	0.3
virtual visit	0.7	1.3	0.3	0.3
continue to monitor with no immediate action	0.7	1.7	0.2	<0.1
outpatient diagnostic testing‡	0.2	0.2	0.2	0.1
nurse to educate patient§	0.2	0.4	<0.1	<0.1
patient to follow-up with non-study physician	0.1	0.2	0.1	<0.1
other	0.1	0.2	0.1	0.1

* escalation of care to healthcare provider per patient at centre

† Some patients had escalation of care to both a perioperative medicine physician and a surgeon. Therefore, sums of perioperative medicine physician and surgeon surpasses total number of patients.

‡ outpatient diagnostic testing included blood and urine tests, imaging, and electrocardiogram.

§ nurses educated patient about drug dosing, monitoring wound, etc.

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

Sponsor and Study Coordinating Group:
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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)

Contents

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.

7 REFERENCES

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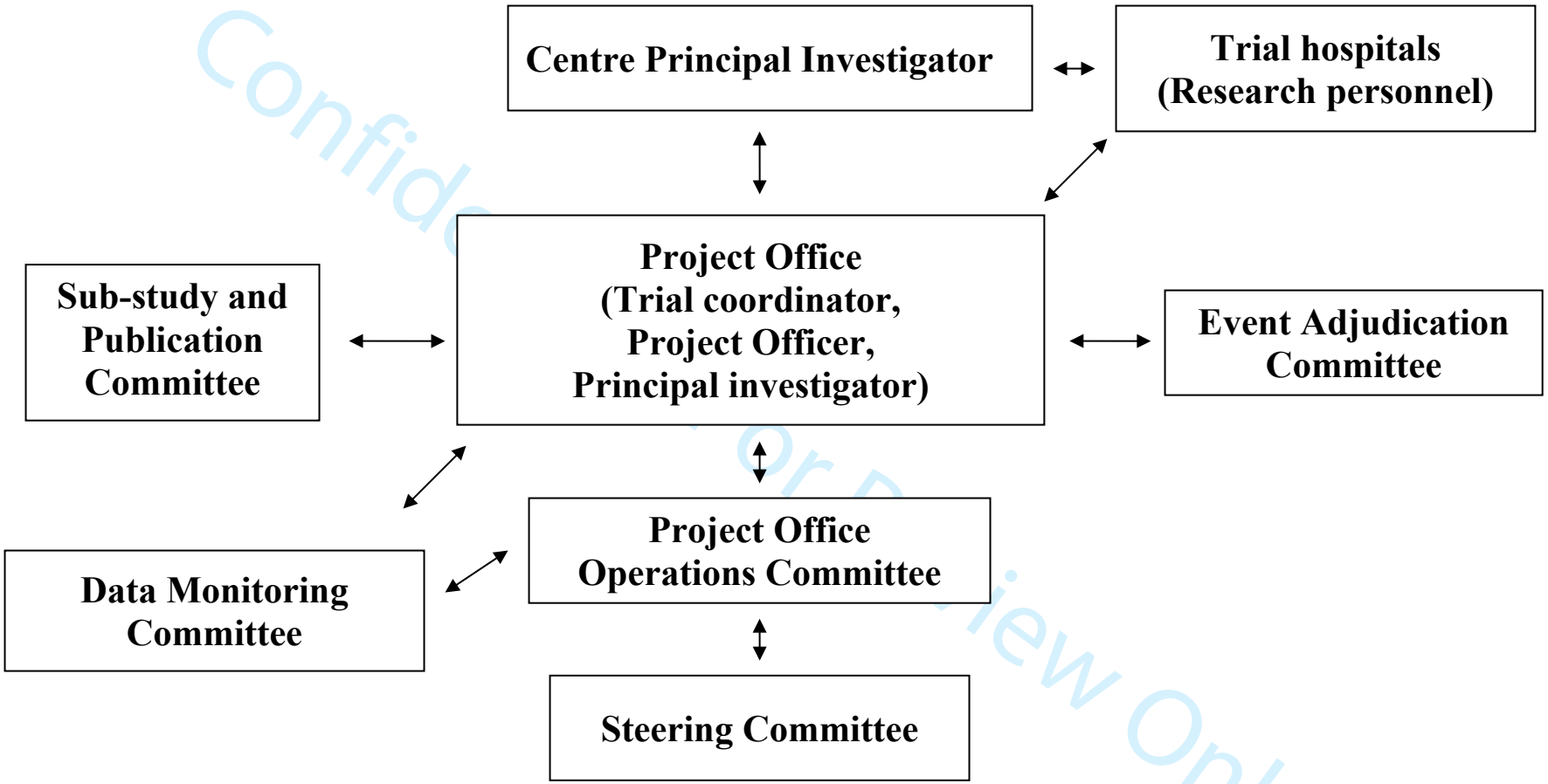
8 APPENDIX 1: Tables and Figures

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

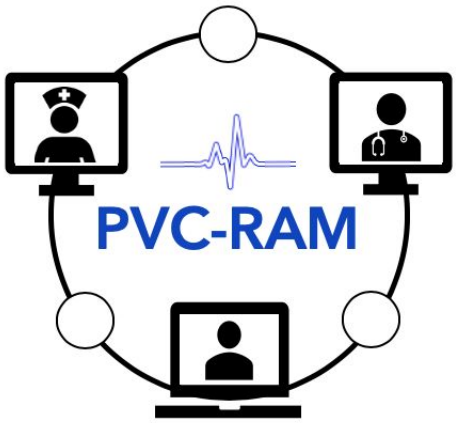
	symptoms OR fluctuating course of symptoms, AND b. inattention AND either c. disorganized thinking or d. altered level of consciousness. 2. Patient unable to complete the interview because too confused. This criterion is applicable when patients are able to complete telephone interviews at baseline, 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 ≥ 30 milliseconds; C. new or presumed new 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
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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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 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.

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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.

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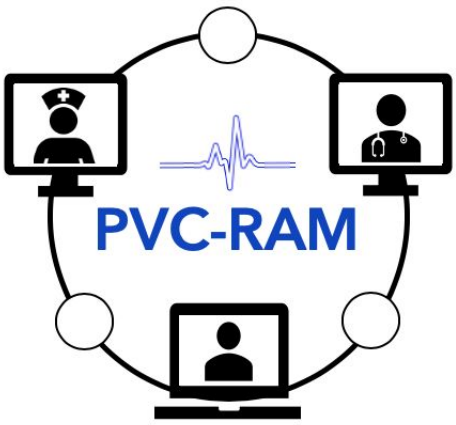
THE FOLLOWING TEXT IS MODIFIED:

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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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

Page 6/27
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]

Page 9/27
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~~

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; ~~7~~8. medication error correction; ~~8~~9. 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;

Page 9/47
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 London~~and, ~~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.~~ ~~W~~we ~~will recruit 900 patients; this~~ will ~~have~~provide ~~95~~81%, ~~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 home~~hazard ratio is 0.70~~, assuming no average virtual care with RAM results in 29.69 days alive at home~~a control group event rate of 20%~~.

Page 10/27
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*. *O*utcome adjudicators (expert physicians), blind to treatment allocation, will adjudicate the following outcomes: 1. days alive at home; 2. delirium; ~~3~~2. 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; 1~~0~~1. surgeon, family physician, or specialist virtual clinic visit; 1~~1~~2. sepsis; 1~~2~~3. acute heart failure; and 1~~3~~4. 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 3~~1~~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.

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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%~~

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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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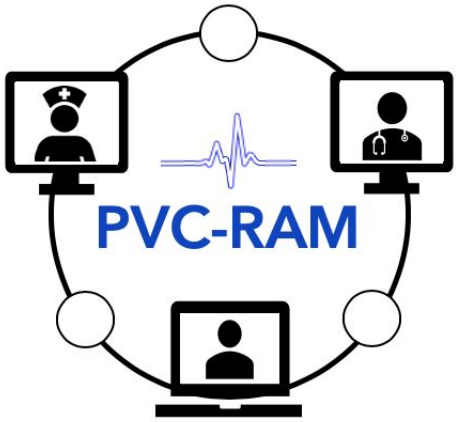
THE FOLLOWING TEXT IS REMOVED:

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

Page 26/27

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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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; 78. medication error detection; 89. 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, 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; 89. medication error correction; 910. delirium; 10~~1~~. surgeon, family physician, or specialist in-person clinic visit; 11~~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.

Page 14/28

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%

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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.

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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.

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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.

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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.

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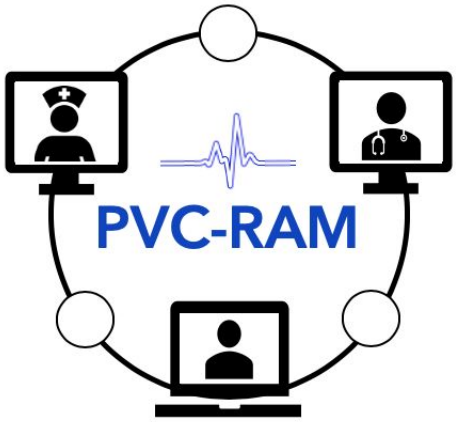
THE FOLLOWING TEXT IS ADDED:

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
Hamilton General Hospital Campus, DBCVSRI
237 Barton Street East
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Principal Investigators:
Dr. Michael McGillion RN, PhD & Dr. PJ Devereaux, MD, PhD, FRCPC
Population Health Research Institute
DBCVSRI, 237 Barton Street East
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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; 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 ~~159~~. 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.

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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; 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 ~~159~~. 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.

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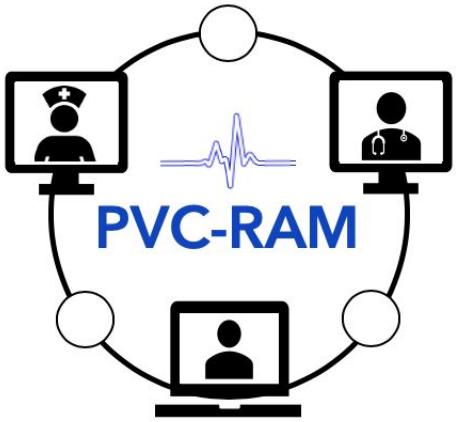
THE FOLLOWING TEXT IS ADDED:

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:
Dr. Michael McGillion RN, PhD & Dr. PJ Devereaux, MD, PhD, FRCPC
Population Health Research Institute
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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) (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.

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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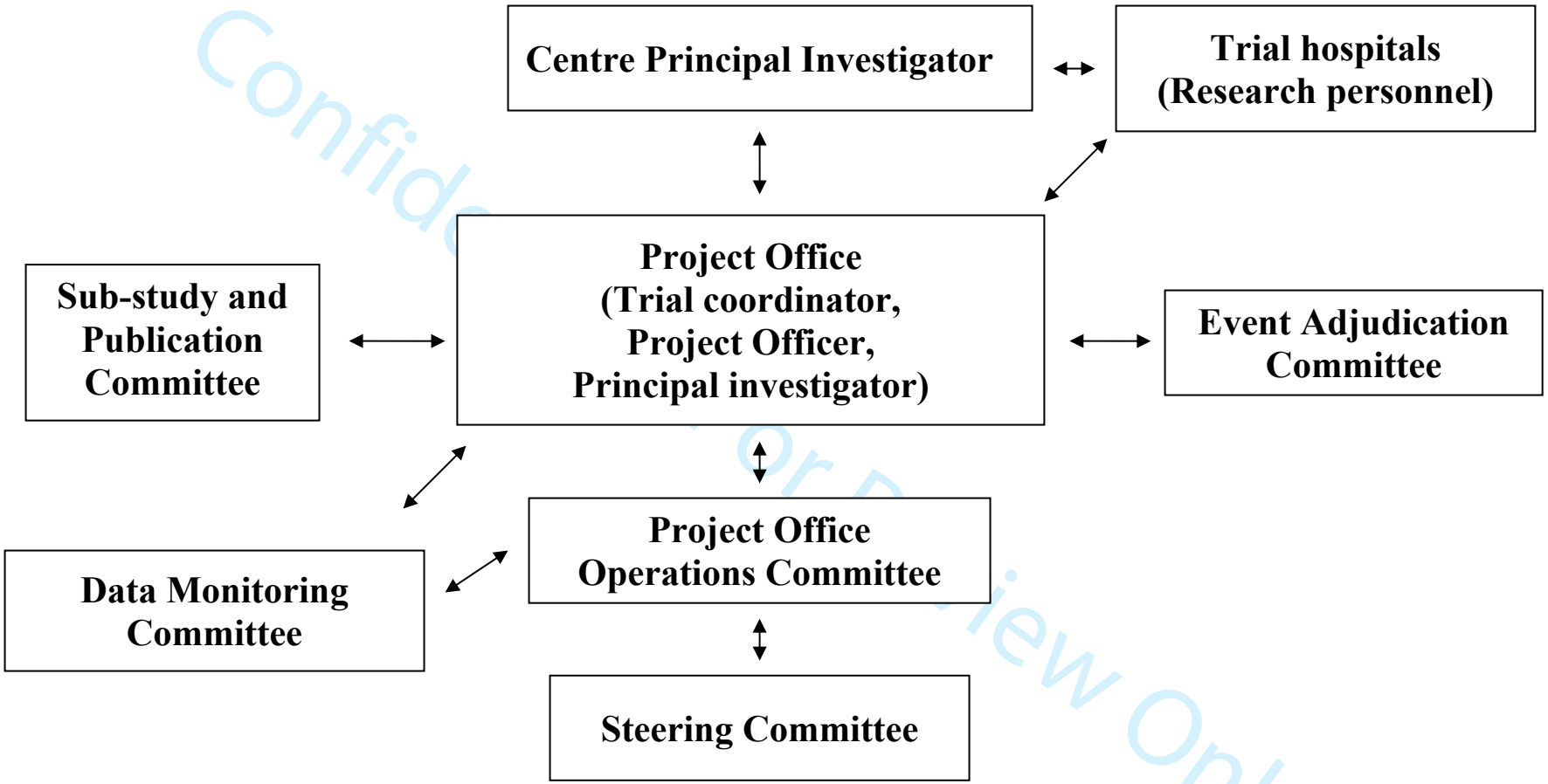
14 APPENDIX 1: Tables and Figures

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.

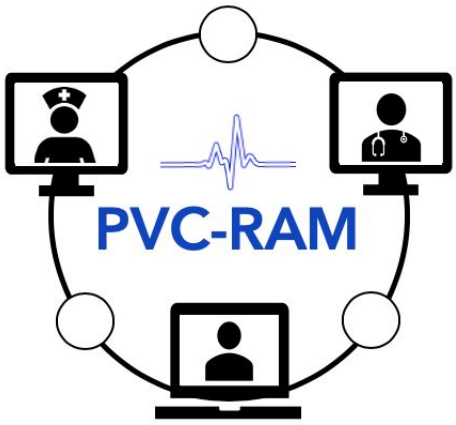
Re-operation	Re-operation refers to any surgical procedure undertaken for any reason (e.g., wound dehiscence, infection)
Arrythmia resulting in electrical cardioversion	Any arrythmia that leads to electrical cardioversion.
Acute renal failure resulting in dialysis	This outcome is defined as acute renal 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 ≤ 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: 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 ≥ 30 milliseconds; I. new or presumed new 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
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.

ONLINE-ONLY SUPPLEMENT 2



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

STATISTICAL ANALYSIS PLAN

Version 1.0
September 12, 2020

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LIST OF ABBREVIATIONS

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

1. INTRODUCTION

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

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

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

2. TRIAL DESCRIPTION

2.1 Study Design

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

3. STUDY OBJECTIVES

3.1 Primary objective

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

3.2 Secondary objectives

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

3.3 Tertiary objectives

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

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

4. OUTCOMES

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

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

4.1 Primary Outcome

The primary outcome is

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

4.2 Secondary Outcomes

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

4.3 Tertiary Outcomes

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

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

5. POPULATIONS TO BE ANALYZED

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

6. STATISTICAL ANALYSES

6.1 General Methods

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

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

6.1.1 Primary Outcome – Poisson Regression

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

6.1.2 Secondary and Tertiary Outcomes: Binary – Poisson Regression

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

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

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

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

6.1.4 Handling Missing Data

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

6.2 Study follow-up time

6.2.1 Missing date information

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

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

6.2.2 Baseline, Time Windows, and Calculated Visits

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

7. EFFICACY ANALYSES

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

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

8. SUBGROUP ANALYSES

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

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

9. SENSITIVITY ANALYSES

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

Table 1. Outcome definitions

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

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

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

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

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

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

obtained, or before cardiac biomarker values would be increased.

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

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

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

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

	B. development of pathologic Q waves present in any two contiguous leads that are ≥ 30 milliseconds; C. new or presumed new 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
Clinically important atrial fibrillation	The definition of clinically important atrial fibrillation requires the documentation of atrial fibrillation or atrial flutter on a 12 lead electrocardiogram, or confirmed atrial fibrillation or atrial flutter (e.g., rhythm strip) that results in angina, congestive heart failure, symptomatic hypotension, or requires treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
Symptomatic proximal venous thrombo-embolism	Venous thromboembolism that includes symptomatic pulmonary embolism or symptomatic proximal deep vein thrombosis.
Symptomatic pulmonary embolism	The diagnosis of symptomatic pulmonary embolism requires symptoms (e.g., dyspnea, pleuritic chest pain) and any one of the following: 1. A high probability ventilation/perfusion lung scan; 2. An intraluminal filling defect of segmental or larger artery on a helical CT scan; 3. An intraluminal filling defect on pulmonary angiography; or 4. A positive diagnostic test for DVT (e.g., positive compression ultrasound) and one of the following: A. non-diagnostic (i.e., low or intermediate probability) ventilation/perfusion lung scan, or B. non-diagnostic (i.e., subsegmental defects or technically inadequate study) helical CT scan
Symptomatic proximal deep venous thrombosis	The diagnosis of symptomatic proximal deep venous thrombosis (DVT) requires: 1. symptoms or signs that suggest DVT (e.g., leg pain or swelling), 2. thrombosis involving the popliteal vein or more proximal veins for leg DVT OR axillary or more proximal veins for arm DVTs Any of the following defines evidence of vein thrombosis:

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

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APPROVAL

Version #	**1.0**
Version Date	2020-09-12

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

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

Name	**Michael McGillion**
Role	**Co-Principal Investigator**
Signature	
Date (yyyy/mm/dd)	

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

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

ONLINE-ONLY SUPPLEMENT 3

Supplement Table of Contents

Supplemental Trial Investigators, Coordinating Centre, and Committees

Participating centres and investigators – *Kingston Health Sciences:* Darrin Payne, Rachael DaCunha, Sunil Patel, Michael Yacob, Siddhartha Srivastava, Lisa Nguyen, Curtis Nickel, Tyler Hands, Elorm Vowotor, Emile Peponoulas, Angela Webster, Tammy Doyle; *Hamilton Health Sciences, Hamilton General Hospital*: Kajenny Srivaratharajah, David Szalay, Deborah Bedini, Victor Chu, Jason Busse, Sandra Carroll, Duane Bender, Dina Brooks, Krysten Gregus, Patricia Power, Dale Williams; *Hamilton Health Sciences, Juravinski Hospital and Cancer Centre*: Amitabha Chakroborty, Samir Raza, Amna Ahmed, Kelly Lawrence, Derek Hunt, David Cowan, Jehonathan Pinthus, David Wilson, Clare Reade, Leslie Gauthier, Stephen Kelly, Kirsten Krull, Kim Alvarado, Susan Reid, Mohit Bhandari; *University of Alberta Hospital*: Derek Dillane, James Greene, David Bigam, Ryan Snelgrove, Brian Buchanan, Oleksa Rewa, Ronald Brisebois, Nadr Jomha, Bruce Ritchie, Sherry Reid, Adrian Fairey, Greg Hrynchyshyn; *St. Joseph's Healthcare Hamilton*: Bobby Shayegan, Christian Finley, Wendy Lim, Maria Tiboni, David Choi, Anne-Marie MacDonald, Deanna Burnette, Tom Stewart, Melissa Farrell, Carolyn Goss, Faraaz Quiraishi; *The Ottawa Hospital*: Daniel McIsaac, Sarah Tierney, Shawn Hicks, Kathryn Wheeler, Josh Robert, Colleen McFaul, Greg Krolczyk, Purnima Rao, Stephane Moffett, Dan Dubois, Catherine Code, Heather Clark, Melissa Rousseau, Catherine Gray, Dominique Yelle, Youssef Tawil, Babak Rashidi, Weiwei Beckerleg, Shipa Gupta, Sudhir Sundaresan, Suzanne Madore, Andrew Seely, Reece Bearnes, Dean Fergusson, Susan Madden, Jad Abou Khalil, John Sinclair, Moein Momtazi, Rodney Breau, Humberto Vigil, James Chan, Freddy Ngyuen; *London Health Sciences (University and Victoria Hospitals)*: George Nicolaou, Yamini Subramani, Ashraf Fayad, Amit Garg, Cathy Vandersluis, Glen Kearns, Cheryl Churcher, Carla Cormack, Brenda Maxwell, Johana Halabi, James Calvin, Douglas Naudie, Melfort Boulton, Stephanie Handsor, Heather Whittle, Charlotte Kenning.

Coordinating Centre: The Population Health Research Institute – which is part of Hamilton Health Sciences and McMaster University in Hamilton, Ontario, Canada – was the trial coordinating centre and was responsible for the randomisation system, maintenance of the database, data monitoring, analyses, and study-centre coordination.

Coordinating Centre Personnel: Lori Blake, Sanela Dragic-Taylor, Leanne Dyal, Arielle Fernandez, Peggy Gao, Valerie Harvey, Peter Koh, Louise Mastrangelo, John Liu, Yan Yun Liu, Rajibul Mian, Wesley Tong, Jessica Vincent, Heidi Wilton.

Operations Committee: PJ Devereaux, Michael McGillion, Sandra Ofori, Carley Ouellette, Marissa Bird, Jessica Vincent, Valerie Harvey, Pavel Roshanov, David Conen, Gordon Guyatt, Ameen Patel, Flavia K. Borges, Susan O'Leary, Maura Marcucci, Anthony Adili, Vikas Tandon, Homer Yang, Marko Mrkobrada, Joel Parlow, Manoj Lalu, Gavin Hamilton, Michael Jacka, Shrikant Bangdiwala, Rajibul Mian, Peggy Gao.

Event Adjudication Committee: Flavia K Borges (Chair), Sandra Ofori, Michael Wang, James Khan, Rahima Nenshi, Maura Marcucci, Marko Simunovic.

Data Monitoring Committee: Victor M. Montori (Chair), Finlay McAlister, Kristian Thorlund. The members of the Data Monitoring Committee have expertise in clinical trials, perioperative care, virtual care, and statistics.

APPENDIX 1. Biophysical measurements and recovery survey

Based on a schedule developed by a nurse, the tablet prompted patients to measure their biophysical parameters. The frequency of daily biophysical measurements was 3 times a day for the first 15 days, and then twice a day from day 16 until 30 days after randomisation. Weight was measured daily in the morning before breakfast. Nurses or physicians could adjust the frequency of biophysical measurements and parameters for alerts based on a patient's normal biophysical measurements, acuity, or tolerance. The tablet prompted patients daily to complete the recovery survey. The recovery survey consisted of questions related to infection, bleeding, pain, dehydration, ileus, and cardiovascular and respiratory complications.

APPENDIX 2. Example of vital sign thresholds and recommended nurse and physician actions

SBP measurement	Flag to nurse on CloudDX Connected Health Dashboard	Nurse recommended action	Physician recommended action
100-115 mm Hg	Mild	Nurse to contact and assess patient during scheduled video call. Advise patient to re-check measurement. Nurse to update perioperative care physician, at daily rounds.	Rule out precipitating factors (e.g. sepsis, volume depletion, bleeding, heart failure). Review medication and fluid intake. Decrease blood pressure medication dosage accordingly. Order back to nurse and coordinate follow up with nurse. Reassess in 24 hours.
86-99 mm Hg	Medium	Nurse to contact and assess patient within 30 minutes. Advise patient to re-check measurement. If unresolved, nurse will inform perioperative care physician within 1 hour.	All of the above and the following. Withhold anti-hypertensives until SBP >100 mmHg if patient with no HFrEF. Assess volume status. Order back to nurse and coordinate follow up. Reassess in 4-6 hours
<85 mm Hg	High	Contact and assist patient immediately. Advise patient to re-check measurement. If unresolved, nurse will inform perioperative care physician within 15 minutes.	Assess patient for symptoms. If patient is asymptomatic then all of the above and the following. Withhold anti-hypertensives. Consider video call with patient. Consider clinic assessment. Order back to nurse and coordinate follow up If patient is symptomatic then all of the above and consider emergency room assessment.

mmHg - millimeters of mercury; HFrEF – heart failure reduced ejection fraction; SBP – systolic blood pressure.

APPENDIX 3. Additional details regarding patient training, how nurses and physicians delivered virtual care, and how devices were returned

The initial patient training on use of the tablet and devices took approximately 35 to 40 minutes. Whenever possible, patients' family members were encouraged to participate.

The registered nurses and physicians delivered care from the hospital sites. At each site, nurses were stationed in specially designated virtual care spaces, outfitted with workstations for the nurses. The nurses worked in scheduled teams in order to facilitate nursing coverage 24 hours a day, 7 days per week. Nurse-to-nurse handover of patient care in the trial was orchestrated similar to how ward nurses transfer patient accountability. The nurses worked in 8 to 12 hours shifts, with the nurses on each shift giving verbal report on their patients to the next oncoming nurse. The nurses also completed a standardized, written nurse-to-nurse transfer of accountability report, which summarized key patient issues. The on-call perioperative physicians were connected with the patients and nurses through the Cloud DX connected health Zoom interface; they could log in to the system through the Cloud DX secure remote access portal.

Hospital-to-home handling and processing of the Cloud DX Connected Health kits was as follows. Patients decided if they would personally deliver the kit back to the hospital or if they wanted it couriered back to the hospital. If they wanted it couriered, the patient was given a pre-paid courier slip. At the end of the 30-day intervention period, patients either called the courier to facilitate kit pick up at their home, or they brought the kit to the nearest courier depot for delivery back to the hospital. Patients and families were oriented to these procedures at the start of their participation in the trial. Once kits were returned, study personnel would clean them

according to procedures approved by hospital site infection control, take inventory to ensure all components were accounted for and working, and repackage the kit for the next trial patient.

APPENDIX 4. Rationale for changing the primary outcome

The initial primary outcome was acute-hospital care. One of the first patients randomised to the virtual care group was an elderly male who was detected to have significant bradycardia based on his remote automated monitoring (RAM) data, on day 2 post randomisation. When the nurse attempted to contact the patient, the patient's wife answered and indicated that the patient had told her that he was exhausted and wanted to be left alone to sleep for the rest of the day. The nurse escalated care to the perioperative physician who contacted the wife and insisted on talking to the patient. Upon interacting with the patient, the perioperative care physician recognised the patient had a decreased level of consciousness and facilitated having an ambulance bring the patient to the hospital. The patient was brought to the hospital and was found to be in complete heart block and received an emergency pacemaker. This case made us recognise that our detection and management of this patient resulted in an acute-hospital care event. In contrast, if a similar patient in the control group died at home, this would create a competing-outcomes problem in that this patient would not be able to meet the primary outcome. We therefore decided to change the primary outcome to days alive at home to avoid the potential competing-outcomes problem identified in this case.

APPENDIX 5. Secondary and tertiary outcomes

Secondary outcomes during the first 30 days after randomisation included: 1. acute-hospital care; 2. brief acute-hospital care; 3. hospital re-admission; 4. emergency department visit; 5. urgent-care centre visit; 6. all-cause hospital days; 7. medication error detection; 8. medication error correction; and 9. death. Pain at 7, 15, and 30 days after randomisation was also a secondary outcome.

Tertiary outcomes during the first 30 days after randomisation included: 1. health services utilisation-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.

APPENDIX 6. Outcome definitions

Outcome	Definition
Days alive at home	Days alive at home were the number of days patients spent 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 lost days alive at home if 1. patients went to an emergency department or urgent-care centre; 2. they became inpatients at a hospital or rehabilitation or convalescence-care facility; or 3. they died. More specifically, our approach to calculating days alive at home follows. If a patient visited an emergency department or urgent-care centre anytime between midnight and 23:59 on a given day, they lost that day as a day alive at home. If a patient visited an emergency department or urgent-care centre anytime between midnight and 23:59 on a given day and they remained in the emergency department or urgent-care centre past midnight into the next day, then they lost 2 days alive at home. If a patient was admitted to the hospital or rehabilitation or convalescence-care facility anytime between midnight and 23:59 on a given day, they lost that day as a day alive at home. They continued to lose days alive at home until the day in which they were home and out of acute-hospital care or a rehabilitation or convalescence-care facility from midnight for an entire day. Patients randomised before hospital discharge did not lose this day alive at home unless after their discharge they died or visited an emergency department or urgent-care centre on the day of their discharge. Patients randomised before hospital discharge lost this day alive at home if their discharge was ultimately delayed and they did not go home on their day of randomisation. Because patients were followed until day 30 after randomisation and the day of randomisation was day 0, if a patient was discharged home after randomisation and remained at home until death on day 2 after randomisation (i.e., they survived at home on the day of randomisation and day 1 after randomisation, but died on the subsequent day) they were counted as having had 2 day alive at home, and lost 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 was a composite outcome of hospital re-admission and emergency department or urgent-care centre visit.
Brief acute-hospital care	Acute-hospital care that lasted <24 hours from the time of arrival to the time of discharge home.
All-cause hospital days	If a patient was admitted to the hospital for any reason anytime between midnight and 23:59 on a given day, this counted as a day in hospital. Study personnel determined the total number of days in the hospital for any reason. Patients randomised before hospital discharge did not have this day counted as a hospital day unless after their discharge they were re-admitted to the hospital on the day of their discharge. Patients randomised before hospital discharge had this day counted as a hospital day if their discharge was ultimately delayed and they do not go home on their day of randomisation.
Medication error detection	Medication errors included 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 included: drug omission (i.e., patient did not take a drug they were supposed to take), drug commission (i.e., patient took a drug they were not supposed to take), duration error, dosing error, frequency error, route error, and timing error. We recorded all drug errors identified and also reported whether they resulted in harm. We used the following definitions for harm: 1. no harm – error that did not cause any clinically appreciable harm to the patient; 2. minor harm – error that led to event resulting in minor treatment or extra monitoring to ensure significant harm was 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 led to event requiring treatment or extra monitoring and caused 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 led to event that required treatment or extra monitoring and resulted 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 hospitalisation); and 5. death – error leading to loss of life.
Medication error correction	Any medication error that was corrected.
Death	The definition of death was all-cause mortality.
Pain	Study personnel collected pain data through administration of the Brief Pain Inventory Short Form (BPI-SF), which captured pain intensity as well as pain-related interference with daily activity related to their surgery. The BPI-SF includes four 11-point numeric rating scales (NRS) of pain intensity, which measured "average", "least", and "worst" pain intensity in the past 24 hours (hrs.), as well as pain intensity "now" (0= no pain, 10= pain as bad as you can imagine). The BPI-SF interference subscale was also used, which measured the degree to which pain interfered 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 pain-related interference score was determined by calculating the sum of these 7 items.
Health services utilisation-related costs	Data on hospital re-admission, healthcare utilisation, and costs of health service utilisation will be obtained from the *Institute for Clinical Evaluative Sciences* (ICES) data repository. Administrative databases used to describe the health service utilisation include: 1. Registered Persons Database (RPDB) – demographics and vital statistics of all legal residents of Ontario; 2. Discharge Abstract Database – records of inpatient hospitalisations 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., nurses), costs of health providers' time will be captured in the system reporting. Costs of health providers' time on the Cloud DX Connected Health mobile application will be calculated by multiplying the time with unit costs from standard costing sources in Ontario.
Patient-level cost of recovery	The Ambulatory and Home Care Record (AHCR) will be used to comprehensively measure patient-level costs of illness from a societal perspective. This approach gives equal consideration to health system costs and costs borne by patients and unpaid

	caregivers (e.g., family members, friends). AHCR items can be categorised as publicly financed (e.g., public sector paid resources) or privately financed care (e.g., all out-of-pocket and third-party insurance payments, and time costs incurred by caregiver). Face validity and reliability of the AHCR is well established in multiple groups, including surgical patients.
Re-operation	Re-operation refers to any surgical procedure undertaken for any reason (e.g., wound dehiscence, infection).
Arrhythmia resulting in electrical cardioversion	Any arrhythmia that led to electrical cardioversion.
Acute renal failure resulting in dialysis	This outcome was defined as acute renal failure that resulted in dialysis (i.e., use of hemodialysis machine or peritoneal dialysis apparatus) in a patient who was not on chronic dialysis before randomisation.
Respiratory failure	Patient intubated or put on bilevel positive airway pressure ventilation (BiPAP).
Infection	Infection was 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 was an infection that involved 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 was bleeding that was fatal, or led to: significant hypotension that required inotrope or vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.
Major bleeding	Major bleeding was defined as bleeding that was not specified under "life- threatening bleeding" and resulted 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. led to one of the following interventions: embolisation, superficial vascular repair, nasal packing.
Critical-organ bleeding	Critical-organ bleeding was bleeding that was intracranial, intraocular, intraspinal, pericardial, retroperitoneal, or intramuscular with compartment syndrome.

Ileus	Ileus was a physician diagnosis of functional obstruction of the gastrointestinal tract in the absence of an alternative diagnosis that led to postoperative decreased bowel activity. The definition required the following criteria: 1. inability to pass flatus or stool for >24 hours; and 2. persistence of one or more of the following signs and symptoms for >24 hours: abdominal distention; diffuse abdominal pain; or nausea or vomiting.
Myocardial infarction	The diagnosis of myocardial infarction required 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; E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or 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 was 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 were elevated and 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 demonstrating new loss of viable myocardium or new regional wall motion abnormality were 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 in the first 48 hours after surgery was 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 embolisation, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. 6. For patients who were believed to have suffered a myocardial infarction within 28 days of a myocardial injury after noncardiac surgery (MINS) event or within 28 days of a prior myocardial infarction, the following criterion for myocardial infarction was 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 ≥30 milliseconds; C. new or presumed new 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; E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or F. identification of intracoronary thrombus on angiography or autopsy.
Clinically important atrial fibrillation	The definition of clinically important atrial fibrillation required 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 resulted in angina, congestive heart failure, symptomatic hypotension, or required treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
Symptomatic proximal venous thrombo-embolism	Venous thromboembolism included symptomatic pulmonary embolism or symptomatic proximal deep vein thrombosis.
Symptomatic pulmonary embolism	The diagnosis of symptomatic pulmonary embolism required 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) required: 1. symptoms or signs that suggested 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 defined evidence of vein thrombosis: A. a persistent intraluminal filling defect on contrast venography (including on computed tomography); B. non-compressibility 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 could not have compressibility assessed (e.g., iliac, inferior vena cava, subclavian).
Stroke	Stroke was defined as either: 1. a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting ≥24 hours or leading to death; or 2. a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting <24 hours with positive neuroimaging consistent with a stroke.
Non-fatal cardiac arrest	Non-fatal cardiac arrest was 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 required 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 was defined as an indwelling device inappropriately left in a bodily organ or passage longer than it was intended.
COVID-19 infection	For COVID-19 infection, we accepted any laboratory confirmed evidence of COVID-19 infection.
Delirium	For the diagnosis of delirium within 30 days after randomisation, any one of the following criteria were required: 1. Patient met the criteria for ongoing delirium on day 31 at the in-person or telephone 3D-CAM administered on day 31; OR 2. Patient was unable to complete the telephone interview on day 31 because they are too confused. This criterion was significant for an acute decline in their cognition when patients were able to complete telephone interviews at baseline, which was consistent with one of our eligibility criteria; OR 3. Positive history of delirium in the 30 days after randomisation as assessed through a telephone interview with a family member/caregiver using the FAM-CAM on day 31; OR 4. Positive history of delirium in the 30 days after randomisation based on the review of electronic hospital health records.
Surgeon, family physician, or specialist in-person clinic visit	Patient had an in-person visit with a surgeon, family physician, or specialist.
Surgeon, family physician, or specialist virtual clinic visit	Patient had a virtual clinical visit with a surgeon, family physician, or specialist.
Sepsis	Our definition of sepsis was based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Sepsis requires a quick Sequential Organ Failure Assessment (qSOFA) Score ≥2 points due to infection. The qSOFA includes the following items and scoring system: 1. altered mental status (1 point); 2. systolic blood pressure ≤100 mm Hg (1 point); and 3. respiratory rate ≥22 breaths per minute (1 point).

Acute heart failure	The definition of acute heart failure required 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.

APPENDIX 7. Follow-up process

If study personnel were unsuccessful in contacting patients, they contacted their primary care physician or one of the two close relatives or friends not residing with the patient, whose contact information the patient provided at the time of enrollment. If patients (or next-of-kin) indicated that they had experienced an outcome, study personnel contacted their physicians to obtain documentation.

Study personnel contacted study patients in both treatment groups at 31 days after randomisation and collected 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. arrhythmia 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; 20. symptomatic proximal venous thrombo-embolism; 21. stroke; 22. non-fatal cardiac arrest; 23. clostridium difficile-associated diarrhea; and 24. indwelling device inappropriately left in patient. Study personnel also collected pain data through the Brief Pain Inventory-Short Form (BPI-SF) in all study patients in both treatment groups at 6 months after randomisation.

Study personnel contacted patients in the standard-care group and collected data on the following outcomes: 1. BPI-SF on days 7, 15, and 30; and 2. medication error detection and medication error corrections on day 31 after randomisation. For patients in the virtual care and RAM group, nurses collected data on the following outcomes: 1. the BPI-SF on days 7, 15, and

30 after randomisation; and 2. medication error detection and medication error corrections on days 1, 8, 15, 22, and 30 after randomisation.

At 6 months after randomization, study personnel contacted patients to obtain data on days alive at home.

APPENDIX 8. Sample size

When we initially designed PVC-RAM-1, the sample size was prospectively based upon the original primary outcome of acute-hospital care at 30-days after randomisation. We determined that enrollment of 900 patients would give the trial 98% power to detect a relative risk of 0.60 in the virtual care with remote automated monitoring (RAM) group, at a two-sided alpha level of 0.05, on the assumption that the rate of acute-hospital care in the standard-care group would be 25%.

When we changed the primary outcome to days alive at home, we undertook analyses to determine if our sample size of 900 patients remained adequate. Using data from an international, 40,000 patient, prospective, cohort study that our group undertook (i.e., the VISION Study),[1] we estimated that patients in the control group would have on average 29.60 days alive at home, of 31 potential days. We then calculated that if, on average, virtual care with RAM resulted in 29.81 days alive at home, we would have 89% power based on a sample size of 450 patients in each study group. An additional 0.21 days alive at home (i.e., the difference between the two study groups) in the virtual care with RAM group corresponds to an additional day alive and out of hospital for each 5 patients assigned to virtual care with RAM, which we viewed as clinically relevant. 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 had 89%-99% power. Our calculations were based on comparing the means of two independent Poisson distributions, using the relevant subroutine in PASS v13.0 software.

APPENDIX 9. Pre-randomisation variables known to be associated with acute-hospital care after discharge post-surgery and adjusted for in models

Pre-randomisation independent variables known to be associated with acute-hospital care after discharge post-surgery and adjusted for in models included: age, sex, active cancer, requiring assistance with activities of daily living, and the following index hospitalisation complications before randomisation: myocardial infarction, bleeding (i.e., life-threatening, major, or critical organ bleeding), pulmonary embolism, and infection.

Figure Legend.

Figure 1. Cloud DX Connected Health kit

Bluetooth-enabled Pulsewave wrist cuff blood pressure monitor, body-weight scale and wireless oximeter, and temperature probe, paired with Android Health Tablet

Figure 2. Subgroup analyses of the primary outcome*

* days alive at home up to 30 days after randomisation
† patients who during their index hospitalisation before randomisation had one or more of the following complications: cardiac (i.e., myocardial infarction, non-fatal cardiac arrest), bleeding (i.e., life-threatening, major, or critical organ bleeding), venous thromboembolism (i.e., deep vein thrombosis or pulmonary embolism), infection, and sepsis

Figure 1: Cloud DX Connected Health kit

Figure 2. Subgroup analyses of the primary outcome*

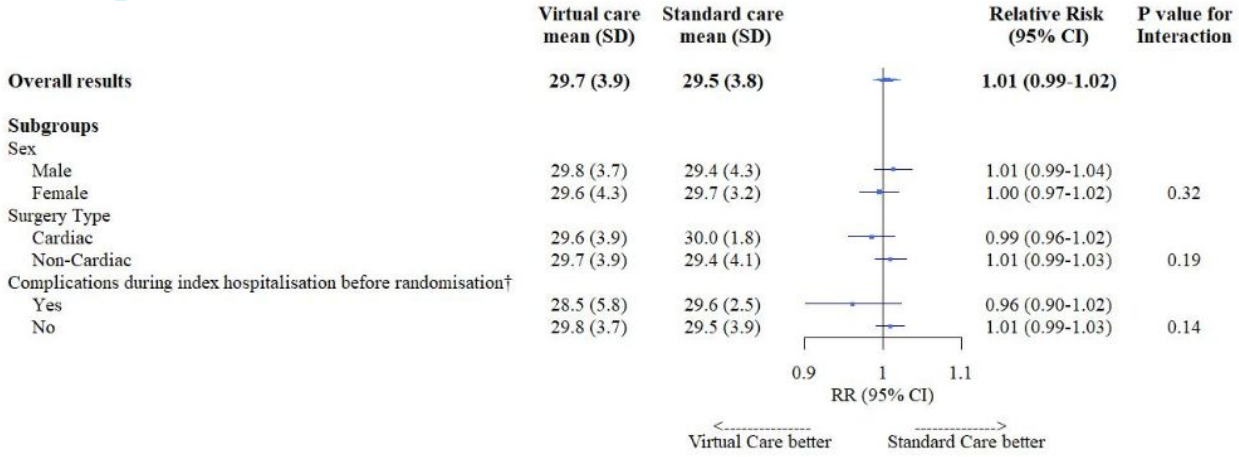

Table 1. Subtypes of surgery patients underwent

Characteristics	Virtual-care group (N=451)	Standard-care group (N=454)
Type of surgery* – no. (%)		
Non-cardiac	366 (81.2)	366 (80.6)
General	146 (32.4)	130 (28.6)
other intra-abdominal	38 (8.4)	24 (5.3)
complex visceral resection	35 (7.8)	26 (5.7)
partial or total colectomy or stomach surgery	33 (7.3)	32 (7.0)
cholecystectomy	28 (6.2)	33 (7.3)
incarcerated hernia, perforated appendectomy or small bowel resection	33 (7.3)	27 (5.9)
major head and neck resection for non-thyroid tumor	8 (1.8)	5 (1.1)
other	4 (0.9)	2 (0.4)
Urology/gynecology	81 (18.0)	91 (20.0)
radical prostatectomy	24 (5.3)	16 (3.5)
radical hysterectomy	23 (5.1)	20 (4.4)
nephrectomy (partial or complete)	13 (2.9)	19 (4.2)
bilateral salpingo-oopherectomy	10 (2.2)	13 (2.9)
cystectomy	10 (2.2)	10 (2.2)
transurethral resection of bladder tumor	4 (0.9)	7 (1.5)
nephrostomy/ureteric stent/ileal conduit	2 (0.4)	6 (1.3)
transurethral prostatectomy	2 (0.4)	5 (1.1)
penectomy/vulvectomy	1 (0.2)	5 (1.1)
cystoscopy	2 (0.4)	4 (0.9)
cytoreductive	0 (0.0)	2 (0.4)
other	12 (2.7)	10 (2.2)
Orthopedic	62 (13.7)	68 (15.0)
major hip	13 (2.9)	17 (3.7)
open reduction internal fixation (excludes hip)	7 (1.6)	5 (1.1)
knee surgery	5 (1.1)	3 (0.7)
pelvic surgery	1 (0.2)	5 (1.1)
ankle surgery	2 (0.4)	4 (0.9)
internal fixation of femur	4 (0.9)	1 (0.2)
spine surgery	3 (0.7)	3 (0.7)
tumor resection	3 (0.7)	2 (0.4)
knee arthroplasty	1 (0.2)	3 (0.7)
lower leg amputation	3 (0.7)	1 (0.2)
shoulder surgery	2 (0.4)	2 (0.4)
above knee amputation(s)	1 (0.2)	1 (0.2)
other	9 (2.0)	5 (1.1)
neurosurgery	30 (6.7)	31 (6.8)
spine surgery	23 (5.1)	19 (4.2)
craniotomy	7 (1.6)	11 (2.4)
shunt surgery	0 (0.0)	2 (0.4)
vascular	22 (4.9)	25 (5.5)
peripheral vascular reconstruction	12 (2.7)	14 (3.1)
endovascular abdominal aortic aneurysm repair	2 (0.4)	5 (1.1)

extracranial cerebrovascular surgery	4 (0.9)	3 (0.7)
aorto-iliac reconstruction	3 (0.7)	2 (0.4)
thoracic aorta reconstruction	1 (0.2)	1 (0.2)
thoracic	23 (5.1)	17 (3.7)
lobectomy	13 (2.9)	12 (2.6)
wedge resection	6 (1.3)	3 (0.7)
thoracotomy	4 (0.9)	1 (0.2)
other	8 (1.8)	5 (1.1)
plastic	10 (2.2)	6 (1.3)
major plastic	7 (1.6)	6 (1.3)
minor plastic	4 (0.9)	0 (0.0)
other	10 (2.2)	15 (3.3)
Cardiac	89 (19.7)	89 (19.6)
coronary artery bypass grafting	69 (15.3)	75 (16.5)
on pump	69 (15.3)	74 (16.3)
off pump	0 (0.0)	1 (0.2)
valve	28 (6.2)	19 (4.2)
aortic	19 (4.2)	13 (2.9)
mitral	10 (2.2)	5 (1.1)
other	0 (0.0)	2 (0.4)
aortic	12 (2.7)	6 (1.3)
atherectomy	5 (1.1)	6 (1.3)
other	7 (1.6)	7 (1.5)

no. = number; % = percentage

* Some patients had more than one type of surgery or multiple surgeries within the same subtype. Therefore, sums of subtypes of surgery and surgical procedures surpass total number of patients.

Table 2. Compliance with virtual care and remote automated monitoring intervention

	All patients in the virtual-care group (N=451)	Virtual-care patients in centres with highest escalation of care (n=177)	Virtual-care patients in centres with intermediate escalation of care (n=189)	Virtual-care patients in centres with lowest escalation of care (n=85)	P value*
Number of scheduled visits between patient and nurse – mean (SD)	22.8 (1.2)	22.8 (1.2)	22.8 (1.3)	23.0 (0)	0.17
Number of completed visits between patient and nurse – mean (SD)	19.7 (6.3)	20.2 (5.7)	20.0 (6.0)	17.7 (7.7)	<0.001
Number of scheduled wound photos – mean (SD)	22.4 (2.7)	22.3 (2.9)	22.4 (3.0)	22.7 (1.0)	0.36
Number of completed wound photos – mean (SD)	15.0 (7.7)	15.3 (7.4)	15.5 (7.7)	13.0 (8.2)	0.02
Number of scheduled days to use RAM – mean (SD)	29.5 (1.9)	29.7 (2.0)	29.6 (1.7)	29.2 (2.3)	0.06
Number of days in which RAM data was obtained – mean (SD)	24.3 (9.6)	24.7 (9.6)	25.5 (8.6)	20.7 (10.7)	<0.001

RAM = remote automated monitoring technology, SD = standard deviation

* Compliance in terms of different virtual care and remote automated parameters were compared among the different centres based on their escalation of care using ANOVA.

Table 3. Drug errors and corrections

Outcome	Virtual-care group (N=451)	Standard-care group (N=454)	Relative Risk* (95% CI)	Absolute difference % (95% CI)	P Value
Medication errors					
Patients detected to have medication error – no. (%)	134 (29.7)	25 (5.5)	5.29 (3.52-7.93)	24.2 (19.5-28.9)	<0.001
Total number of detected medication errors – no.	286	44			
Type of medication error					
Patients with drug omission error – no. (%)	82 (18.2)	16 (3.5)	5.16 (3.07-8.67)	14.7 (10.7-18.6)	<0.001
Total number of drug omission errors – no.	173	28			
Patients with drug dosing error – no. (%)	43 (9.5)	5 (1.1)	8.66 (3.46-21.66)	8.4 (5.6-11.3)	<0.001
Total number of drug dosing errors – no.	52	5			
Patients with drug commission error – no. (%)	20 (4.4)	1 (0.2)	20.13 (2.71-149.38)	4.2 (2.3-6.2)	<0.001
Total number of drug commission errors – no.	28	1			
Patients with drug frequency error – no. (%)	21 (4.7)	1 (0.2)	21.14 (2.86-156.49)	4.4 (2.4-6.4)	<0.001
Total number of drug frequency errors – no.	25	1			
Patients with drug duration error – no. (%)	6 (1.3)	8 (1.8)	0.75 (0.26-2.16)	-0.4 (-2.0-1.2)	0.60
Total number of drug duration errors – no.	7	9			
Reason missing – no.	1	0			
Impact of medication error					
Patients with drug error and no harm – no. (%)	124 (27.5)	22 (4.8)	5.67 (3.68-8.76)	22.6 (18.1-27.2)	<0.001
Total number of drug errors with no harm – no.	263	40			
Patients with drug error and minor harm – no. (%)	16 (3.5)	4 (0.9)	4.03 (1.36-11.95)	2.7 (0.8-4.6)	0.007
Total number of drug errors with minor harm – no.	20	4			
Patients with drug error and moderate harm – no. (%)	3 (0.7)	0 (0.0)	-	0.7 (-0.1-1.4)	0.12
Total number of drug errors with moderate harm – no.	3	0			
Correction of medication errors					
Patients with medication error corrections – no. (%)	128 (28.4)	18 (4.0)	7.01 (4.36-11.27)	24.4 (19.9-28.9)	<0.001
Total number of medication error corrections – no.	238	33			

Who corrected medication error					
Patients who had a physician/nurse correct error – no. (%)	102 (22.6)	6 (1.3)	17.11 (7.59-38.58)	21.3 (17.3-25.3)	<0.001
Total number or medication errors corrected by a physician/nurse – no.	173	9			
Patients who had error corrected by themselves or family – no. (%)	28 (6.2)	7 (1.5)	4.03 (1.78-9.12)	4.7 (2.2-7.2)	<0.001
Total number of medication errors corrected by patient or Family – no.	42	16			
Patients who had error resolve on its own – no. (%)	10 (2.2)	5 (1.1)	2.01 (0.69-5.84)	1.1 (-0.5-2.8)	0.19
Total number of medication errors resolved on its own-no.	14	7			
Patients who had error corrected by others – no. (%)	2 (0.4)	1 (0.2)	2.01 (0.18-22.12)	0.2 (-0.5-1.0)	0.62
Total number of medication errors corrected by others	2	1			
Patients with missing data – no. (%)	2 (0.4)	0 (0.0)	-	0.4 (-0.2-1.1)	0.25
Total number of medication errors with missing data- no	7	0			

no. = number; % = percentage

* For the type of medication error, impact of medication error, and who corrected medication error the relative risk and absolute differences were calculated from the crude proportions. P values were obtained from the Chi-squared or Fischer's exact test.

Table 4. Most responsible person for drug error and reason for drug error

	Virtual-care group (N=451)	Standard-care group (N=454)	P Value
Patients with a drug error – no. (%)	134 (29.7)	25 (5.5)	<0.001
Most responsible person for drug error* - no.			
patient	218	38	
physician/nurse	58	3	
pharmacist	9	3	
unknown	1	0	
Primary reason for drug error made by patient – no.			
intentional patient decision	96	22	
mistake	55	3	
forgot	20	9	
financial barrier	21	1	
did not fill prescription for non-financial reasons	12	1	
intolerance/side effect	10	2	
unknown	4	0	
Primary reason for drug error made by physician/nurse – no.			
failure to communicate clearly what medications patients should or should not take at home	32	1	
failure to write prescription for new medication	19	2	
failure to write prescription to discontinue medication	4	0	
unknown	3	0	
Primary reason for drug error made by pharmacist – no.			
did not provide medication as prescribed	9	3	

no. = number; % = percentage

* Some patients had multiple medication errors. Therefore, sums of most responsible person for error and primary reason for error surpass total number of patients with a medication error.

Table 5: Effects of virtual care and remote automated monitoring on moderate to severe pain and pain-related interference

Outcome	Virtual-care group* (N=451)	Standard-care group* (N=454)	Relative risk (95% CI)	Absolute difference % (95% CI)	P Value
Moderate or severe pain – no./total no. (%)					
at worst in last 24 hours while laying down					
at 7 days after randomisation	118/386 (30.6)	156/425 (36.7)	0.83 (0.68-1.01)	6.1 (-0.4-12.6)	0.06
at 15 days after randomisation	84/402 (20.9)	111/414 (26.8)	0.78 (0.61-1.00)	5.9 (0.1-11.7)	0.04
at 30 days after randomisation	60/411 (14.6)	84/413 (20.3)	0.72 (0.53-0.97)	5.7 (0.5-10.9)	0.03
at worst in last 24 hours while moving					
at 7 days after randomisation	138/386 (35.8)	173/425 (40.7)	0.88 (0.74-1.05)	4.9 (-1.8-11.6)	0.15
at 15 days after randomisation	101/402 (25.1)	135/414 (32.6)	0.77 (0.62-0.96)	7.5 (1.3-13.7)	0.02
at 30 days after randomisation	71/411 (17.3)	102/413 (24.7)	0.70 (0.53-0.92)	7.4 (1.9-12.9)	0.009
Pain-related interference score† – no. /total no. (%)					
moderate or severe					
at 7 days after randomisation	73/386 (18.9)	121/425 (28.5)	0.66 (0.51-0.85)	9.6 (3.8-15.4)	0.001
at 15 days after randomisation	65/402 (16.2)	88/414 (21.3)	0.76 (0.57-1.02)	4.1 (-0.2-10.4)	0.06
at 30 days after randomisation	44/411 (10.7)	64/413 (15.5)	0.69 (0.48-0.99)	4.8 (0.2-9.4)	0.04

no. = number; % = percentage

* in the virtual care group 85.6%, 89.1%, 91.1% of patients provided pain data at 7, 15, and 30 days after randomisation, respectively. In the standard-care group 93.6%, 91.2%, 90.9% of patients provided pain data at 7, 15, and 30 days after randomisation, respectively.

† mean of the mean of the seven pain-related interference items: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. A score of 0 represented no pain-related interference and 10 represented complete interference. A moderate or severe pain-related interference score was ≥4.

Table 6: Pain medication usage at 30-days after randomisation

Drug	Virtual-care group (N=451)	Standard-care group (N=454)	Relative usage (95% CI)	Absolute difference % (95% CI)	P Value*
Acetaminophen					
Usage before index hospitalisation – no. /total no. (%)	95/451 (21.1)	89/454 (19.6)	1.08 (0.83-1.40)	1.5 (-3.8 -6.8)	
Usage at hospital discharge after surgery – no. /total no. (%)	233/449 (51.9)	205/454 (45.2)	1.15 (1.00-1.32)	6.7 (0.2-13.2)	<0.001
Usage at 30-days after randomisation – no. /total no. (%)	218/420 (51.9)	119/446 (26.7)	1.94 (1.62-2.32)	25.2 (18.8-31.6)	
NSAID					
Usage before index hospitalisation – no. /total no. (%)	51/451 (11.3)	40/454 (8.8)	1.28 (0.86-1.90)	2.5 (-1.4 -6.4)	
Usage at hospital discharge after surgery – no. /total no. (%)	75/449 (16.7)	67/454 (14.8)	1.13 (0.83-1.53)	1.9 (-2.9 -6.7)	0.25
Usage at 30-days after randomisation – no. /total no. (%)	69/420 (16.4)	41/446 (9.2)	1.78 (1.24-2.56)	7.2 (2.7-11.7)	
Opioids					
Usage before index hospitalisation – no. /total no. (%)	69/451 (15.3)	56/454 (12.3)	1.24 (0.89-1.72)	3.0 (-1.5 -7.5)	
Usage at hospital discharge after surgery – no. /total no. (%)	330/449 (73.5)	328/454 (72.2)	1.02 (0.94-1.10)	1.3 (-4.5-7.1)	0.35
Usage at 30-days after randomisation – no. /total no. (%)	86/420 (20.5)	63/446 (14.1)	1.45 (1.08-1.95)	6.4 (1.3-11.5)	
GABA analogue					
Usage before index hospitalisation – no. /total no. (%)	29/451 (6.4)	26/454 (5.7)	1.12 (0.67-1.87)	0.7 (-2.4 -3.8)	
Usage at hospital discharge after surgery – no. /total no. (%)	48/449 (10.7)	33/454 (7.3)	1.47 (0.96-2.25)	3.4 (-0.3-7.1)	0.65
Usage at 30-days after randomisation – no. /total no. (%)	46/420 (11.0)	31/446 (7.0)	1.57 (1.02-2.43)	4.0 (0.1-7.9)	
Cannabinoid					
Usage before index hospitalisation – no. /total no. (%)	22/451 (4.9)	7/454 (1.5)	3.27 (1.41-7.58)	3.4 (1.1-5.7)	
Usage at hospital discharge after surgery – no. /total no. (%)	19/449 (4.2)	7/454 (1.5)	2.80 (1.19-6.60)	2.7 (0.5-4.9)	0.96
Usage at 30-days after randomisation – no. /total no. (%)	19/420 (4.5)	6/446 (1.3)	3.46 (1.40-8.58)	3.2 (0.9-5.5)	

Any of these pain medications[†]					
Usage before index hospitalisation – no. /total no. (%)	156/451 (34.6)	134/454 (29.5)	1.17 (0.97-1.42)	5.1 (-1.0-11.2)	
Usage at hospital discharge after surgery – no. /total no. (%)	387/449 (86.2)	380/454 (83.7)	1.03 (0.97-1.09)	2.5 (-2.2 -7.2)	0.003
Usage at 30-days after randomisation – no. /total no. (%)	268/420 (63.8)	179/446 (40.1)	1.59 (1.39-1.82)	23.7 (17.1-30.3)	

no. = number; % = percentage; GABA = gamma-aminobutyric acid; NSAID = non-steroidal anti-inflammatory drug

* We compared the use of pain medication between the virtual-care and RAM group versus the standard-care group over time using repeated measures logistic regression.

[†] acetaminophen, NSAID, opioid, or GABA analogue

Table 7: Effects of virtual care and remote automated monitoring on tertiary outcomes at 31-days

Outcome	Virtual-care group (N=451) no. (%)	Standard-care group (N=454) no. (%)	Relative risk (95% CI)	P Value
surgeon, family physician, or specialist in-person clinic visit	268 (59.4)	258 (56.8)	1.04 (0.93-1.16)	0.46
surgeon, family physician, or specialist virtual clinic visit	183 (40.6)	207 (45.6)	0.89 (0.77-1.03)	0.13
surgeon, family physician, or specialist in-person or virtual clinic visit	348 (77.2)	349 (76.9)	1.00 (0.94-1.08)	0.91
infection	55 (12.2)	65 (14.3)	0.87 (0.62-1.21)	0.41
surgical site infection	34 (7.5)	47 (10.4)	0.74 (0.49-1.14)	0.17
re-operation	5 (1.1)	12 (2.6)	0.42 (0.15-1.20)	0.11
life-threatening, major, or critical-organ bleeding	5 (1.1)	3 (0.7)	NR	0.51
clinically important atrial fibrillation	5 (1.1)	3 (0.7)	NR	0.51
stroke	3 (0.7)	2 (0.4)	NR	0.69
acute heart failure	1 (0.2)	3 (0.7)	NR	0.62
symptomatic proximal venous thrombo-embolism	1 (0.2)	3 (0.7)	NR	0.62
myocardial infarction	1 (0.2)	2 (0.4)	NR	1.00
sepsis	1 (0.2)	1 (0.2)	NR	1.00
arrhythmia resulting in electrical cardioversion	2 (0.4)	0 (0)	NR	0.25

delirium	0 (0)	1 (0.2)	NR	0.50
ileus	1 (0.2)	1 (0.2)	NR	1.00
respiratory failure	1 (0.2)	2 (0.4)	NR	1.00
Clostridium difficile-associated diarrhea	1 (0.2)	1 (0.2)	NR	1.00
indwelling device inappropriately left in a patient	1 (0.2)	0 (0)	NR	0.50
acute renal failure resulting in dialysis	1 (0.2)	0 (0)	NR	0.50
non-fatal cardiac arrest	0 (0)	0 (0)	NR	1.00
COVID-19 infection	0 (0)	0 (0)	NR	1.00

NR = not reported, because too few events

Table 8. Variation across centres in frequency of nurse escalation of care to a physician, among patients in the virtual-care and remote automated monitoring group

Centre	Patients with escalation of care no. (%)
Centre 1 (n=75)	66 (88.0)
Centre 2 (n=97)	88 (90.7)
Centre 3 (n=44)	24 (54.5)
Centre 4 (n=5)	4 (80.0)
Centre 5 (n=21)	5 (23.8)
Centre 6 (n=101)	55 (54.5)
Centre 7 (n=44)	24 (54.5)
Centre 8 (n=64)	24 (37.5)

Table 9: Effects of virtual care and remote automated monitoring on tertiary 6-month outcomes

Outcome	Virtual-care group (N=451)	Standard-care group (N=454)	Relative risk* (95% CI)	Absolute difference† % (95% CI)	P Value#
Days alive at home – mean (± SD)	176.7 (25.5)	176.7 (26.1)	1.00 (0.98-1.02)	0.0 (-1.7-1.7) ^	0.59
Acute-hospital care – no. (%)	170 (37.7)	189 (41.6)	0.91 (0.78-1.07)	3.9 (-2.5-10.3)	0.23
Hospital re-admission – no. (%)	101 (22.4)	107 (23.6)	0.97 (0.76-1.22)	1.2 (-4.3-6.7)	0.67
Emergency department visit – no. (%)	151 (33.5)	166 (36.6)	0.92 (0.77-1.10)	3.1 (-3.1-9.3)	0.33
Urgent-care centre visit – no. (%)	7 (1.6)	13 (2.9)	0.54 (0.21-1.35)	1.3 (-0.6-3.2)	0.18
All-cause hospital days (median [IQR])	0 (0-2.0)	0 (0-2.0)	0.89 (0.60-1.33)	0.4 (0.2-0.6) ^	0.58
Death – no. (%)	17 (3.8)	18 (4.0)	0.95 (0.51-1.80)	0.2 (-2.3-2.7)	0.88

CI = confidence interval; IQR = interquartile range; no. = number; SD = standard deviation; % = percentage

* Relative risks and 95% confidence intervals were obtained from Modified Poisson model

† Absolute differences and 95% confidence intervals were calculated from the crude proportions.

^ Absolute rate differences and 95% confidence intervals were determined based on a Normal Approximation to Poisson.

P values are from Wilcoxon, Student's t and Chi-square test

REFERENCE

1. Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study I. Association between complications and death within 30 days after noncardiac surgery. CMAJ 2019;191:E830-E7.

ONLINE-ONLY SUPPLEMENT 3

Supplement Table of Contents

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Coordinating Centre: The Population Health Research Institute – which is part of Hamilton Health Sciences and McMaster University in Hamilton, Ontario, Canada – was the trial coordinating centre and was responsible for the randomisation system, maintenance of the database, data monitoring, analyses, and study-centre coordination.

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Event Adjudication Committee: Flavia K Borges (Chair), Sandra Ofori, Michael Wang, James Khan, Rahima Nenshi, Maura Marcucci, Marko Simunovic.

Data Monitoring Committee: Victor M. Montori (Chair), Finlay McAlister, Kristian Thorlund. The members of the Data Monitoring Committee have expertise in clinical trials, perioperative care, virtual care, and statistics.

APPENDIX 1. Biophysical measurements and recovery survey

Based on a schedule developed by a nurse, the tablet prompted patients to measure their biophysical parameters. The frequency of daily biophysical measurements was 3 times a day for the first 15 days, and then twice a day from day 16 until 30 days after randomisation. Weight was measured daily in the morning before breakfast. Nurses or physicians could adjust the frequency of biophysical measurements and parameters for alerts based on a patient's normal biophysical measurements, acuity, or tolerance. The tablet prompted patients daily to complete the recovery survey. The recovery survey consisted of questions related to infection, bleeding, pain, dehydration, ileus, and cardiovascular and respiratory complications.

APPENDIX 2. Example of vital sign thresholds and recommended nurse and physician actions

SBP measurement	Flag to nurse on CloudDX Connected Health Dashboard	Nurse recommended action	Physician recommended action
100-115 mm Hg	Mild	Nurse to contact and assess patient during scheduled video call. Advise patient to re-check measurement. Nurse to update perioperative care physician, at daily rounds.	Rule out precipitating factors (e.g. sepsis, volume depletion, bleeding, heart failure). Review medication and fluid intake. Decrease blood pressure medication dosage accordingly. Order back to nurse and coordinate follow up with nurse. Reassess in 24 hours.
86-99 mm Hg	Medium	Nurse to contact and assess patient within 30 minutes. Advise patient to re-check measurement. If unresolved, nurse will inform perioperative care physician within 1 hour.	All of the above and the following. Withhold anti-hypertensives until SBP >100 mmHg if patient with no HFrEF. Assess volume status. Order back to nurse and coordinate follow up. Reassess in 4-6 hours
<85 mm Hg	High	Contact and assist patient immediately. Advise patient to re-check measurement. If unresolved, nurse will inform perioperative care physician within 15 minutes.	Assess patient for symptoms. If patient is asymptomatic then all of the above and the following. Withhold anti-hypertensives. Consider video call with patient. Consider clinic assessment. Order back to nurse and coordinate follow up If patient is symptomatic then all of the above and consider emergency room assessment.

mmHg - millimeters of mercury; HFrEF – heart failure reduced ejection fraction; SBP – systolic blood pressure.

APPENDIX 3. Additional details regarding patient training, how nurses and physicians delivered virtual care, and how devices were returned

The initial patient training on use of the tablet and devices took approximately 35 to 40 minutes. Whenever possible, patients' family members were encouraged to participate.

The registered nurses and physicians delivered care from the hospital sites. At each site, nurses were stationed in specially designated virtual care spaces, outfitted with workstations for the nurses. The nurses worked in scheduled teams in order to facilitate nursing coverage 24 hours a day, 7 days per week. Nurse-to-nurse handover of patient care in the trial was orchestrated similar to how ward nurses transfer patient accountability. The nurses worked in 8 to 12 hours shifts, with the nurses on each shift giving verbal report on their patients to the next oncoming nurse. The nurses also completed a standardized, written nurse-to-nurse transfer of accountability report, which summarized key patient issues. The on-call perioperative physicians were connected with the patients and nurses through the Cloud DX connected health Zoom interface; they could log in to the system through the Cloud DX secure remote access portal.

Hospital-to-home handling and processing of the Cloud DX Connected Health kits was as follows. Patients decided if they would personally deliver the kit back to the hospital or if they wanted it couriered back to the hospital. If they wanted it couriered, the patient was given a pre-paid courier slip. At the end of the 30-day intervention period, patients either called the courier to facilitate kit pick up at their home, or they brought the kit to the nearest courier depot for delivery back to the hospital. Patients and families were oriented to these procedures at the start of their participation in the trial. Once kits were returned, study personnel would clean them

according to procedures approved by hospital site infection control, take inventory to ensure all components were accounted for and working, and repackage the kit for the next trial patient.

APPENDIX 4. Rationale for changing the primary outcome

The initial primary outcome was acute-hospital care. One of the first patients randomised to the virtual care group was an elderly male who was detected to have significant bradycardia based on his remote automated monitoring (RAM) data, on day 2 post randomisation. When the nurse attempted to contact the patient, the patient's wife answered and indicated that the patient had told her that he was exhausted and wanted to be left alone to sleep for the rest of the day. The nurse escalated care to the perioperative physician who contacted the wife and insisted on talking to the patient. Upon interacting with the patient, the perioperative care physician recognised the patient had a decreased level of consciousness and facilitated having an ambulance bring the patient to the hospital. The patient was brought to the hospital and was found to be in complete heart block and received an emergency pacemaker. This case made us recognise that our detection and management of this patient resulted in an acute-hospital care event. In contrast, if a similar patient in the control group died at home, this would create a competing-outcomes problem in that this patient would not be able to meet the primary outcome. We therefore decided to change the primary outcome to days alive at home to avoid the potential competing-outcomes problem identified in this case.

APPENDIX 54. Secondary and tertiary outcomes

Secondary outcomes during the first 30 days after randomisation included: 1. acute-hospital care; 2. brief acute-hospital care; 3. hospital re-admission; 4. emergency department visit; 5. urgent-care centre visit; 6. all-cause hospital days; 7. medication error detection; 8. medication error correction; and 9. death. Pain at 7, 15, and 30 days after randomisation was also a secondary outcome.

Tertiary outcomes during the first 30 days after randomisation included: 1. health services utilisation-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.

APPENDIX 65. Outcome definitions

Outcome	Definition
Days alive at home	Days alive at home were the number of days patients spent 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 lost days alive at home if 1. patients went to an emergency department or urgent-care centre; 2. they became inpatients at a hospital or rehabilitation or convalescence-care facility; or 3. they died. More specifically, our approach to calculating days alive at home follows. If a patient visited an emergency department or urgent-care centre anytime between midnight and 23:59 on a given day, they lost that day as a day alive at home. If a patient visited an emergency department or urgent-care centre anytime between midnight and 23:59 on a given day and they remained in the emergency department or urgent-care centre past midnight into the next day, then they lost 2 days alive at home. If a patient was admitted to the hospital or rehabilitation or convalescence-care facility anytime between midnight and 23:59 on a given day, they lost that day as a day alive at home. They continued to lose days alive at home until the day in which they were home and out of acute-hospital care or a rehabilitation or convalescence-care facility from midnight for an entire day. Patients randomised before hospital discharge did not lose this day alive at home unless after their discharge they died or visited an emergency department or urgent-care centre on the day of their discharge. Patients randomised before hospital discharge lost this day alive at home if their discharge was ultimately delayed and they did not go home on their day of randomisation. Because patients were followed until day 30 after randomisation and the day of randomisation was day 0, if a patient was discharged home after randomisation and remained at home until death on day 2 after randomisation (i.e., they survived at home on the day of randomisation and day 1 after randomisation, but died on the subsequent day) they were counted as having had 2 day alive at home, and lost 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 was a composite outcome of hospital re-admission and emergency department or urgent-care centre visit.
Brief acute-hospital care	Acute-hospital care that lasted <24 hours from the time of arrival to the time of discharge home.
All-cause hospital days	If a patient was admitted to the hospital for any reason anytime between midnight and 23:59 on a given day, this counted as a day in hospital. Study personnel determined the total number of days in the hospital for any reason. Patients randomised before hospital discharge did not have this day counted as a hospital day unless after their discharge they were re-admitted to the hospital on the day of their discharge. Patients randomised before hospital discharge had this day counted as a hospital day if their discharge was ultimately delayed and they do not go home on their day of randomisation.
Medication error detection	Medication errors included 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 included: drug omission (i.e., patient did not take a drug they were supposed to take), drug commission (i.e., patient took a drug they were not supposed to take), duration error, dosing error, frequency error, route error, and timing error. We recorded all drug errors identified and also reported whether they resulted in harm. We used the following definitions for harm: 1. no harm – error that did not cause any clinically appreciable harm to the patient; 2. minor harm – error that led to event resulting in minor treatment or extra monitoring to ensure significant harm was 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 led to event requiring treatment or extra monitoring and caused 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 led to event that required treatment or extra monitoring and resulted 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 hospitalisation); and 5. death – error leading to loss of life.
Medication error correction	Any medication error that was corrected.
Death	The definition of death was all-cause mortality.
Pain	Study personnel collected pain data through administration of the Brief Pain Inventory Short Form (BPI-SF), which captured pain intensity as well as pain-related interference with daily activity related to their surgery. The BPI-SF includes four 11-point numeric rating scales (NRS) of pain intensity, which measured "average", "least", and "worst" pain intensity in the past 24 hours (hrs.), as well as pain intensity "now" (0= no pain, 10= pain as bad as you can imagine). The BPI-SF interference subscale was also used, which measured the degree to which pain interfered 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 pain-related interference score was determined by calculating the sum of these 7 items.
Health services utilisation-related costs	Data on hospital re-admission, healthcare utilisation, and costs of health service utilisation will be obtained from the *Institute for Clinical Evaluative Sciences* (ICES) data repository. Administrative databases used to describe the health service utilisation include: 1. Registered Persons Database (RPDB) – demographics and vital statistics of all legal residents of Ontario; 2. Discharge Abstract Database – records of inpatient hospitalisations 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., nurses), costs of health providers' time will be captured in the system reporting. Costs of health providers' time on the Cloud DX Connected Health mobile application will be calculated by multiplying the time with unit costs from standard costing sources in Ontario.
Patient-level cost of recovery	The Ambulatory and Home Care Record (AHCR) will be used to comprehensively measure patient-level costs of illness from a societal perspective. This approach gives equal consideration to health system costs and costs borne by patients and unpaid

	caregivers (e.g., family members, friends). AHCR items can be categorised as publicly financed (e.g., public sector paid resources) or privately financed care (e.g., all out-of-pocket and third-party insurance payments, and time costs incurred by caregiver). Face validity and reliability of the AHCR is well established in multiple groups, including surgical patients.
Re-operation	Re-operation refers to any surgical procedure undertaken for any reason (e.g., wound dehiscence, infection).
Arrhythmia resulting in electrical cardioversion	Any arrhythmia that led to electrical cardioversion.
Acute renal failure resulting in dialysis	This outcome was defined as acute renal failure that resulted in dialysis (i.e., use of hemodialysis machine or peritoneal dialysis apparatus) in a patient who was not on chronic dialysis before randomisation.
Respiratory failure	Patient intubated or put on bilevel positive airway pressure ventilation (BiPAP).
Infection	Infection was 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 was an infection that involved 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 was bleeding that was fatal, or led to: significant hypotension that required inotrope or vasopressor therapy, urgent (within 24 hours) surgery (other than superficial vascular repair), or intracranial hemorrhage.
Major bleeding	Major bleeding was defined as bleeding that was not specified under "life- threatening bleeding" and resulted 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. led to one of the following interventions: embolisation, superficial vascular repair, nasal packing.
Critical-organ bleeding	Critical-organ bleeding was bleeding that was intracranial, intraocular, intraspinal, pericardial, retroperitoneal, or intramuscular with compartment syndrome.

Ileus	Ileus was a physician diagnosis of functional obstruction of the gastrointestinal tract in the absence of an alternative diagnosis that led to postoperative decreased bowel activity. The definition required the following criteria: 1. inability to pass flatus or stool for >24 hours; and 2. persistence of one or more of the following signs and symptoms for >24 hours: abdominal distention; diffuse abdominal pain; or nausea or vomiting.
Myocardial infarction	The diagnosis of myocardial infarction required 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; E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or 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 was 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 were elevated and 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 demonstrating new loss of viable myocardium or new regional wall motion abnormality were 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 in the first 48 hours after surgery was 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 embolisation, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. 6. For patients who were believed to have suffered a myocardial infarction within 28 days of a myocardial injury after noncardiac surgery (MINS) event or within 28 days of a prior myocardial infarction, the following criterion for myocardial infarction was 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 ≥30 milliseconds; C. new or presumed new 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; E. new cardiac wall motion abnormality on echocardiography or new fixed defect on radionuclide imaging; or F. identification of intracoronary thrombus on angiography or autopsy.
Clinically important atrial fibrillation	The definition of clinically important atrial fibrillation required 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 resulted in angina, congestive heart failure, symptomatic hypotension, or required treatment with a rate controlling drug, antiarrhythmic drug, or electrical cardioversion.
Symptomatic proximal venous thrombo-embolism	Venous thromboembolism included symptomatic pulmonary embolism or symptomatic proximal deep vein thrombosis.
Symptomatic pulmonary embolism	The diagnosis of symptomatic pulmonary embolism required 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) required: 1. symptoms or signs that suggested 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 defined evidence of vein thrombosis: A. a persistent intraluminal filling defect on contrast venography (including on computed tomography); B. non-compressibility 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 could not have compressibility assessed (e.g., iliac, inferior vena cava, subclavian).
Stroke	Stroke was defined as either: 1. a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting ≥24 hours or leading to death; or 2. a new focal neurological deficit thought to be vascular in origin with signs or symptoms lasting <24 hours with positive neuroimaging consistent with a stroke.
Non-fatal cardiac arrest	Non-fatal cardiac arrest was 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 required 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 was defined as an indwelling device inappropriately left in a bodily organ or passage longer than it was intended.
COVID-19 infection	For COVID-19 infection, we accepted any laboratory confirmed evidence of COVID-19 infection.
Delirium	For the diagnosis of delirium within 30 days after randomisation, any one of the following criteria were required: 1. Patient met the criteria for ongoing delirium on day 31 at the in-person or telephone 3D-CAM administered on day 31; OR 2. Patient was unable to complete the telephone interview on day 31 because they are too confused. This criterion was significant for an acute decline in their cognition when patients were able to complete telephone interviews at baseline, which was consistent with one of our eligibility criteria; OR 3. Positive history of delirium in the 30 days after randomisation as assessed through a telephone interview with a family member/caregiver using the FAM-CAM on day 31; OR 4. Positive history of delirium in the 30 days after randomisation based on the review of electronic hospital health records.
Surgeon, family physician, or specialist in-person clinic visit	Patient had an in-person visit with a surgeon, family physician, or specialist.
Surgeon, family physician, or specialist virtual clinic visit	Patient had a virtual clinical visit with a surgeon, family physician, or specialist.
Sepsis	Our definition of sepsis was based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Sepsis requires a quick Sequential Organ Failure Assessment (qSOFA) Score ≥2 points due to infection. The qSOFA includes the following items and scoring system: 1. altered mental status (1 point); 2. systolic blood pressure ≤100 mm Hg (1 point); and 3. respiratory rate ≥22 breaths per minute (1 point).

Acute heart failure	The definition of acute heart failure required 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.

APPENDIX 76. Follow-up process

If study personnel were unsuccessful in contacting patients, they contacted their primary care physician or one of the two close relatives or friends not residing with the patient, whose contact information the patient provided at the time of enrollment. If patients (or next-of-kin) indicated that they had experienced an outcome, study personnel contacted their physicians to obtain documentation.

Study personnel contacted study patients in both treatment groups at 31 days after randomisation and collected 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. arrhythmia 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; 20. symptomatic proximal venous thrombo-embolism; 21. stroke; 22. non-fatal cardiac arrest; 23. clostridium difficile-associated diarrhea; and 24. indwelling device inappropriately left in patient. Study personnel also collected pain data through the Brief Pain Inventory-Short Form (BPI-SF) in all study patients in both treatment groups at 6 months after randomisation.

Study personnel contacted patients in the standard-care group and collected data on the following outcomes: 1. BPI-SF on days 7, 15, and 30; and 2. medication error detection and medication error corrections on day 31 after randomisation. For patients in the virtual care and RAM group, nurses collected data on the following outcomes: 1. the BPI-SF on days 7, 15, and

30 after randomisation; and 2. medication error detection and medication error corrections on days 1, 8, 15, 22, and 30 after randomisation.

At 6 months after randomization, study personnel contacted patients to obtain data on days alive at home.

APPENDIX 8~~7~~. Sample size

When we initially designed PVC-RAM-1, the sample size was prospectively based upon the original primary outcome of acute-hospital care at 30-days after randomisation. We determined that enrollment of 900 patients would give the trial 98% power to detect a relative risk of 0.60 in the virtual care with remote automated monitoring (RAM) group, at a two-sided alpha level of 0.05, on the assumption that the rate of acute-hospital care in the standard-care group would be 25%.

When we changed the primary outcome to days alive at home, we undertook analyses to determine if our sample size of 900 patients remained adequate. Using data from an international, 40,000 patient, prospective, cohort study that our group undertook (i.e., the VISION Study),[1] we estimated that patients in the control group would have on average 29.60 days alive at home, of 31 potential days. We then calculated that if, on average, virtual care with RAM resulted in 29.81 days alive at home, we would have 89% power based on a sample size of 450 patients in each study group. An additional 0.21 days alive at home (i.e., the difference between the two study groups) in the virtual care with RAM group corresponds to an additional day alive and out of hospital for each 5 patients assigned to virtual care with RAM, which we viewed as clinically relevant. 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 had 89%-99% power. Our calculations were based on comparing the means of two independent Poisson distributions, using the relevant subroutine in PASS v13.0 software.

APPENDIX 9. Pre-randomisation variables known to be associated with acute-hospital care after discharge post-surgery and adjusted for in models

Pre-randomisation independent variables known to be associated with acute-hospital care after discharge post-surgery and adjusted for in models included: age, sex, active cancer, requiring assistance with activities of daily living, and the following index hospitalisation complications before randomisation: myocardial infarction, bleeding (i.e., life-threatening, major, or critical organ bleeding), pulmonary embolism, and infection.

Figure Legend.

Figure 1. Cloud DX Connected Health kit

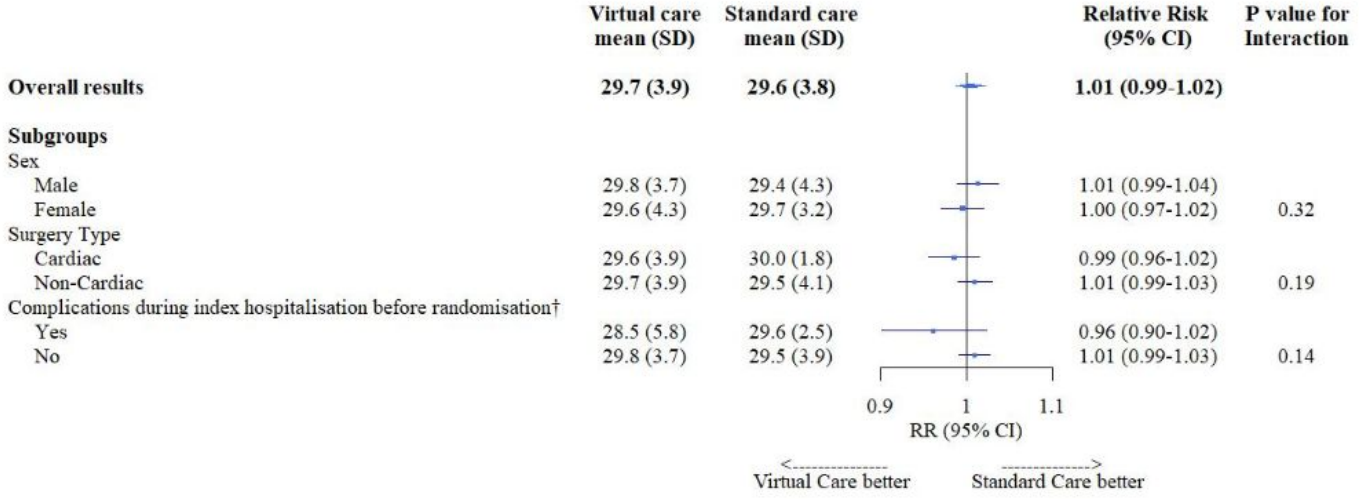
Bluetooth-enabled Pulsewave wrist cuff blood pressure monitor, body-weight scale and wireless oximeter, and temperature probe, paired with Android Health Tablet

Figure 2. Subgroup analyses of the primary outcome*

* days alive at home up to 30 days after randomisation
† patients who during their index hospitalisation before randomisation had one or more of the following complications: cardiac (i.e., myocardial infarction, non-fatal cardiac arrest), bleeding (i.e., life-threatening, major, or critical organ bleeding), venous thromboembolism (i.e., deep vein thrombosis or pulmonary embolism), infection, and sepsis

Figure 1: Cloud DX Connected Health kit

Figure 2. Subgroup analyses of the primary outcome*



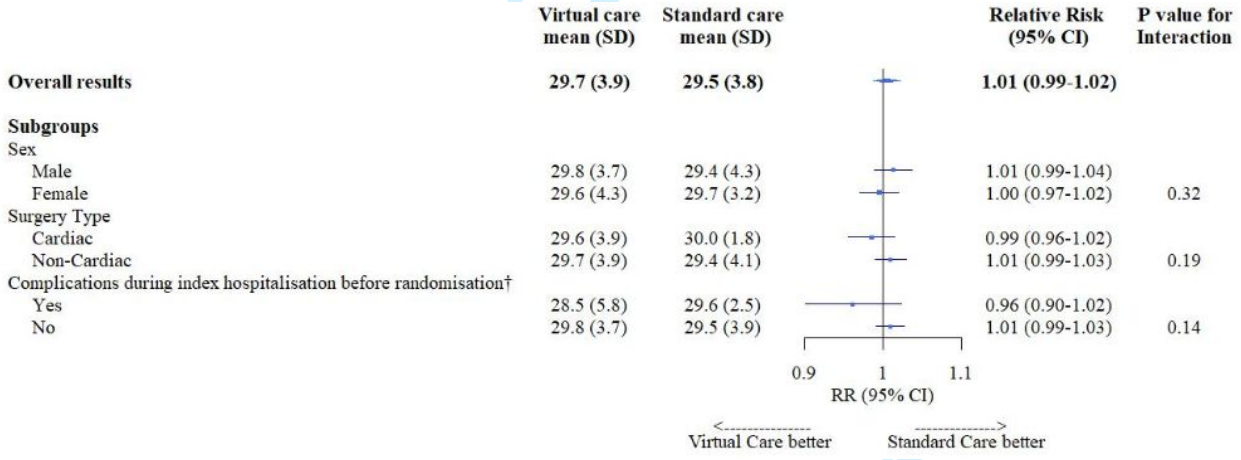

Virtual care mean (SD)
Standard care mean (SD)
Relative Risk (95% CI)
P value for Interaction
Overall results
29.7 (3.9)
29.5 (3.8)
1.01 (0.99-1.02)
Subgroups
Sex
Male
29.8 (3.7)
29.4 (4.3)
1.01 (0.99-1.04)
Female
29.6 (4.3)
29.7 (3.2)
1.00 (0.97-1.02)
0.32
Surgery Type
Cardiac
29.6 (3.9)
30.0 (1.8)
0.99 (0.96-1.02)
Non-Cardiac
29.7 (3.9)
29.4 (4.1)
1.01 (0.99-1.03)
0.19
Complications during index hospitalisation before randomisation†
Yes
28.5 (5.8)
29.6 (2.5)
0.96 (0.90-1.02)
No
29.8 (3.7)
29.5 (3.9)
1.01 (0.99-1.03)
0.14
0.9
1
1.1
RR (95% CI)
Virtual Care better
Standard Care better

Table 1. Subtypes of surgery patients underwent

Characteristics	Virtual-care group (N=451)	Standard-care group (N=454)
Type of surgery* – no. (%)		
Non-cardiac	366 (81.2)	366 (80.6)
General	146 (32.4)	130 (28.6)
other intra-abdominal	38 (8.4)	24 (5.3)
complex visceral resection	35 (7.8)	26 (5.7)
partial or total colectomy or stomach surgery	33 (7.3)	32 (7.0)
cholecystectomy	28 (6.2)	33 (7.3)
incarcerated hernia, perforated appendectomy or small bowel resection	33 (7.3)	27 (5.9)
major head and neck resection for non-thyroid tumor	8 (1.8)	5 (1.1)
other	4 (0.9)	2 (0.4)
Urology/gynecology	81 (18.0)	91 (20.0)
radical prostatectomy	24 (5.3)	16 (3.5)
radical hysterectomy	23 (5.1)	20 (4.4)
nephrectomy (partial or complete)	13 (2.9)	19 (4.2)
bilateral salpingo-oopherectomy	10 (2.2)	13 (2.9)
cystectomy	10 (2.2)	10 (2.2)
transurethral resection of bladder tumor	4 (0.9)	7 (1.5)
nephrostomy/ureteric stent/ileal conduit	2 (0.4)	6 (1.3)
transurethral prostatectomy	2 (0.4)	5 (1.1)
penectomy/vulvectomy	1 (0.2)	5 (1.1)
cystoscopy	2 (0.4)	4 (0.9)
cytoreductive	0 (0.0)	2 (0.4)
other	12 (2.7)	10 (2.2)
Orthopedic	62 (13.7)	68 (15.0)
major hip	13 (2.9)	17 (3.7)
open reduction internal fixation (excludes hip)	7 (1.6)	5 (1.1)
knee surgery	5 (1.1)	3 (0.7)
pelvic surgery	1 (0.2)	5 (1.1)
ankle surgery	2 (0.4)	4 (0.9)
internal fixation of femur	4 (0.9)	1 (0.2)
spine surgery	3 (0.7)	3 (0.7)
tumor resection	3 (0.7)	2 (0.4)
knee arthroplasty	1 (0.2)	3 (0.7)
lower leg amputation	3 (0.7)	1 (0.2)
shoulder surgery	2 (0.4)	2 (0.4)
above knee amputation(s)	1 (0.2)	1 (0.2)
other	9 (2.0)	5 (1.1)
neurosurgery	30 (6.7)	31 (6.8)
spine surgery	23 (5.1)	19 (4.2)
craniotomy	7 (1.6)	11 (2.4)
shunt surgery	0 (0.0)	2 (0.4)
vascular	22 (4.9)	25 (5.5)
peripheral vascular reconstruction	12 (2.7)	14 (3.1)
endovascular abdominal aortic aneurysm repair	2 (0.4)	5 (1.1)

extracranial cerebrovascular surgery	4 (0.9)	3 (0.7)
aorto-iliac reconstruction	3 (0.7)	2 (0.4)
thoracic aorta reconstruction	1 (0.2)	1 (0.2)
thoracic	23 (5.1)	17 (3.7)
lobectomy	13 (2.9)	12 (2.6)
wedge resection	6 (1.3)	3 (0.7)
thoracotomy	4 (0.9)	1 (0.2)
other	8 (1.8)	5 (1.1)
plastic	10 (2.2)	6 (1.3)
major plastic	7 (1.6)	6 (1.3)
minor plastic	4 (0.9)	0 (0.0)
other	10 (2.2)	15 (3.3)
Cardiac	89 (19.7)	89 (19.6)
coronary artery bypass grafting	69 (15.3)	75 (16.5)
on pump	69 (15.3)	74 (16.3)
off pump	0 (0.0)	1 (0.2)
valve	28 (6.2)	19 (4.2)
aortic	19 (4.2)	13 (2.9)
mitral	10 (2.2)	5 (1.1)
other	0 (0.0)	2 (0.4)
aortic	12 (2.7)	6 (1.3)
atherectomy	5 (1.1)	6 (1.3)
other	7 (1.6)	7 (1.5)

no. = number; % = percentage

* Some patients had more than one type of surgery or multiple surgeries within the same subtype. Therefore, sums of subtypes of surgery and surgical procedures surpass total number of patients.

Table 21. Compliance with virtual care and remote automated monitoring intervention

	All patients in the virtual-care group (N=451)	Virtual-care patients in centres with highest escalation of care (n=177)	Virtual-care patients in centres with intermediate escalation of care (n=189)	Virtual-care patients in centres with lowest escalation of care (n=85)	P value*
Number of scheduled visits between patient and nurse – mean (SD)	22.8 (1.2)	22.8 (1.2)	22.8 (1.3)	23.0 (0)	0.17
Number of completed visits between patient and nurse – mean (SD)	19.7 (6.3)	20.2 (5.7)	20.0 (6.0)	17.7 (7.7)	<0.001
Number of scheduled wound photos – mean (SD)	22.4 (2.7)	22.3 (2.9)	22.4 (3.0)	22.7 (1.0)	0.36
Number of completed wound photos – mean (SD)	15.0 (7.7)	15.3 (7.4)	15.5 (7.7)	13.0 (8.2)	0.02
Number of scheduled days to use RAM – mean (SD)	29.5 (1.9)	29.7 (2.0)	29.6 (1.7)	29.2 (2.3)	0.06
Number of days in which RAM data was obtained – mean (SD)	24.3 (9.6)	24.7 (9.6)	25.5 (8.6)	20.7 (10.7)	<0.001

RAM = remote automated monitoring technology, SD = standard deviation

* Compliance in terms of different virtual care and remote automated parameters were compared among the different centres based on their escalation of care using ANOVA.

Table 32. Drug errors and corrections

Outcome	Virtual-care group (N=451)	Standard-care group (N=454)	Relative Risk* (95% CI)	Absolute difference % (95% CI)	P Value
Medication errors					
Patients detected to have medication error – no. (%)	134 (29.7)	25 (5.5)	5.29 (3.52-7.93)	24.2 (19.5-28.9)	<0.001
Total number of detected medication errors – no.	286	44			
Type of medication error					
Patients with drug omission error – no. (%)	82 (18.2)	16 (3.5)	5.16 (3.07-8.67)	14.7 (10.7-18.6)	<0.001
Total number of drug omission errors – no.	173	28			
Patients with drug dosing error – no. (%)	43 (9.5)	5 (1.1)	8.66 (3.46-21.66)	8.4 (5.6-11.3)	<0.001
Total number of drug dosing errors – no.	52	5			
Patients with drug commission error – no. (%)	20 (4.4)	1 (0.2)	20.13 (2.71-149.38)	4.2 (2.3-6.2)	<0.001
Total number of drug commission errors – no.	28	1			
Patients with drug frequency error – no. (%)	21 (4.7)	1 (0.2)	21.14 (2.86-156.49)	4.4 (2.4-6.4)	<0.001
Total number of drug frequency errors – no.	25	1			
Patients with drug duration error – no. (%)	6 (1.3)	8 (1.8)	0.75 (0.26-2.16)	-0.4 (-2.0-1.2)	0.60
Total number of drug duration errors – no.	7	9			
Reason missing – no.	1	0			
Impact of medication error					
Patients with drug error and no harm – no. (%)	124 (27.5)	22 (4.8)	5.67 (3.68-8.76)	22.6 (18.1-27.2)	<0.001
Total number of drug errors with no harm – no.	263	40			
Patients with drug error and minor harm – no. (%)	16 (3.5)	4 (0.9)	4.03 (1.36-11.95)	2.7 (0.8-4.6)	0.007
Total number of drug errors with minor harm – no.	20	4			
Patients with drug error and moderate harm – no. (%)	3 (0.7)	0 (0.0)	-	0.7 (-0.1-1.4)	0.12
Total number of drug errors with moderate harm – no.	3	0			
Correction of medication errors					
Patients with medication error corrections – no. (%)	128 (28.4)	18 (4.0)	7.01 (4.36-11.27)	24.4 (19.9-28.9)	<0.001
Total number of medication error corrections – no.	238	33			

Who corrected medication error					
Patients who had a physician/nurse correct error – no. (%)	102 (22.6)	6 (1.3)	17.11 (7.59-38.58)	21.3 (17.3-25.3)	<0.001
Total number or medication errors corrected by a physician/nurse – no.	173	9			
Patients who had error corrected by themselves or family – no. (%)	28 (6.2)	7 (1.5)	4.03 (1.78-9.12)	4.7 (2.2-7.2)	<0.001
Total number of medication errors corrected by patient or Family – no.	42	16			
Patients who had error resolve on its own – no. (%)	10 (2.2)	5 (1.1)	2.01 (0.69-5.84)	1.1 (-0.5-2.8)	0.19
Total number of medication errors resolved on its own-no.	14	7			
Patients who had error corrected by others – no. (%)	2 (0.4)	1 (0.2)	2.01 (0.18-22.12)	0.2 (-0.5-1.0)	0.62
Total number of medication errors corrected by others	2	1			
Patients with missing data – no. (%)	2 (0.4)	0 (0.0)	-	0.4 (-0.2-1.1)	0.25
Total number of medication errors with missing data- no	7	0			

no. = number; % = percentage

* For the type of medication error, impact of medication error, and who corrected medication error the relative risk and absolute differences were calculated from the crude proportions. P values were obtained from the Chi-squared or Fischer's exact test.

Table 4. Most responsible person for drug error and reason for drug error

	Virtual-care group (N=451)	Standard-care group (N=454)	P Value
Patients with a drug error – no. (%)	134 (29.7)	25 (5.5)	<0.001
Most responsible person for drug error* - no.			
patient	218	38	
physician/nurse	58	3	
pharmacist	9	3	
unknown	1	0	
Primary reason for drug error made by patient – no.			
intentional patient decision	96	22	
mistake	55	3	
forgot	20	9	
financial barrier	21	1	
did not fill prescription for non-financial reasons	12	1	
intolerance/side effect	10	2	
unknown	4	0	
Primary reason for drug error made by physician/nurse – no.			
failure to communicate clearly what medications patients should or should not take at home	32	1	
failure to write prescription for new medication	19	2	
failure to write prescription to discontinue medication	4	0	
unknown	3	0	
Primary reason for drug error made by pharmacist – no.			
did not provide medication as prescribed	9	3	

no. = number; % = percentage

* Some patients had multiple medication errors. Therefore, sums of most responsible person for error and primary reason for error surpass total number of patients with a medication error.

Table 53: Effects of virtual care and remote automated monitoring on moderate to severe pain and pain-related interference

Outcome	Virtual-care group* (N=451)	Standard-care group* (N=454)	Relative risk (95% CI)	Absolute difference % (95% CI)	P Value
Moderate or severe pain – no./total no. (%)					
at worst in last 24 hours while laying down					
at 7 days after randomisation	118/386 (30.6)	156/425 (36.7)	0.83 (0.68-1.01)	6.1 (-0.4-12.6)	0.06
at 15 days after randomisation	84/402 (20.9)	111/414 (26.8)	0.78 (0.61-1.00)	5.9 (0.1-11.7)	0.04
at 30 days after randomisation	60/411 (14.6)	84/413 (20.3)	0.72 (0.53-0.97)	5.7 (0.5-10.9)	0.03
at worst in last 24 hours while moving					
at 7 days after randomisation	138/386 (35.8)	173/425 (40.7)	0.88 (0.74-1.05)	4.9 (-1.8-11.6)	0.15
at 15 days after randomisation	101/402 (25.1)	135/414 (32.6)	0.77 (0.62-0.96)	7.5 (1.3-13.7)	0.02
at 30 days after randomisation	71/411 (17.3)	102/413 (24.7)	0.70 (0.53-0.92)	7.4 (1.9-12.9)	0.009
Pain-related interference score† – no. /total no. (%)					
moderate or severe					
at 7 days after randomisation	73/386 (18.9)	121/425 (28.5)	0.66 (0.51-0.85)	9.6 (3.8-15.4)	0.001
at 15 days after randomisation	65/402 (16.2)	88/414 (21.3)	0.76 (0.57-1.02)	4.1 (-0.2-10.4)	0.06
at 30 days after randomisation	44/411 (10.7)	64/413 (15.5)	0.69 (0.48-0.99)	4.8 (0.2-9.4)	0.04

no. = number; % = percentage

* in the virtual care group 85.6%, 89.1%, 91.1% of patients provided pain data at 7, 15, and 30 days after randomisation, respectively. In the standard-care group 93.6%, 91.2%, 90.9% of patients provided pain data at 7, 15, and 30 days after randomisation, respectively.

† mean of the mean of the seven pain-related interference items: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. A score of 0 represented no pain-related interference and 10 represented complete interference. A moderate or severe pain-related interference score was ≥4.

Table 64: Pain medication usage at 30-days after randomisation

Drug	Virtual-care group (N=451)	Standard-care group (N=454)	Relative usage (95% CI)	Absolute difference % (95% CI)	P Value*
Acetaminophen					
Usage before index hospitalisation – no. /total no. (%)	95/451 (21.1)	89/454 (19.6)	1.08 (0.83-1.40)	1.5 (-3.8 -6.8)	
Usage at hospital discharge after surgery – no. /total no. (%)	233/449 (51.9)	205/454 (45.2)	1.15 (1.00-1.32)	6.7 (0.2-13.2)	<0.001
Usage at 30-days after randomisation – no. /total no. (%)	218/420 (51.9)	119/446 (26.7)	1.94 (1.62-2.32)	25.2 (18.8-31.6)	
NSAID					
Usage before index hospitalisation – no. /total no. (%)	51/451 (11.3)	40/454 (8.8)	1.28 (0.86-1.90)	2.5 (-1.4 -6.4)	
Usage at hospital discharge after surgery – no. /total no. (%)	75/449 (16.7)	67/454 (14.8)	1.13 (0.83-1.53)	1.9 (-2.9 -6.7)	0.25
Usage at 30-days after randomisation – no. /total no. (%)	69/420 (16.4)	41/446 (9.2)	1.78 (1.24-2.56)	7.2 (2.7-11.7)	
Opioids					
Usage before index hospitalisation – no. /total no. (%)	69/451 (15.3)	56/454 (12.3)	1.24 (0.89-1.72)	3.0 (-1.5 -7.5)	
Usage at hospital discharge after surgery – no. /total no. (%)	330/449 (73.5)	328/454 (72.2)	1.02 (0.94-1.10)	1.3 (-4.5-7.1)	0.35
Usage at 30-days after randomisation – no. /total no. (%)	86/420 (20.5)	63/446 (14.1)	1.45 (1.08-1.95)	6.4 (1.3-11.5)	
GABA analogue					
Usage before index hospitalisation – no. /total no. (%)	29/451 (6.4)	26/454 (5.7)	1.12 (0.67-1.87)	0.7 (-2.4 -3.8)	
Usage at hospital discharge after surgery – no. /total no. (%)	48/449 (10.7)	33/454 (7.3)	1.47 (0.96-2.25)	3.4 (-0.3-7.1)	0.65
Usage at 30-days after randomisation – no. /total no. (%)	46/420 (11.0)	31/446 (7.0)	1.57 (1.02-2.43)	4.0 (0.1-7.9)	
Cannabinoid					
Usage before index hospitalisation – no. /total no. (%)	22/451 (4.9)	7/454 (1.5)	3.27 (1.41-7.58)	3.4 (1.1-5.7)	
Usage at hospital discharge after surgery – no. /total no. (%)	19/449 (4.2)	7/454 (1.5)	2.80 (1.19-6.60)	2.7 (0.5-4.9)	0.96
Usage at 30-days after randomisation – no. /total no. (%)	19/420 (4.5)	6/446 (1.3)	3.46 (1.40-8.58)	3.2 (0.9-5.5)	

Any of these pain medications[†]					
Usage before index hospitalisation – no. /total no. (%)	156/451 (34.6)	134/454 (29.5)	1.17 (0.97-1.42)	5.1 (-1.0-11.2)	
Usage at hospital discharge after surgery – no. /total no. (%)	387/449 (86.2)	380/454 (83.7)	1.03 (0.97-1.09)	2.5 (-2.2 -7.2)	0.003
Usage at 30-days after randomisation – no. /total no. (%)	268/420 (63.8)	179/446 (40.1)	1.59 (1.39-1.82)	23.7 (17.1-30.3)	

no. = number; % = percentage; GABA = gamma-aminobutyric acid; NSAID = non-steroidal anti-inflammatory drug

* We compared the use of pain medication between the virtual-care and RAM group versus the standard-care group over time using repeated measures logistic regression.

[†] acetaminophen, NSAID, opioid, or GABA analogue

Table 75: Effects of virtual care and remote automated monitoring on tertiary outcomes at 31-days

Outcome	Virtual-care group (N=451) no. (%)	Standard-care group (N=454) no. (%)	Relative risk (95% CI)	P Value
surgeon, family physician, or specialist in-person clinic visit	232 268 (59.41.4)	221 258 (48.756.8)	1.054 (0.93-1.2016)	0.416
surgeon, family physician, or specialist virtual clinic visit	177 183 (39.240.6)	204 207 (44.945.6)	0.898 (0.757-1.023)	0.0813
surgeon, family physician, or specialist in-person or virtual clinic visit	34811 (69.077.2)	3409 (68.176.9)	1.001 (0.943-1.1108)	0.7491
infection	55 (12.2)	64 65 (14.31)	0.878 (0.623-1.214)	0.471
surgical site infection	34 (7.5)	47 (10.4)	0.74 (0.49-1.14)	0.17
re-operation	5 (1.1)	11 12 (2.64)	0.426 (0.165-1.20134)	0.151
life-threatening, major, or critical-organ bleeding	5 (1.1)	3 (0.7)	NR	0.51
clinically important atrial fibrillation	5 (1.1)	3 (0.7)	NR	0.51
stroke	3 (0.7)	2 (0.4)	NR	0.69
acute heart failure	1 (0.2)	3 (0.7)	NR	0.62
symptomatic proximal venous thrombo-embolism	1 (0.2)	3 (0.7)	NR	0.62
myocardial infarction	1 (0.2)	2 (0.4)	NR	1.00
sepsis	1 (0.2)	1 (0.2)	NR	1.00

arrhythmia resulting in electrical cardioversion	2 (0.4)	0 (0)	NR	0.25
delirium	0 (0)	1 (0.2)	NR	0.50
ileus	1 (0.2)	1 (0.2)	NR	1.00
respiratory failure	1 (0.2)	~~1~~ 2 (0.~~2~~4)	NR	1.00
Clostridium difficile-associated diarrhea	1 (0.2)	1 (0.2)	NR	1.00
indwelling device inappropriately left in a patient	1 (0.2)	0 (0)	NR	0.50
acute renal failure resulting in dialysis	1 (0.2)	0 (0)	NR	0.50
non-fatal cardiac arrest	0 (0)	0 (0)	NR	1.00
COVID-19 infection	0 (0)	0 (0)	NR	1.00

NR = not reported, because too few events

Table 86. Variation across centres in frequency of nurse escalation of care to a physician, among patients in the virtual-care and remote automated monitoring group

Centre	Patients with escalation of care no. (%)
Centre 1 (n=75)	66 (88.0)
Centre 2 (n=97)	88 (90.7)
Centre 3 (n=44)	24 (54.5)
Centre 4 (n=5)	4 (80.0)
Centre 5 (n=21)	5 (23.8)
Centre 6 (n=101)	55 (54.5)
Centre 7 (n=44)	24 (54.5)
Centre 8 (n=64)	24 (37.5)

Table 9: Effects of virtual care and remote automated monitoring on tertiary 6-month outcomes

Outcome	Virtual-care group (N=451)	Standard-care group (N=454)	Relative risk* (95% CI)	Absolute difference† % (95% CI)	P Value#
Days alive at home – mean (± SD)	176.7 (25.5)	176.7 (26.1)	1.00 (0.98-1.02)	0.0 (-1.7-1.7) ^	0.59
Acute-hospital care – no. (%)	170 (37.7)	189 (41.6)	0.91 (0.78-1.07)	3.9 (-2.5-10.3)	0.23
Hospital re-admission – no. (%)	101 (22.4)	107 (23.6)	0.97 (0.76-1.22)	1.2 (-4.3-6.7)	0.67
Emergency department visit – no. (%)	151 (33.5)	166 (36.6)	0.92 (0.77-1.10)	3.1 (-3.1-9.3)	0.33
Urgent-care centre visit – no. (%)	7 (1.6)	13 (2.9)	0.54 (0.21-1.35)	1.3 (-0.6-3.2)	0.18
All-cause hospital days (median [IQR])	0 (0-2.0)	0 (0-2.0)	0.89 (0.60-1.33)	0.4 (0.2-0.6) ^	0.58
Death – no. (%)	17 (3.8)	18 (4.0)	0.95 (0.51-1.80)	0.2 (-2.3-2.7)	0.88

CI = confidence interval; IQR = interquartile range; no. = number; SD = standard deviation; % = percentage

* Relative risks and 95% confidence intervals were obtained from Modified Poisson model

† Absolute differences and 95% confidence intervals were calculated from the crude proportions.

^ Absolute rate differences and 95% confidence intervals were determined based on a Normal Approximation to Poisson.

P values are from Wilcoxon, Student's t and Chi-square test

REFERENCE

1. Vascular Events in Noncardiac Surgery Patients Cohort Evaluation Study I. Association between complications and death within 30 days after noncardiac surgery. CMAJ 2019;191:E830-E7.

SUMMARY BOX

What is already known on this topic:

Patients discharged after non-elective surgeries frequently utilise acute-hospital care (i.e., hospital re-admission, emergency department visit, or urgent-care centre visit) in the 30 days following discharge.

As hospitals struggle with COVID-19, there is the need to reduce surgical patients' post-discharge use of acute-hospital care to ensure hospital capacity and facilitate management of the backlog of individuals waiting for elective surgeries.

A strong rationale and preliminary evidence suggest that virtual care and remote automated monitoring (RAM) may decrease acute-hospital care, in adults discharged after surgery.

What this study adds:

Virtual care and RAM did not significantly increase days alive at home compared to standard care, but significantly improved detection and correction of medication errors and decreased pain.

In post hoc analyses of centres with high escalation of care that commonly led to changes in medical management, virtual-care and RAM reduced the risk of acute-hospital care, brief acute-hospital care, and emergency department visits.