

Virtual Integrated Reliable Transformative User-driven E-health System for pacemakers and implantable cardioverter defibrillators

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Virtual Integrated Reliable Transformative User-driven E-health System for pacemakers and implantable cardioverter defibrillators: two randomized, open-label, controlled trials (VIRTUES-PM and VIRTUES-ICD)

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Abstract

Background: Clinical burden of remote monitoring (RM) in cardiac implantable electronic devices (CIEDs) is high, yet uptake is variable. A digital health platform (VIRTUES) is posited to fill these gaps, with acceptable safety, efficacy and lower costs.

Methods: VIRTUES-PM (V-PM) and VIRTUES-ICD (V-ICD) were multicenter, open-label, randomized controlled trials with blinded endpoint adjudication conducted in 13 Canadian centers for V-PM and 11 Canadian centers for V-ICD for patients with RM-eligible CIEDs. Allocation was 1:1 to standard of care (SOC) or VIRTUES care. In V-PM, there were two objectives: demonstration of non-inferiority of safety (time to major adverse cardiac or device-related hospitalizations) and superiority in cost; the secondary outcome was efficacy (time from clinical event to decision). In V-ICD, the first co-primary outcomes were safety and efficacy; cost was considered a second primary outcome. Analysis in each study used a sequential strategy of non-inferiority of the primary outcome, followed by superiority in cost. Outcome assessment was performed by blinded adjudication.

Results: Between May 29, 2020 and February 28, 2025, 848 participants were randomized in V-PM (n=428 VIRTUES; n=420 SOC) and 1115 in V-ICD (n=526 VIRTUES; n=553 SOC). The mean age was 70±12 years; 34% were women in V-PM, and 65±12 years, 22% were women in V-ICD. Over a follow-up of 18 months, the safety outcome in V-PM occurred in 26 participants (6.1%) in the VIRTUES care arm, compared to 31 (7.4%) in SOC; hazard ratio 0.83; 95% CI (0.49, 1.39); p for non-inferiority=0.0213. Cost was lower by -\$77; 95% CI(-\$100, -\$54), p<0.01. In V-ICD, the safety outcome occurred in 62 (11.0%) in VIRTUES, and 62 (11.2%) in SOC, hazard ratio 0.98, 95% CI (0.69,1.39); p for non-inferiority 0.007. Efficacy was also non-inferior with time from clinical events to decision: median 2.0 interquartile range (0 to15) in the VIRTUES care arm vs 1.00 IQR(0 to 8) days in the SOC arm (p =0.003 for non-inferiority). The second primary outcome of cost per participant was significantly lower in the VIRTUES care arm as compared with SOC (mean adjusted cost difference/participant -C\$77; 95% CI (-\$105, -\$49); p<0.01.

Conclusion: VIRTUES care was non-inferior to SOC for safety in patients with PMs and ICDs, as well as in efficacy in ICDs. In both trials, significant cost-savings were found. These two trials support the use of this technology for comprehensive CIED management.

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Trial Registration: VIRTUES PM NCT03636230 first posted August 17, 2018, VIRTUES ICD NCT03405740 first posted January 23, 2018.

Introduction

Cardiac implantable electronic devices (CIED) are implanted worldwide and are increasing in numbers as the population ages and longevity improves. The number of pacemakers (PMs) implanted each year globally is estimated to be 1.25 million.¹ The resources, cost and effect on the carbon footprint to manage this number of patients is enormous.² Implantable cardioverter defibrillators (ICDs) are indicated for both primary and secondary prevention of sudden cardiac death. The risk of ventricular arrhythmia in a primary prevention patient is approximately 30% at five years, and for a secondary prevention patient, 30% at one year,^{3,4} resulting in a high burden of events for any device clinic that is following a large number of these patients. Coupled with high alert events such as an ICD shock, these patients may have numerous other clinical events including low battery, lead abnormalities, device advisories necessitating increased monitoring, and worsening heart failure.⁵ Yet, the majority of device clinic visits consist of routine device checks without any issue with the device or needing device reprogramming or changes to patient management.

Current management strategies have included remote monitoring (RM) to improve management of patients with CIEDs.⁶ A survey performed by the European Society of Cardiology showed that remote monitoring was used at a rate of 0.5/million and 15 of 51 countries had no availability of RM.⁷ In Canada, 8500 out of a potential 120 000 patients with CIEDs are actively enrolled in RM.⁸ Prior studies have demonstrated the safety of an RM-only follow-up for patients with pacemakers; however, this system has not yet been widely adopted.^{9,10} Some of the reasons for lack of RM use include the cost of the monitor itself, reimbursement, patient mistrust in an RM system, inability for clinics to reorganize resources to manage RM and maintaining communication with the patient regarding their device. The burden of handling the volume and acuity of RM for these patients is high for device clinics using the current RM workflow. Digital solutions to assist in the management of such patients could ease clinical burden, improve efficiency, while maintaining safety and possibly reducing cost.

The Cardiovascular Network of Canada (CANet, canetinc.ca) has launched a web-based platform to assist with the high burden of care for patients with CIEDs. VIRTUES (Virtual Integrated Reliable Transformative User-driven E-health system) was designed to improve CIED follow-up for patients and clinic efficiency, and reduce cost without sacrificing safety. The VIRTUES-PM and VIRTUES-ICD randomized controlled trials assessed whether VIRTUES is non-inferior to SOC for safety and efficacy, but with cost-saving, in patients with PMs and ICDs.

Methods

VIRTUES-PM (V-PM) and VIRTUES-ICD (V-ICD) were two multicenter, open-label, randomized controlled trials with blinded endpoint adjudication, performed in 13 Canadian centers for V-PM and 11 centers for V-ICD) designed to assess whether VIRTUES care was non-inferior to SOC, with superiority in cost-saving. Two protocols were implemented as part of the program of study, each for pacemaker and ICD patients. The protocols were approved by institutional research ethics boards at the Nova Scotia Health Authority and at each participating center, and individual patient consent was obtained. The trial was performed according to the ICH-GCP guidelines and was in compliance with the Declaration of Helsinki. Participating sites and members of the executive, adjudication committees and patient council are available in Supplementary Tables 1 and 2. This trial was performed with the inclusion of patients with lived experience in the design and execution of the trial. The trial has been reported according to the CONSORT guideline. The most recent approved protocols and statistical analysis plans are provided in the Supplementary materials. The methods have been previously published.¹¹

Participants

In V-PM, Participants who had a new or existing Medtronic or Abbott PM and more than 18 years of age were included. Participants were excluded if they had no access to a primary care provider, were involved in a clinical trial with competing outcomes, or had unreliable automated capture verification by the device in a pacemaker-dependent patient (defined as no underlying heart rhythm less than 30 beats per minute). In V-ICD, participants who had a new or existing Medtronic, Abbott or Boston Scientific ICD and more than 18 years of age were included. Participants were excluded if they had unreliable automated capture verification, no access to specialty care or were actively followed in a heart function clinic. Automated capture verification refers to a pacemaker feature that automatically adjusts pacing output to ensure myocardial capture while minimizing energy use. All participants in both trials underwent standardized programming on entry into the study, which included minimization of right ventricular pacing, optimization of rate responsiveness, and programming to optimize battery longevity. In V-ICD, optimization of cardiac resynchronization pacing to >98% and shock reduction programming where appropriate and optimizing discrimination for SVT and VT were part of standardized programming.

Randomization and masking

Participants were randomized 1:1 to VIRTUES or standard of care (SOC), in each of the V-PM and V-ICD trials. A randomization schedule was prepared by the University of Ottawa Heart Institute data coordinating center, using a computerized random number generator. Balanced randomization was maintained by each center using a block randomization scheme with randomly permutating block sizes using the REDCap system. Participants were stratified by center, remoteness and presence of cardiac resynchronization therapy in V-ICD; in V-PM, they were stratified by center and pacemaker dependence. It was not possible to blind participants to the randomized arm; however, outcomes were adjudicated by a committee blinded to the assigned arm.

Intervention

In both trials, the VIRTUES care arm was identical. Participants in the VIRTUES care arm were followed by remote monitoring and VIRTUES, with no routine in-clinic visits unless deemed necessary. Each participant was onboarded to the VIRTUES platform using a web-based portal guided by trained research personnel. Onboarding included patient demographics, frailty score, past medical history, current medications, echocardiographic data, most recent electrocardiogram, other pertinent imaging (e.g. coronary angiography, chest radiography, magnetic resonance imaging), and history of cardiovascular hospitalizations. Participants were instructed to inform the study personnel of any changes in their personal or medical profile during the course of the study. In the first week of enrolment, the participant underwent a test transmission from the RM home monitor; this was routed through the VIRTUES platform (Figure 1). Artificial intelligence was used to ‘read’ the device transmission and extract the following information for VIRTUES: battery longevity, alerts, atrial or ventricular arrhythmia, lower limit for pacing, percentage pacing; additionally, in V-ICD, the occurrence of an ICD shock and tachycardia detection were automatically populated. These were chosen to be most important by the patient council for knowledge regarding device function. The device clinic providers sent a message back through the VIRTUES platform to the patient using a traffic light system (Figure 2) to indicate the status of their device and whether any further action was required. The assignment of the traffic light was left to the discretion of the device clinic healthcare provider. For the remainder of the study, transmissions were routinely scheduled biannually. Unscheduled transmissions may have occurred and were dealt with through the VIRTUES platform. All participants were asked to follow up with their general practitioner at least annually while in V-PM and their specialist every two years in V-ICD. Communication through the VIRTUES platform was conducted via phone call, text messaging, email, through the portal/app as per

the participant's preference, and via fax to the general practitioner, or other healthcare provider as requested by the participant.

For details regarding the architecture, privacy and security of the platform, see Supplementary Figure 1.

Standard of Care arm

The participants in the SOC arm underwent standardized programming as described above and in-clinic visits alternating with RM transmissions biannually as per current guidelines in V-ICD and annually in V-PM.^{6,12}

Follow up

Baseline information was obtained after randomization. Demographic and clinical characteristics were collected. The Clinical Frailty Scale was utilized to document frailty.¹³ Participants' residence was determined to be rural if they lived in a town with <10 000 residents. Participants were followed for 18 months. VIRTUES transmissions occurred as described in the intervention; clinic visits occurred as needed and as per SOC. Study-specific follow-ups were performed at 18 months in both arms; to ensure clinical data was kept up to date throughout the study in V-ICD, additional study visits were performed at six and 12 months.

Outcomes

VIRTUES-PM

The primary objective was to demonstrate non-inferiority in the primary outcome of safety. The safety outcome was measured as major adverse events including: death, stroke, hospitalization for complications related to the device system, or unplanned cardiovascular hospitalizations. Cardiovascular hospitalizations included acute coronary syndrome, presyncope or syncope, transient ischemic attack or stroke, ventricular arrhythmias, atrial fibrillation, atrial flutter, pulmonary embolism, deep vein thrombosis, systemic embolism, worsening congestive heart failure including pulmonary edema or dyspnea of cardiac origin. The secondary objective was to demonstrate superiority in cost savings to patients and the healthcare system with VIRTUES. Efficacy, defined as time from detection of a clinically important device event to clinical decision, was a secondary outcome in V-PM. A clinically important event was categorized as an arrhythmia defined as AT/AF more than 12 hours, rapid ventricular rate during AF (120

bpm for ≥ 6 hours AT/AF per day), lead impedance out of range, low battery voltage, or advisory alert. The number of days to clinical decision in the VIRTUES arm was calculated from the onset of the event to the time at which the clinical decision was made as evidenced by an in-clinic visit, or sign-off of the VIRTUES report. The number of days to clinical decision in the SOC arm was calculated from the onset of the event to the time of physician review and documentation to the patient's health care provider; this could be gleaned from the electronic health record or manually if no electronic system existed.

VIRTUES-ICD

The first objective was to demonstrate non-inferiority in the co-primary outcomes: safety and efficacy. The safety outcome was measured as indicated in V-PM. Efficacy was defined as indicated in V-PM, with the inclusion of ICD-specific events: excessive charge time, ICD shock, need for device programming, ≥ 3 anti-tachycardia pacing (ATP) therapies within 24 hours separated by 5 minutes (VT Storm), sustained VT (>30 seconds) in the monitor zone. The number of days to clinical decision was defined as in the secondary outcome for V-PM. The second primary objective was to determine if VIRTUES care reduced cost to the patients and to the healthcare system.

Secondary outcomes included: the rate of in-clinic and remote transmissions, as well as scheduled and unscheduled visits, was measured and compared between the two care arms in each trial. Patient satisfaction with the VIRTUES platform was measured using the Acceptance Questionnaire for the first 5 years of the two trials, derived from Canada Health Infoway for assessment of digital health tools.¹⁴ Privacy breaches due to the platform were collated throughout the two trials. A tertiary outcome included quality of life as measured by the SF-36 in both trials.^{15,16}

Statistical Analysis

VIRTUES-PM

The primary safety outcome of the composite of major adverse events is assumed to be 15.% in the standard of care (SOC) control group, and the non-inferiority margin (NIM) is taken to be 5.55% or a HR of 1.42 when the SOC hazard rate is 0.15. These values at 12 months are prorated from the event rate 19.1% and NIM 7% reported for 18 months in COMPAS trial.¹⁰ Using a one-tail test for non-inferiority with a significance level of 0.025 and a power of 80%, an overall sample size of 830 (415 per group) is required based on a log-rank test assuming recruitment over a

2-year period and total study period of 3.5 years, a loss to follow up of 2.5% in each group, a 5% crossover from VIRTUES to SOC and no crossover from SOC to VIRTUES.

. Using a one-tail test for non-inferiority with a significance level of 0.025 and a power of 80%, an overall sample size of 830 (415 per group) is required based on a log-rank test assuming uniform recruitment over 2 years and total study period of 3.5 years, a loss to follow up of 2.5% in each group, a 5% crossover from VIRTUES to SOC and no crossover from SOC to VIRTUES.

VIRTUES-ICD

For assessing the co-primary endpoint consisting of the primary safety outcome (time to the composite of death, cardiovascular hospitalization or device-related hospitalization) and the primary efficacy outcome (time to clinical event), will have $(83)(96)=80\%$ power for the non-inferiority of the primary composite endpoint of the trial to be detected with level of significance of 0.025. This sample size is based on the power in the calculation of the sample size for each of the primaries as follows:

The primary safety outcome of the composite of major adverse events is assumed to be 10.4% in the standard of care (SOC) control group, and the non-inferiority margin is taken to be 5% based on the TRUST trial or a HR of 1.52 when the SOC hazard rate is 10.4%.⁵ Using a one-tail test for non-inferiority with a significance level of 0.025 and a power of 83%, an overall sample size of 860 (430 per group) is required based on a log-rank test assuming recruitment over a 2-year period and total study period of 3.5 years, a loss to follow up of 2.5% in each group, a 5% crossover from VIRTUES to SOC and no crossover from SOC to VIRTUES.

For the primary efficacy outcome of time to clinical decision of a clinically important event is assumed, the non-inferiority margin is taken to be 20% or 3.48 days based on the median difference between remote monitoring and control groups in the CONNECT trial.¹⁷ Using a one-tail test for non-inferiority of significance level with a significance level of 0.025 and a power of 96%, an overall sample size of 1146 (573 per group) is required based on a two-sample equal variance t-test, a standard deviation of 15.5 days based on the conversion of the results reported in medians from the CONNECT trial, a loss to follow up of 2.5% in each group, a 5% crossover from VIRTUES to SOC and no crossover from SOC to VIRTUES.

These sample size calculations for safety were modified from the original protocol with the extension of the recruitment period to 2 years due to slower-than-anticipated recruitment encountered due to the COVID-19 pandemic. Power calculations were performed with PASS 2019 v19.0.3.

A prespecified sequential analysis was planned as follows: non-inferiority for safety and non-inferiority for efficacy followed by superiority for cost. Evaluation for superiority of cost proceeded only if rejection of the null hypothesis of non-inferiority of safety and efficacy was fulfilled in V-ICD, and safety alone in V-PM; otherwise, cost analysis was not performed.¹⁸

The baseline demographic and clinical variables of the two arms VIRTUES care vs SOC were compared using the standardized mean difference, with an absolute difference of < 0.10 considered negligible. Intention-to-treat (ITT) populations were used for all analyses, and the per-protocol (PP) population was also used for the non-inferiority analyses.

The time-to-event of the primary safety outcome in the two care arms was summarized using the Kaplan-Meier product limit estimates, and the hazard ratio (HR) and associated 95 percent confidence interval (95% CI) were calculated. In addition, the Cox proportional hazards model was used to assess the consistency of the care arm effect on this outcome, adjusting for key baseline covariate differences. Underlying assumptions for these statistical procedures were assessed; in particular, the proportional hazards assumption. The null hypothesis was that the time-to-event of the composite outcome for VIRTUES care is inferior to SOC, and the alternative hypothesis was that it is non-inferior to SOC. The p-value for non-inferiority was calculated using the non-inferiority margin $HR=1.52$ in V-ICD and $HR=1.42$ in V-PM, and a $p\text{-value} < 0.025$ will be considered significant. The time to each secondary safety outcome in the two care arms was also compared using time-to-event analysis techniques. For secondary outcomes other than death, a competing risk analysis was performed with death as the competing risk. The cumulative incidence function was used in estimating the probability of outcomes in each of the two care arms, and the sub-distribution hazard model proposed by Fine and Gray was used to compare the cumulative incidence curves, and the HR and 95% CI were calculated. For the primary composite efficacy outcome in V-ICD of the time to clinical decision of important clinical events, the median time in the two care arms was compared and the median difference (MD) calculated. A bootstrapping approach based on 1000 samples with replacement of the full sample size and the median difference calculated for each sample was conducted, and the 95%CI for the median difference was based on

the 2.5 and 97.5 percentile of the distribution of the median differences. The null hypothesis was that the time to clinical decision of the composite outcome for VIRTUES care is inferior to SOC, and the alternative hypothesis was that the time for VIRTUES care is non-inferior to SOC. The p-value for non-inferiority was calculated using the non-inferiority margin 3.5 days, and a p-value < 0.025 was considered significant. Although efficacy was a secondary outcome in V-PM, the same approach for calculation of non-inferiority was used. The quality of life, the frequency distribution for each of the domains and component scores of the SF-36 were tabulated and the mean and 95% CIs calculated. A mixed model repeated measures comparing the two care arms on changes in health-related quality of life over time was conducted. Mixed-method repeated measures was used for handling missing data. Healthcare resource-use counts were compared between the two care arms using negative binomial regression models to account for overdispersion in the utilization outcomes.¹⁹ Results were reported as adjusted incidence rate ratios (IRRs) with 95% confidence intervals. Costs were analyzed using two-part regression models to account for the proportion of participants with no costs and the right-skewed distribution of positive costs.²⁰ The first part used logistic regression to estimate the probability of incurring any cost. The second part used a generalized linear model with a gamma distribution and log link to estimate costs among participants with positive costs. Adjusted mean costs were estimated using predictive margins that combined predictions from both parts. Between-arms differences in adjusted mean costs and corresponding 95% confidence intervals will be estimated using robust standard errors. The costs that were considered are included in Supplementary Table 3. All analyses were performed using SAS software, version 9.4.

Participants who were lost to follow-up were censored at the time of last known visit. No interim analyses were prespecified. A data monitoring committee oversaw the conduct of the study, reviewed all deaths occurring during the study and examined the combined endpoint of safety biannually for the duration of the study.

Role of the funding source

The Cardiovascular Network of Canada was responsible for construction and maintenance of the VIRTUES platform for the duration of the study. The remaining funders had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Results

VIRTUES-PM

Between October 15, 2020 and Feb 17, 2025, a total of 848 participants were enrolled and randomized; one participant withdrew immediately after randomization without providing any baseline data and was not included in the final analysis. (Figure 3) There were a further 25 participants who withdrew from the trial (17 in the VIRTUES arm and 8 in the SOC arm); 8 patients were lost to follow-up (6 in the VIRTUES arm,,11 in the SOC arm). Follow-up was completed in 839 (99.1%) participants. Data lock occurred on June 10, 2026. Baseline characteristics are shown in Table 1. Of the participants, 299 (35.3%) were women; the mean age was 70.5±12.3 years; 118 (27.6%) had a high frailty score (>3 of the Clinical Frailty Index), and 241 (28.5%) were pacemaker dependent. There were 110 (22.0%) patients who were located in a rural location (town population <10 000), with a greater number of rural patients in the VIRTUES arm (25.7% vs 18%). There were more participants with current smoking (6.6% vs 4.1%) in the VIRTUES arm, compared to SOC. More participants were on mineralocorticoid antagonists in the VIRTUES arm (10.8% vs 5.2%). Programming compliance was similar in both arms with the exception of automated capture verification on more frequently in the SOC arm.(Supplementary Table 4)

As the initial step in the sequential testing strategy, V-PM achieved non-inferiority in the safety outcome in the ITT analysis. (Figure 4) Over 18 months, the primary safety outcome occurred in 26 (6.1%) participants in the VIRTUES arm, compared with 31 (7.4%) participants in the SOC arm, hazard ratio 0.83 95%CI (0.49, 1.39) p-value for non-inferiority 0.0213; this was adjusted for differences in baseline characteristics as a prespecified analysis resulting in a hazard ratio 0.76 95%CI (0.45, 1.29), p for non-inferiority 0.0101.(Table 2) Death occurred in 12 (2.8%) and 11 (2.6%) participants in the VIRTUES arm and SOC arm.

VIRTUES care had lower adjusted mean costs/participant for the patients themselves (-C\$28/participant; 95% CI (-45, -11)) and the healthcare system (-C\$49/participant; 95% CI (-68, -28)). This resulted in an overall cost-savings of -C\$77/participant; 95% CI (-\$100, -\$54); p<0.01. (Table 3) Compared with SOC, participants in the VIRTUES care arm had fewer in-clinic device interrogation visits (adjusted IRR 0.34; 95% CI (0.29, 0.39)), and more remote interrogations (adjusted IRR 3.78; 95% CI 3.33, 4.30). (Figure 5) The reduction in total costs was primarily driven by lower costs of in-clinic device interrogations and travel fees incurred by patients and caregivers.

As a prespecified sensitivity analysis, the per-protocol analysis was conducted for the primary outcomes; no change in the results was found.

Efficacy was measured as a secondary outcome in V-PM. VIRTUES care was superior in the time from event to clinical decision with a median of 0 (interquartile range 0 to 3) days, compared to 3.25 (interquartile range 0 to 102) days in the SOC arm, $p=0.003$ for non-inferiority. (Table 2)

Quality of life was no different in the VIRTUES arm compared to the SOC arm, as measured by the SF-36.(Table 5)

VIRTUES-ICD

Between May 29, 2020 and February 28, 2025, 1115 participants were enrolled and randomized. (Figure 6) There were 28 participants who withdrew from the trial (16 in VIRTUES, 12 in SOC), 6 participants were lost to follow-up (1 in VIRTUES and 5 in SOC), and two patients underwent a cardiac transplant in the VIRTUES arm. Follow-up was completed in 1109 (99.5%) participants. Data lock occurred on June 10, 2026. Baseline characteristics are shown in Table 6. There were 237 (21.3%) women; the mean age was 64.7 ± 11.8 years; 435 (39.0%) had a secondary prevention ICD, and 320 (28.7%) had a cardiac resynchronization therapy device. The mean ejection fraction was $42 \pm 13.5\%$, approximately 1/3 of the participants lived in a rural location. There were more participants with diabetes (32.2% vs 25.0%) and current smoking (11.9% vs 8.1%) in the VIRTUES care arm. Programming compliance was similar in both arms, with the exception of automatic capture verification more frequently on in the SOC.(Supplementary Table 5)

As the initial step in the sequential testing strategy, VIRTUES-ICD achieved all prespecified safety and efficacy endpoints for non-inferiority in the ITT analysis. The safety outcome occurred in 62 (11.0%) of the VIRTUES care arm, and 62 (11.2%) of the SOC arm (HR 0.98; 95% CI (0.69, 1.39); p -value for non-inferiority 0.0070; adjusted HR 0.90; 95% CI (0.63, 1.29); p for non-inferiority=0.0022). (Figure 7, Table 7) There was no difference in the rate of death between the two care arms (3.2% in VIRTUES, 4.0% in SOC). The time to clinical decision was non-inferior in the VIRTUES care arm (median 2.00 (interquartile range 0 to 15) days), compared to 1.00 (interquartile range 0 to 8) days in the SOC arm (median difference 1.0 (95% CI -2, 1) days; p for non-inferiority=0.003). The results for the components of the efficacy endpoint are provided in Table 7.

As the co-primary outcomes demonstrated non-inferiority, the cost analysis was performed as part of the next step in the sequential testing strategy. In the ITT population, VIRTUES care resulted in significant cost savings to both patients (adjusted mean difference per patient C\$41/participant; 95% CI (-60, -26)) and the healthcare system (adjusted mean difference per patient --C\$36/participant; 95% CI (-64, -9)), resulting in an overall cost savings of -C\$77/participant; 95% CI (-\$105, -\$49).(Table 8) VIRTUES care was associated with fewer in-clinic visits among participants (adjusted IRR 0.47; 95% CI (0.4, 0.54)), and more remote interrogations (adjusted IRR 1.24; 95% CI: (1.16, 1.33)). (Figure 8) Unscheduled visits occurred with the same frequency in both care arms.

The PP analysis for non-inferiority was conducted for the primary safety and efficacy outcomes, removing 28 patients lost to follow-up, there were no substantive differences in the results compared to the ITT analysis. The PP result for safety was HR, 0.89; 95% CI (0.66, 1.20); p=0.0069 for non-inferiority and for efficacy was median difference, 0; 95% CI (-1.5, 1); p<0.0001 for non-inferiority.

Quality of life was no different in the VIRTUES arm compared to the SOC arm, as measured by the SF-36. (Table 9)

Patient acceptance of VIRTUES care

The acceptance questionnaire was administered at 12 or 18 months to 688 consecutive VIRTUES care participants, 309 participants in V-PM and 379 participants in V-ICD. On a Likert scale of 1 (strongly disagree) to 5 (strongly agree), the mean response was 3.97/5 on eight questions evaluating VIRTUES care in V-ICD and 4.01/5 in V-PM, consistent with excellent acceptance of the platform. When asked if continuing in VIRTUES is desirable, 93% were agreeable to do so, while 51% felt strongly about continuing with VIRTUES care.

Privacy and Security

The VIRTUES platform tracked any occurrences of privacy or security breaches throughout the study. There were four instances of privacy breaches, none of which led to patient harm. There were two privacy breaches of patient reports that resulted in no harm; in another instance, the upload of the remote transmission was not done in the correct order, which led to incorrect parsing/miscommunication to a patient, but no harm; one privacy breach on the patient feedback section and another privacy breach when an incorrect user was provided unauthorized access to

patient data. These were corrected quickly and resulted in no harm to the patient. The overall rate of privacy breaches was 4/4758 (0.084%) in both trials combined.

Discussion

These two multicenter, randomized trials are the first studies to evaluate a digital health platform to assist with management of PM and ICD follow-up, confirming the hypothesis of non-inferiority in safety, efficacy and superiority in cost reduction for patients and for the healthcare system; in the PM trial, the use of the VIRTUES platform was found to be superior in efficacy, although this was a secondary outcome. Security breaches of the VIRTUES platform were minimal without causing harm to the patients.

The occurrence of safety events in these trials was lower than what has been observed in prior studies of device patients. There could be several factors that account for this. There may be some selection bias that contributed to this, as participants who may have been inclined to participate in the study may have been less comorbid. This is particularly evident in V-PM, where the mean age is lower than would be expected in a pacemaker cohort; this could be due to the use of technology as part of the trial. During recruitment, caregivers were encouraged to help participants, if possible, to avoid bias; however, older patients are known to be less comfortable with technology.²⁰ Medical therapy for patients with PMs and ICDs has improved significantly in the last decade, resulting in the lower rate of cardiovascular events in this study. This could render our study underpowered; however, the margins set for the non-inferiority bound were both absolute and relative, to account for a lower event rate.

Efficacy was found to be non-inferior to standard of care in V-ICD, but superior in V-PM. The difference in the two trials may be due to the current standard of care for management of these populations. PM patients are mostly seen in-clinic, and as a result, any clinical event would not be recognized unless the patient exhibits symptoms and presents for an unscheduled visit, or comes in for a routine follow-up. ICD patients, however, are followed both in-clinic and remotely; hence, the VIRTUES care arm was not able to demonstrate superiority. This does not minimize the benefits of VIRTUES care, which are many: ease of use of remote monitoring by the clinic facilitated by the platform, integration of relevant clinical and device data, automated data extraction from the remote transmission, patient satisfaction with the intervention, decreased cost to the healthcare system and to the patient, without any

sacrifice in overall care of the patient. In addition, the VIRTUES care presented device clinic providers with a complete picture in an instant without having to review the medical record.

Prior studies have demonstrated the acceptance of RM only for follow-up, mostly for ICD patients.^{9,10,17,21,22} In surveys of patient acceptance of this method of follow-up, it is variable. The REMOTE-CIED study found that only 43% preferred remote follow-up, and 19% preferred to continue in-clinic.²³ Factors associated with higher RM preference included patients with a higher education profile, ongoing employment and fewer comorbidities. In our prior work, we demonstrated that patients desire knowledge regarding their device and its function, as well as demonstrating that remote-only follow-up was safe.^{2,20} While some patients prefer human contact obtained at an in-clinic visit, the use of VIRTUES care was able to bridge the gap of patient preference for rapid feedback of their CIED performance and device-related care.

In the prespecified secondary analysis of VIRTUES in the PM and ICD groups, non-inferiority was achieved in both safety and efficacy, and cost-savings were significant in both PM and ICD groups. When projecting costs in a country such as Canada with an estimated 200,000 patients living with these devices, the annual cost savings for both patients and the healthcare system are projected to be \$10 million Canadian, based on the findings of our study.

There is little prior data in this area of study, as determined by a comprehensive review.²⁴ In China, a 5G-Cloud Technology Platform was tested to perform remote parameter testing and reprogramming in a single center, using the Abbott RM system. In 480 patients, the study demonstrated non-inferiority in parameter testing time and reduced personnel contact.²⁵ This study was done in the context of the COVID-19 pandemic but did not provide definitive evidence for use of that system. There is a trial protocol published to test the use of an SMS messaging system in 100 participants that has not yet been completed.²⁶ The REM-HF study utilized RM data to treat heart failure with a primary outcome of death and unplanned hospitalizations in 1650 participants, but failed to show any difference, including in healthcare utilization.²⁷

Digital health platforms are ubiquitous in the current era. Many are industry-driven without any evidence base supporting their use, particularly in improving health outcomes. The cornerstone of digital health must be to increase efficiency, reduce cost, and result in delivery of high-quality care irrespective of geography, socio-economic status and other determinants of health that lead to worse outcomes. Prior studies have found some promising outcomes in

the use of digital health in the areas of cardiometabolic parameters and hypertension control.^{28,29} While there were some positive outcomes, these reviews highlighted the lack of studies in low- to middle-income countries, mixed results and lack of long-term follow-up. The concept evaluated and tested in VIRTUES-PM and VIRTUES-ICD, adds to the growing body of literature on how digital health platforms may contribute to the future of healthcare. The patient populations in our trial encompassed complex medical conditions including frail patients, heart failure, recurrent ventricular arrhythmias, new-onset atrial fibrillation, and yet remained safe and efficacious, suggesting that this method of care can be used in the management of a device population, particularly for those residing in rural geography. The trial was performed in tertiary care institutions with on-site cardiac electrophysiology, yet VIRTUES care remained non-inferior to what most would construe as the highest standard of care for CIEDs. Not only did VIRTUES provide a single platform for PM and ICD care, but it also provided the added benefits of direct patient communication. This is not currently available worldwide, even in electronic health records, where customizability and individualizing information for the patient is a challenge.

One of the strengths of these trials is that we were inclusive of participants residing in a diverse geographic distribution in Canada, consisting of both ICDs and PMs, including those implanted for secondary prevention of sudden cardiac death and with pacemaker dependence. The use of this platform in many provinces in Canada supports its use in varied geographies, including urban, rural or remote sites. The impact on the environment with reduction in travel for thousands of CIED patients worldwide would be immediate and sustained. The study designs used prespecified non-inferiority margins based on prior studies to minimize overinflation of the findings.³⁰ There was high adherence to both SOC and VIRTUES care, strengthening the non-inferior findings. Finally, patients were central to the study design and conduct, with an active patient council involved at each step of the design of the VIRTUES care platform and the study itself. There are, however, some limitations to note. The event rates in the two trials were lower than anticipated, and although the relative risk ratios were used to avoid over-inflation of the claim to non-inferiority, rather than using the absolute risk difference, the result should be interpreted with caution.³¹ This trial was conducted in Canada with a single-payer healthcare system; thus, the results may not apply to other healthcare systems. The follow-up of this trial is 18 months, which may underestimate the true cost saving for the lifetime of CIED care.

Conclusions

VIRTUES-CIED demonstrated that this digital platform in combination with remote monitoring was non-inferior in safety and efficacy to the standard of care, providing excellent patient satisfaction and generating cost-savings for patients and the healthcare system. This method of patient-centric management should be implemented to improve care for patients with CIEDs worldwide.

Contributors

RP composed the first draft of the manuscript. RP, AT, and GW formulated the overarching research goals and aims and directly accessed and verified the underlying data. RP, KT, and GW completed the analysis for the study. All other authors contributed to the enrolment of patients, clinical follow-up and revised the manuscript for important intellectual content. All authors had full access to all the data in the study, verified the data and vouch for the fidelity of the trial to the protocol. All authors approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

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Data Sharing

De-identified individual participant data, the statistical code, and a data dictionary defining each field in the dataset will be made available 9 months after study publication, subject to approval by the Executive Committee. Access will be reviewed by the Executive Committee and provided only to researchers with a methodologically sound research proposal, and after signing a data access agreement. Requests should be directed to the corresponding author via email. The study protocol (versions 19 (ICD) and 10 (PM)) and statistical analysis plan are available in the Supplement.

Table 1. Baseline characteristics VIRTUES PM

Demographics	VIRTUES n (%)	SOC n(%)
	n=427	n=420
Age (years) (mean $\pm$ SD)	70.7 $\pm$ 12.3	70.4 $\pm$ 12.4
Sex (Male,%)	147 (34.4)	152 (36.2)
Type of Device (n,%)		
Pacemaker	388 (90.9)	390 (92.9)
Cardiac Resynchronization Therapy	39 (9.1)	30 (7.1)
New York Heart Association Class II/ III/IV	129 (30.2)	126 (30.0)
Hypertension	257 (60.2)	234 (55.7)
Dyslipidemia	212 (49.7)	201 (47.9)
Diabetes	90 (21.1)	86 (20.5)
Current Smoker	28 (6.6)	17 (4.1)
Stroke/transient ischemic attack	44 (10.3)	41 (9.8)
Valvular Heart Disease	61 (14.3)	69 (16.4)
Chronic Obstructive Pulmonary Disease	18 (4.2)	14 (3.3)
Congenital Heart Disease	20 (4.7)	17 (4.0)
Peripheral Vascular Disease	18 (4.2)	14 (3.3)
Coronary Artery Disease	82 (19.2)	73 (17.4)
Percutaneous coronary intervention	31 (7.3)	22 (5.2)
Coronary artery bypass grafting	30 (7.0)	26 (6.2)
Frailty score >3	65 (15.2)	53 (12.6)
Ejection Fraction, % (mean $\pm$ SD)	56.5 $\pm$ 9.1	57.1 $\pm$ 8.6
Pacemaker dependent	122 (28.6)	119 (28.3)
Rural location	103 (24.1)	72 (17.1)
Medications		
Beta blocker	161 (37.7)	155 (36.9)
Angiotensin Converting Enzyme inhibitor/Angiotensin II Receptor Blocker/ARNI	192 (45.0)	191 (45.4)
Mineralocorticoid receptor antagonist	46 (10.8)	22 (5.2)
Sodium Glucose cotransporter 2 inhibitor	53 (12.4)	41 (9.8)
Oral anticoagulation	200 (46.8)	168 (40.0)
Antiarrhythmic drug	32 (7.5)	31 (7.4)
Diuretic	105 (24.6)	98 (23.3)

SD=Standard deviation; ARNI=angiotensin receptor-neprilysin inhibitor; Wilcoxon test used for age.

Table 2. Primary and Secondary Outcomes VIRTUES PM: Safety and Efficacy

	VIRTUES n=427	Standard of Care n=420	Hazard Ratio (95% CI)	P value
Safety	26(6.1)	31(7.4)	0.83 (0.49,1.39) 0.76 (0.45,1.29)*	0.0213 0.0101
Components of composite				
Device related hospitalization	0	2(0.48)		
Hospitalization due to a cardiovascular cause	15(3.5)	21(5.0)	0.71 (0.37,1.38)	
Death	12 (2.8)	11(2.6)	1.08 (0.48,2.45)	
Stroke	0	2(0.48)		
	Time from clinical event to decision (days) N(%) median (IQR)	Time from clinical event to decision (days) N(%) median (IQR)	Difference in Means Difference in medians (95% Confidence Interval)	P value non-inferiority
Efficacy	18 (4.2) 0 (0,3)	12 (2.9) 3.25 (0,102)	-3.5 (-102,2)	0.003

Data are displayed as n(%). ** HR adjusted for remoteness,current smoker,anticoagulant and baseline mineralocorticoid antagonist; CI=confidence interval

Table 3. Cost savings VIRTUES-PM

	VIRTUES (n=420)	Standard of Care (n=415)	Adjusted Difference	P-Value*
Adjusted Mean Cost (95% CI) CAD 2026				
Cost to health care system				
Remote device interrogation	\$76 (\$72 - \$80)	\$20 (\$17 - \$23)	\$56 (\$52 - \$62)	<0.01
In-clinic device visit	\$53 (\$44 - \$62)	\$158 (\$145 - \$170)	-\$105 (-\$120 - -\$90)	<0.01
Cost to patient and personal caregiver				
Patient	\$7 (\$3 - \$12)	\$31 (\$19 - \$42)	-\$23 (-\$36 - (-\$11))	<0.01
Caregiver	\$0 (\$0 - \$1)	\$5 (\$1 - \$9)	-\$5 (-\$9 - \$0)	0.04
Total	\$137 (\$126 - \$148)	\$214 (\$193 - \$234)	-\$77 (-\$100 - (-\$54))	<0.01

*P-values were estimated using two-part models (logistic regression for any costs and gamma generalized linear models with a log link and robust variance estimation), adjusted for smoking status and diabetes.

Table 5. SF-36 PM

	VIRTUES	Standard of Care	P-time	P-treatment
Physical Component summary			0.016	0.72
Baseline	47.0± 9.9	46.5± 9.6		
End of study	46.1 ± 10.2	46.1±10.8		
Mental Component summary			0.142	0.0742
Baseline	53.1± 9.0	52.0± 9.7		
End of study	53.4± 9.1	52.6± 9.7		
Physical functioning			0.0042	0.60
Baseline	72.6±26.5	71.3±27.3		
End of study	70.6±27.8	69.4±28.5		
Role-Physical			0.32	0.46
Baseline	71.0±27.8	68.3±29.3		
End of study	70.8±29.9	71.0±30.8		
Bodily Pain			0.31	0.76
Baseline	68.2±25.9	67.4±27.0		
End of study	66.5±26.6	66.5±27.6		
General health			0.0017	0.77
Baseline	66.5±20.3	65.8±19.7		
End of study	64.6±21.7	64.0±21.7		
Vitality			0.60	0.048
Baseline	61.8±19.8	58.6±21.2		
End of study	61.0±20.6	59.3±21.4		
Social Functioning			0.74	0.013
Baseline	83.4±21.9	79.5±25.7		
End of study	83.5 ± 24.4	80.0±26.3		
Role-emotional			0.21	0.20
Baseline	84.1±23.1	82.2±24.7		
End of study	85.1±23.6	83.4±24.5		
Mental health			0.59	0.45
Baseline	78.9 ±16.0	77.7±16.7		
End of study	78.7±16.8	78.6±17.2		

Data reported as mean with standard deviation. All p-values reported in following sequence. First assessed interaction model and then reported p-values for non interaction model if interaction not significant. If interaction significant all p-values are reported from the interaction model.

Table 6. Baseline Characteristics VIRTUES-ICD

Demographics	VIRTUES n (%)	SOC N(%)
	n=562	N=553
Age (years) (mean $\pm$ SD)	64.6 $\pm$ 11.5	77 $\pm$ 12.2
Sex (Male,%)	441 (78.5)	437 (79.0)
Type of Device (n,%)		
ICD	397 (70.6)	398 (72.0)
Cardiac Resynchronization Therapy	165 (29.4)	155 (28.0)
New York Heart Association Class II/ III/IV	210 (37.4)	206 (37.3)
Hypertension	287 (51.1)	263 (47.6)
Dyslipidemia	308 (54.8)	278 (50.3)
Diabetes	181 (32.2)	138 (24.9)
Current Smoker	67 (11.9)	45 (8.1)
Stroke/transient ischemic attack	47 (8.4)	52 (9.4)
Valvular Heart Disease	56 (9.9)	45 (8.1)
Chronic Obstructive Pulmonary Disease	43 (7.7)	49 (8.9)
Congenital Heart Disease	15 (2.7)	18 (3.3)
Peripheral Vascular Disease	26 (4.6)	21 (3.8)
Coronary Artery Disease	251 (44.7)	240 (43.4)
Percutaneous coronary intervention	155 (27.6)	138 (24.9)
Coronary artery bypass grafting	79 (14.1)	67 (12.1)
Frailty score >3	90(16.0)	71 (12.8)
Ejection Fraction, % (mean $\pm$ SD)	41.8 $\pm$ 13.7	43.0 $\pm$ 13.5
Pacemaker dependent	49 (8.7)	45 (8.1)
Rural location	143 (25.4)	141 (25.5)
Medications		
Beta blocker	454 (80.8)	439 (79.4)
Angiotensin Converting Enzyme inhibitor/Angiotensin II Receptor Blocker/ARNI	423 (75.3)	393 (71.1)
Mineralocorticoid receptor antagonist	252 (44.8)	233 (42.1)
Sodium Glucose cotransporter 2 inhibitor	170 (30.3)	155 (28.0)
Oral anticoagulation	195 (34.7)	210 (38.0)
Antiarrhythmic drug	107 (19.0)	115 (20.8)
Diuretic	161 (28.7)	122 (22.1)

Wilcoxon test used for age. ICD=implantable cardioverter defibrillator; SD=standard deviation;ARNI= angiotensin receptor-neprolysin inhibitor;

Table 7. Co-Primary outcomes VIRTUES ICD: Safety and Efficacy

	VIRTUES	Standard of Care	Hazard Ratio (95% CI)	P value Non-inferiority
	n=562	n=553		
Safety	62 (11.0)	62 (11.2)	0.98(0.69,1.39) *0.90(0.63,1.29)	0.023 0.0079
Components of composite				
Device related hospitalization	3 (0.53)	4 (0.72)	0.73 (0.16, 3.26)	
Hospitalization due to a cardiovascular cause	54 (9.6)	51(9.2)	1.03 (0.70,1.51)	
Death	18 (3.2)	22 (4.0)	0.81 (0.44,1.51)	
Stroke	1 (0.18)	1 (0.18)	0.99 (0.062,15.9)	
	Time from clinical event to decision (days) median (IQR)	Time from clinical event to decision (days) median (IQR)	Difference in medians (95% Confidence Interval)	
Efficacy	73 (13.0) 2 (0,14)	83 (15.0) 1 (0,7)	1.00 (-1,2)	0.003

* adjusted for current smoking, diabetes, diuretics at baseline; SD=standard deviation; IQR=interquartile range

Table 8. Cost Savings: second primary outcome VIRTUES-ICD

	VIRTUES (n=551)	Standard of Care (n=546)	Adjusted Difference	P- Value*
	Adjusted Mean Cost (95% CI) CAD 2026			
Cost to health care system				
Remote device interrogation	\$201 (\$190 - \$211)	\$161 (\$152 - \$170)	\$40 (\$26 - \$53)	<0.01
In-clinic device visit	\$67 (\$58 - \$77)	\$144 (\$133 - \$154)	-\$76 (-\$90 – (-\$62))	<0.01
Cost to patient and personal caregiver				
Patient	\$14 (\$9 - \$19)	\$50 (\$39 - \$61)	-\$36 (-\$48 – (-\$23))	<0.01
Caregiver	\$3 (\$0 - \$6)	\$7 (\$1 - \$14)	-\$5 (-\$12 - \$3)	0.23
Total	\$286 (\$269 - \$302)	\$363 (\$340 - \$385)	-\$77 (-\$105 – (-\$49))	<0.01

*P-values were estimated using two-part models (logistic regression for any costs and gamma generalized linear models with a log link and robust variance estimation), adjusted for smoking status and diabetes.

Table 9. SF-36 VIRTUES-ICD

	VIRTUES	Standard of Care	P-time	P-treatment
Physical Component summary			0.12	0.48
Baseline	45.9± 9.3	46.2± 9.5		
End of study	45.5 ±10.2	46.5±9.8		
Mental Component summary			0.46	0.07
Baseline	50.5±10.6	51.5±9.3		
End of study	50.7±11.2	52.1±9.8		
Physical functioning			0.25	0.18
Baseline	69.2±24.9	71.2±24.2		
End of study	68.9±26.6	71.7±25.5		
Role-Physical				
Baseline	67.5±28.6	67.3±29.2		
End of study	67.7±30.0	71.4±29.5		
Bodily Pain			0.90	0.26
Baseline	68.2±25.7	69.4±26.6		
End of study	67.7±26.7	70.2±26.2		
General health			0.0002	0.28
Baseline	59.1±21.7	60.0±20.9		
End of study	56.7±22.2	59.2±21.9		
Vitality			0.0058	0.030
Baseline	56.3 ± 20.7	59.1±19.5		
End of study	55.1±22.5	57.9±20.4		
Social Functioning			0.27	0.20
Baseline	78.8±26.4	79.7±24.7		
End of study	78.9±26.7	82.4±25.1		
Role-emotional			0.13	0.014
Baseline	77.7±26.6	81.0 ± 24.4		
End of study	79.0±27.5	82.8±24.5		
Mental health			0.45	0.26
Baseline	75.6±19.1	76.6±16.8		
End of study	75.7±19.7	77.9±17.3		

Data reported as mean with standard deviation. All p-values reported in following sequence. First assessed interaction model and then reported p-values for non interaction model if interaction not significant. If interaction significant all p-values are reported from the interaction model.

Figure Legends

Figure 1. VIRTUES care process: Patients are informed through an alert via the app on their phone or tablet, or by email/text/phone call if the app was no longer accessible. The platform automatically populates: device longevity, percent atrial and ventricular pacing, alerts, atrial and ventricular arrhythmias.

Figure 2. VIRTUES care transmission guide

The * indicates: automatically inserted from the remote transmission into the platform

Figure 3. Consort diagram for VIRTUES-PM

Figure 4 Primary safety outcome VIRTUES-PM: Time to death, stroke, unplanned cardiovascular hospitalizations, device-related hospitalizations

Figure 5. This figure illustrates the rate of in-clinic and remote visits, scheduled and unscheduled in VIRTUES-PM. The blue bars represent the VIRTUES arm, the orange bars the standard of care arm. All comparisons between the arms are significant to a $p < 0.0001$ except where indicated on the figure ($p = \text{ns}$ (not significant)).

Figure 6. Consort diagram for VIRTUES-ICD

Figure 7. Primary safety outcome VIRTUES-ICD: Time to death, stroke, unplanned cardiovascular hospitalizations, device-related hospitalizations

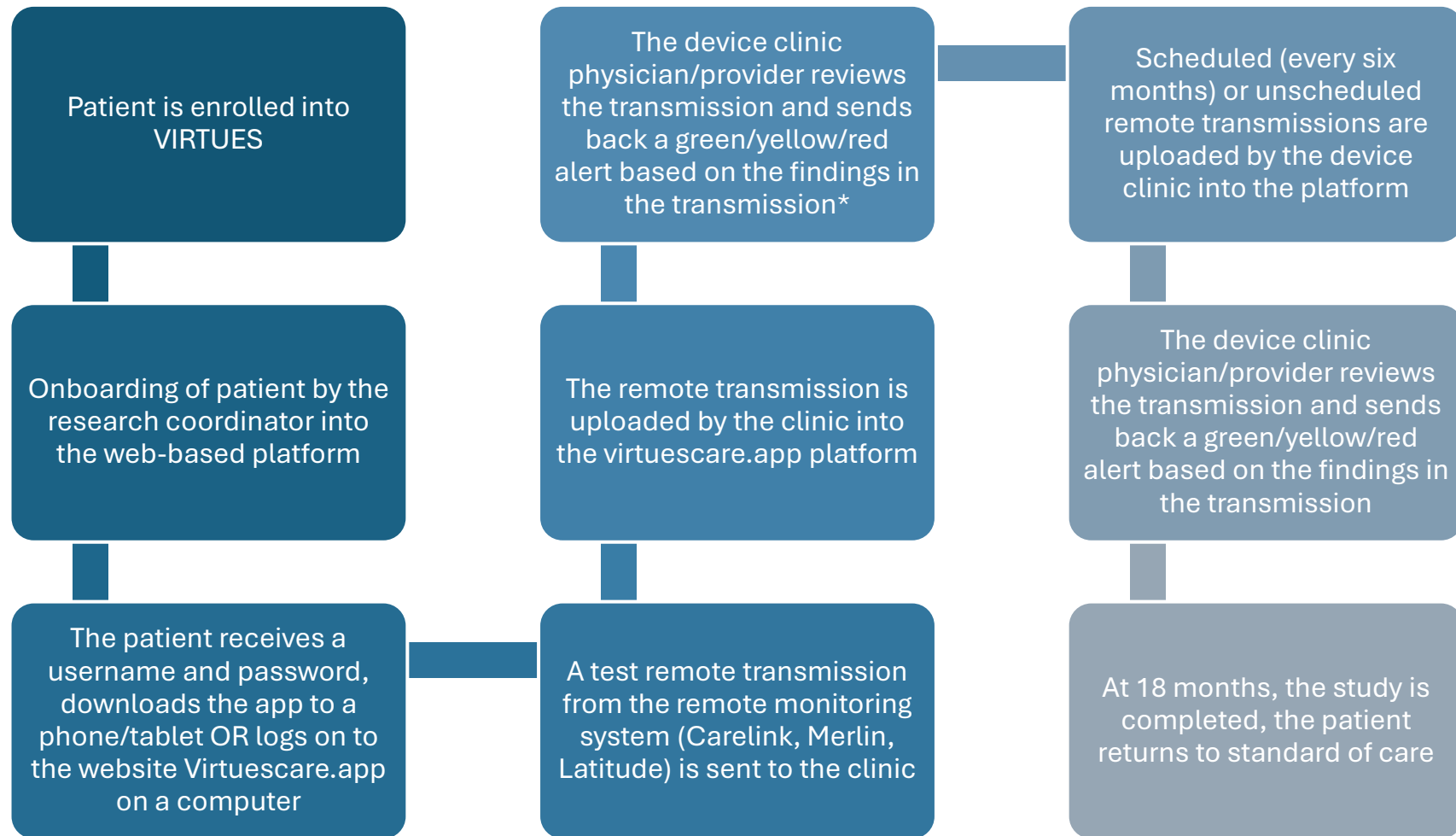
Figure 8. This figure illustrates the rate of in-clinic and remote visits, scheduled and unscheduled in VIRTUES-ICD. The blue bars represent the VIRTUES arm, the orange bars the standard of care arm. All comparisons between the arms are significant to a $p < 0.0001$ except where indicated on the figure ($p = \text{ns}$ (not significant)).

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Figure 1 VIRTUES process



*Patients are informed through an alert via the app on their phone or tablet, or by email/text/phone call if the app was no longer accessible. The platform automatically populates: device longevity, percent atrial and ventricular pacing, alerts

Figure 2 VIRTUES transmission *automatically inserted from the remote transmission into the platform

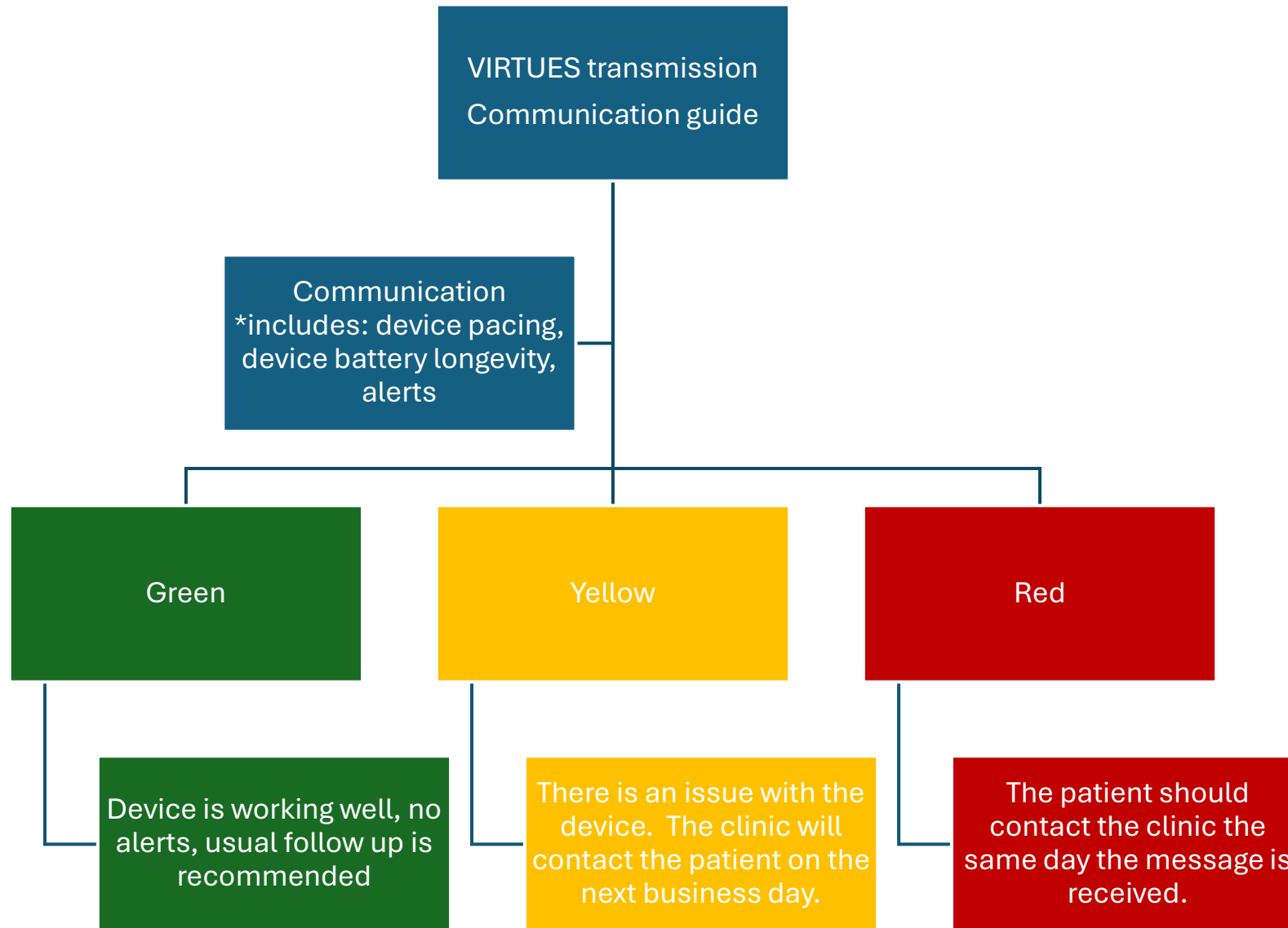


Figure 3. CONSORT diagram VIRTUES-PM

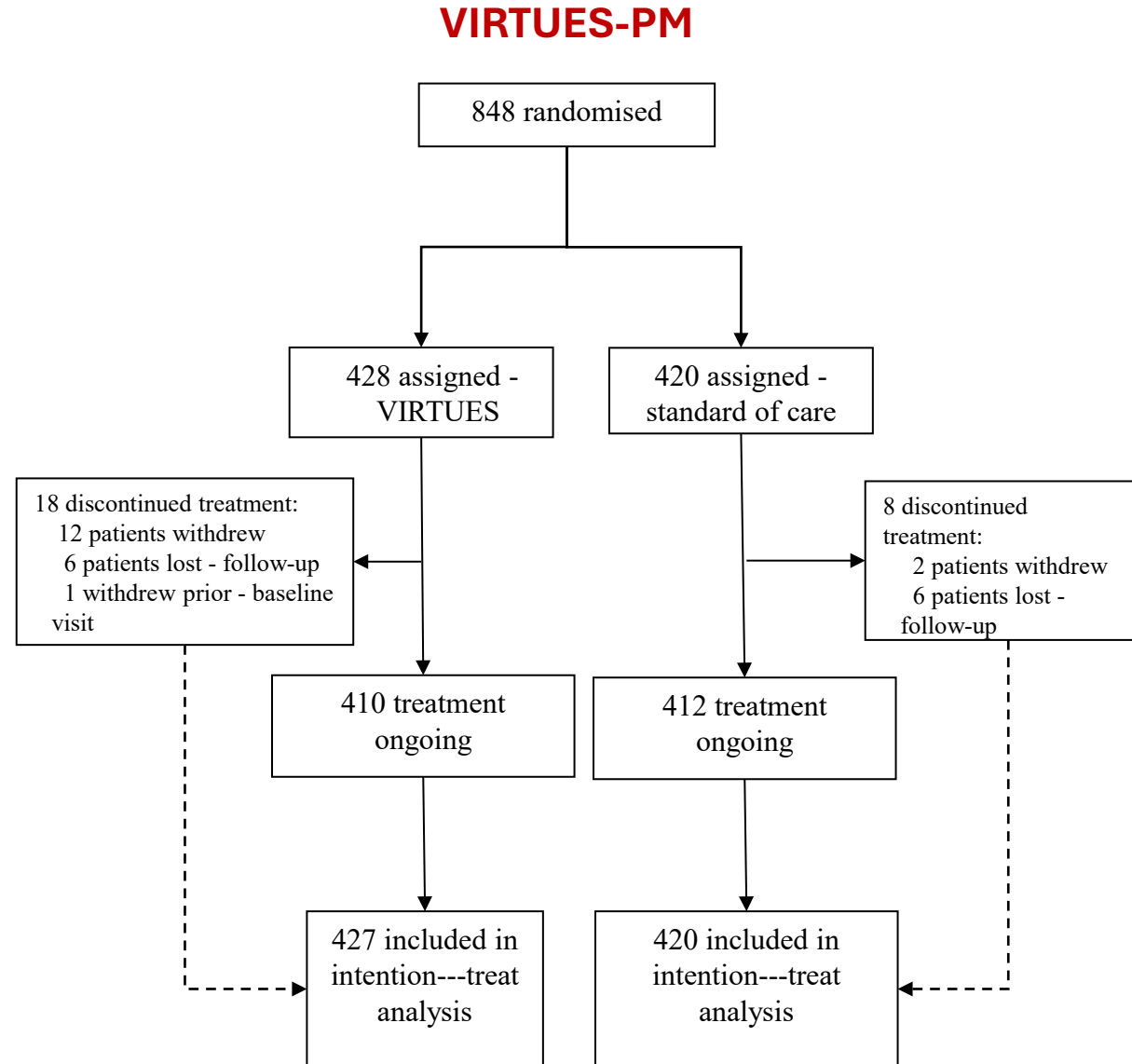
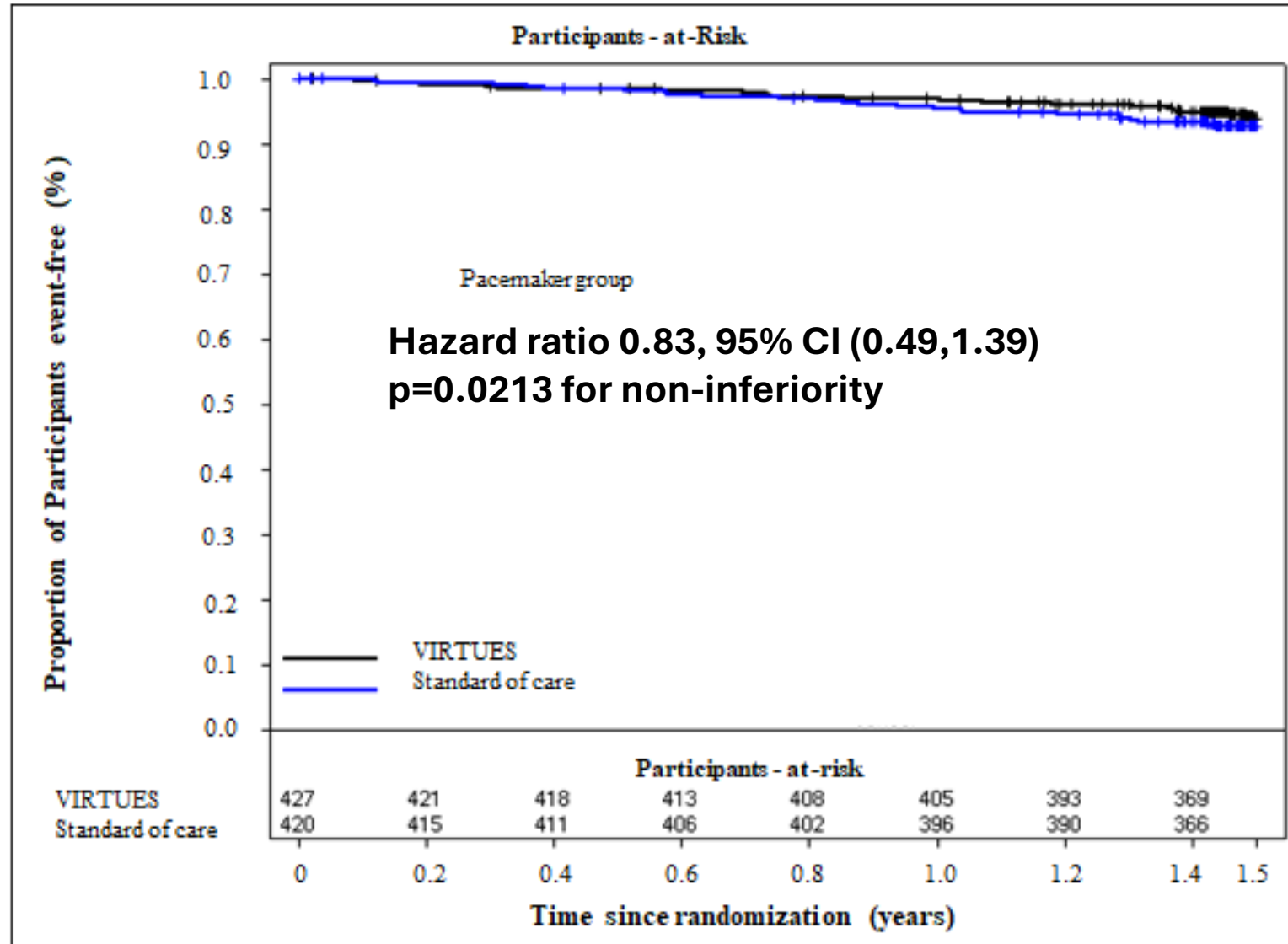


Figure 4. Primary Safety Outcome: VIRTUES-PM



This figure illustrates the rate of in-clinic and remote visits, scheduled and unscheduled. The blue bars represent the VIRTUES group, the orange bars the standard of care group. All comparisons between the groups are significant to a $p < 0.0001$ except where indicated on the figure ($p = \text{ns}$ (not significant)).

Figure 5

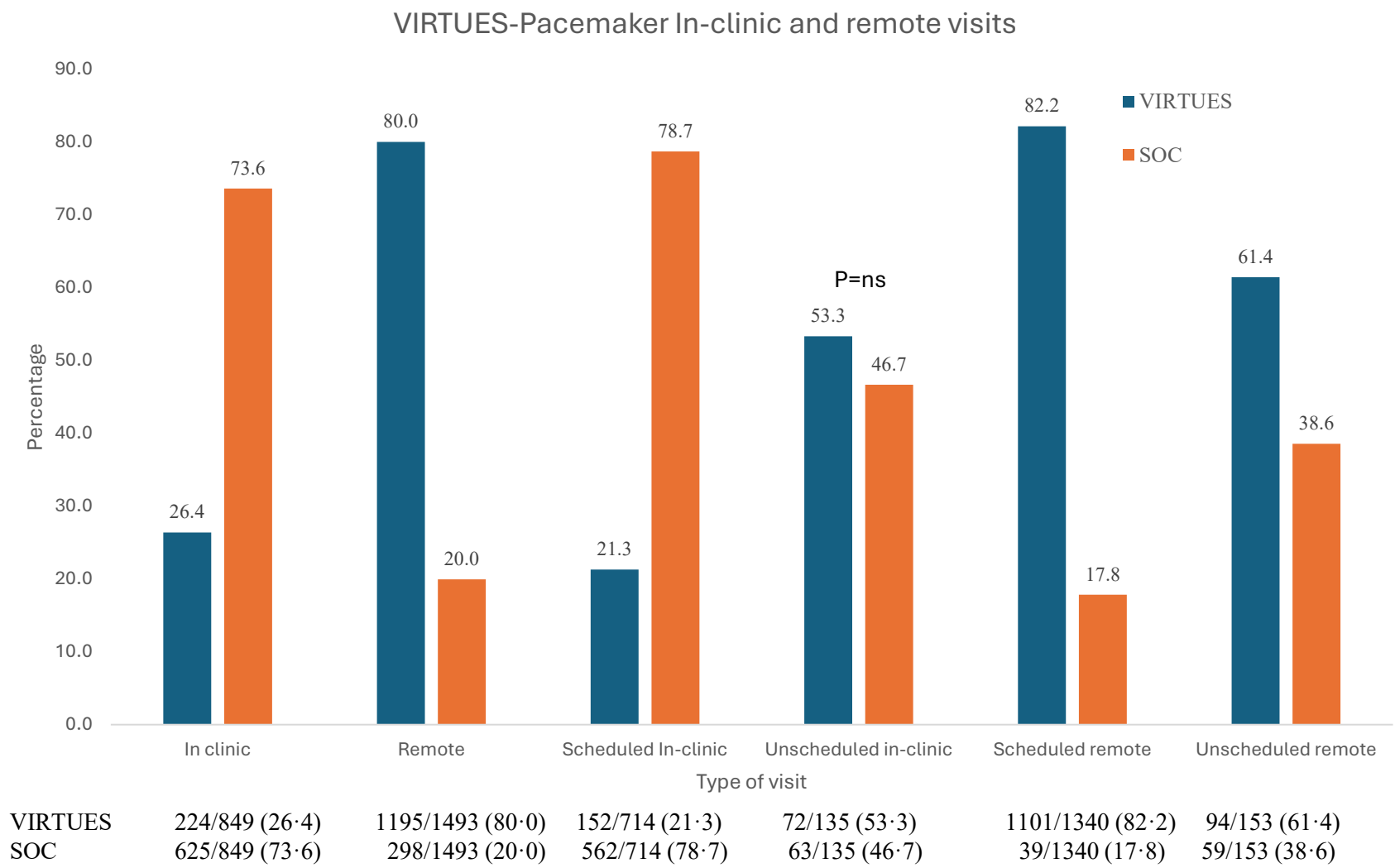


Figure 6. CONSORT diagram VIRTUES-ICD

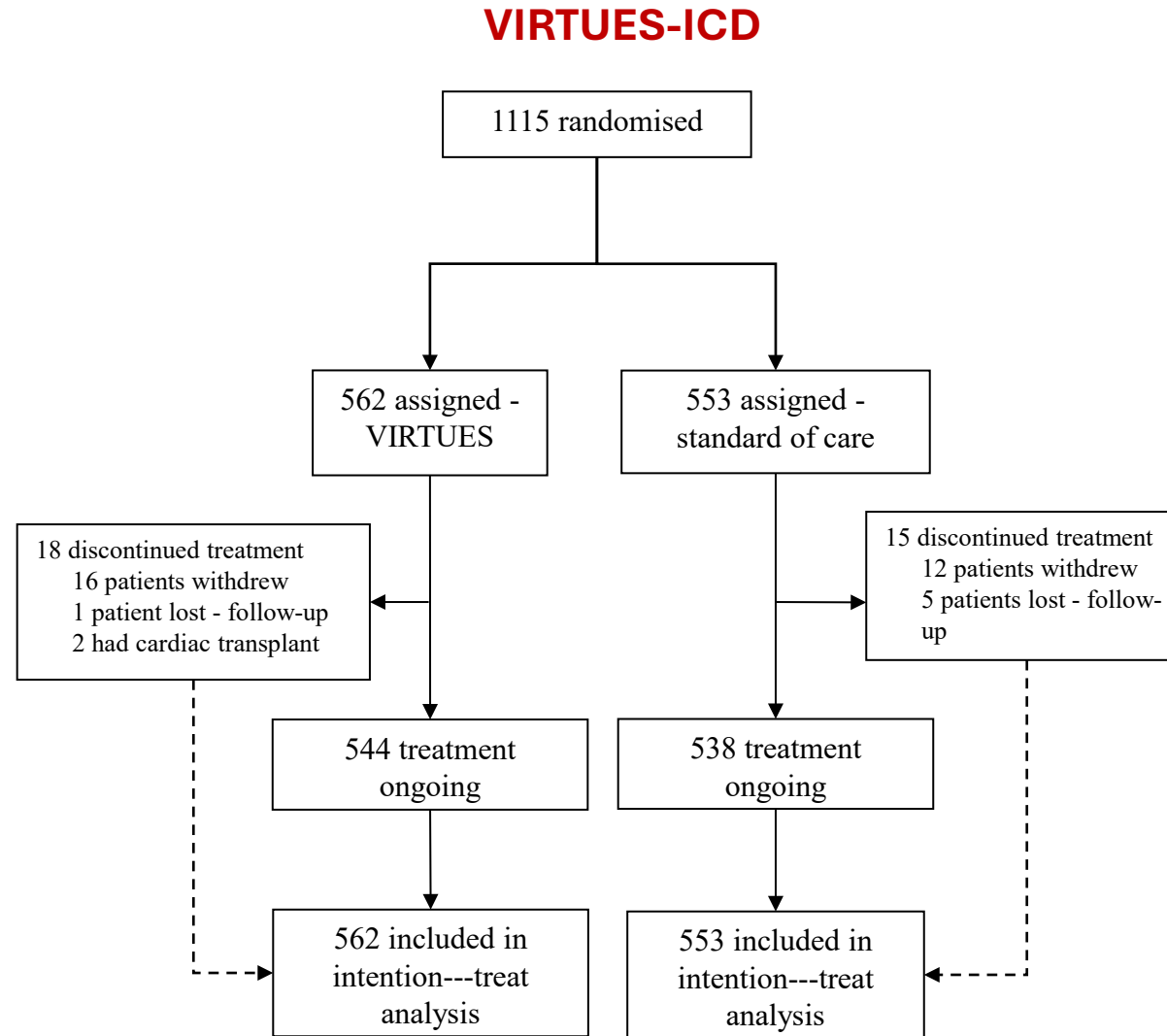
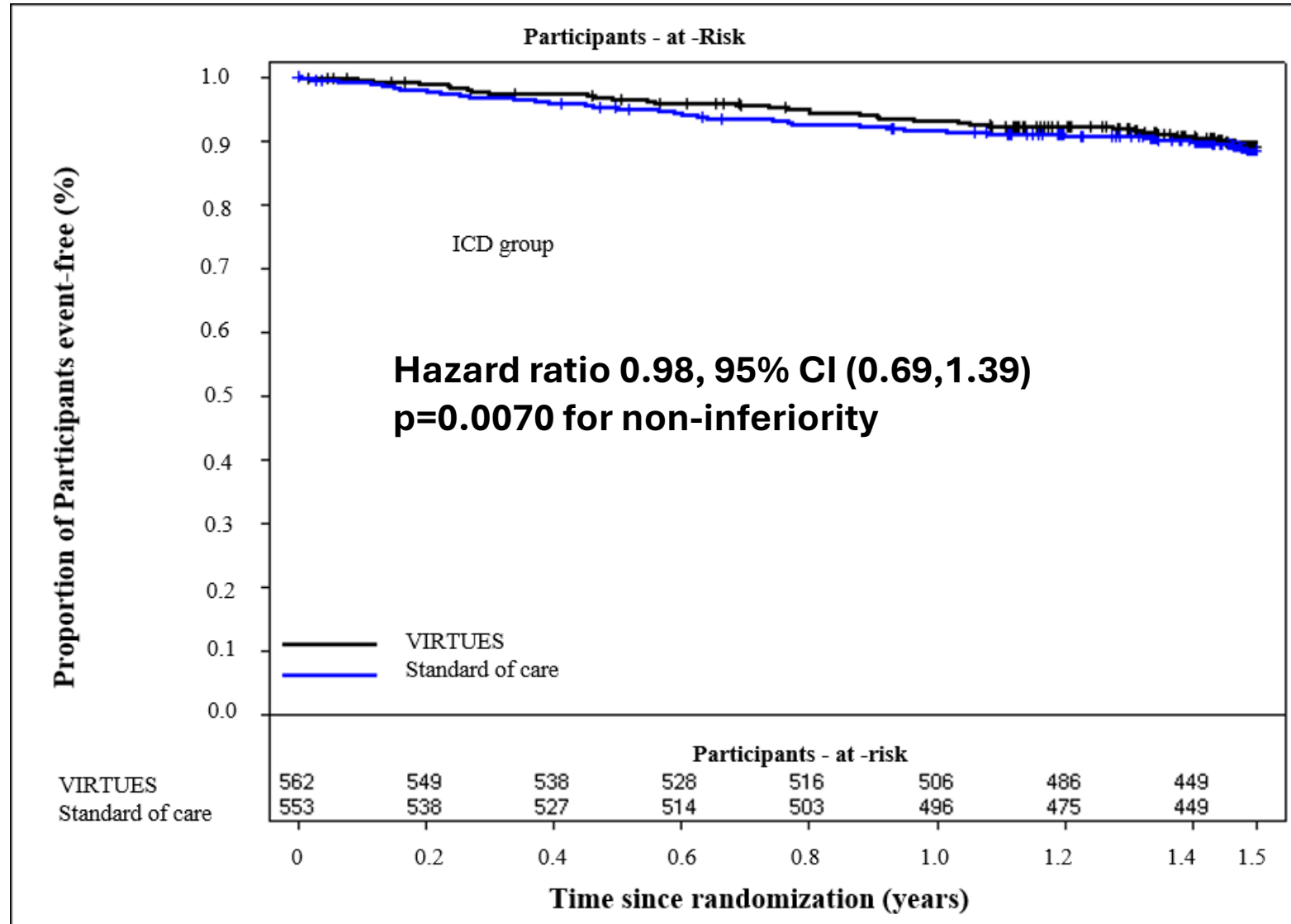


Figure 7. Primary Safety Outcome: VIRTUES-ICD



VIRTUES-ICD in clinic and remote visits

VIRTUES-ICD in clinic and remote visits



Supplementary Files

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