Interventions Supporting Long-term Adherence aNd Decreasing cardiovascular events: pragmatic randomized trial protocol.

Brief title: ISLAND Pragmatic Trial Protocol

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Abstract

Background
Guidelines recommend cardiac rehabilitation (CR) and long-term use of cardiac medications for most patients who have had a myocardial infarction (MI), but adherence to these secondary prevention treatments is sub-optimal.

Methods/Design
This is a multi-center, pragmatic, three-arm randomized trial. Eligible patients are randomized post-MI to usual care or one of two intervention arms. Patients in the first intervention arm receive mail-outs sent on behalf of their cardiologist at 4, 8, 20, 32, and 44 weeks post-MI; content is designed to address determinants of adherence, and facilitate discussion between the patient and their health care team. Patients in the second intervention arm receive mail-outs plus automated interactive voice response system (IVRS) phone calls 2 weeks after each letter, as well as a telephone call by trained lay health workers if the IVRS identifies challenges with adherence. Outcomes are assessed 12 months post-MI via patient self-report and administrative data sources. Co-primary outcomes are adherence to cardiac medications and completion of CR. Secondary outcomes include cardiovascular events and mortality. An embedded, theory-informed process evaluation will explore the mechanism of action; an economic evaluation is also planned.

Discussion
We describe a complete program evaluation of a highly pragmatic, health-system intervention to support adherence to recommended treatments. Research ethics boards approved waiver of consent for patients enrolled in the trial with provision of multiple opportunities to opt-out and a debrief at the time of outcome assessment. The methods used here may provide a model for similar interventions.

Keywords: myocardial infarction, adherence, cardiac rehabilitation, secondary prevention, behavioural interventions

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Introduction

Description of the problem: adherence to treatment post myocardial infarction (MI)

Coronary artery disease (CAD) is responsible for about one-third of the mortality in individuals over age 35[1]. Almost half of all middle-aged men and a third of middle-aged women in high-income countries will develop clinical manifestations of CAD, such as a myocardial infarction (MI)[2]. Half of MIs and 70% of CV deaths occur in patients with a history of CAD[3]. Secondary prevention medications may reduce mortality by a remarkable 65%-75%[4-6]. For nearly all MI patients, guidelines recommend four medication classes for greater than 12 months: statins, anti-platelets, beta-blockers, and an angiotensin-agent. The recommended medications have an additive effect; strong evidence from multiple trials indicate that adherence to more of these medications is inversely associated with mortality, morbidity, and health system cost[7-10]. However, sub-optimal adherence to cardiac medications is common; up to half of patients discontinue their cardiac medications by one year[11-14] and this in turn associated with increased mortality[7-9] and higher health costs[10,11].

In addition to medications, a core component of secondary prevention is cardiac rehabilitation (CR), which can reduce mortality by 25% and improve quality of life[12], with greater risk reduction achieved amongst those who complete the program[15]. Therefore, international guidelines strongly recommend that patients complete CR as soon as feasible post-MI. Unfortunately, only one-third of MI patients complete CR[13,16]; utilization of CR may be even worse for certain sub-groups[17]. Thus, interventions to improve adherence to recommended treatments post-MI are urgently needed that address both persistence with secondary prevention medications and CR participation.

Addressing the problem: improving adherence to medication and rehabilitation post-MI

A 2014 Cochrane review of interventions to enhance medication adherence identified 109 trials, but lamented the poor quality of evidence and was unable to recommend specific strategies[18]. The authors noted that many trials feature multifaceted interventions that would be expensive to implement at scale. A recent economic analysis indicated that of all the strategies available to improve medication adherence post-MI, educational reminders sent via mail represented the option with the greatest potential to be cost-effective[19].

With respect to CR, a 2014 Cochrane review concluded that "recommendations for increasing adherence to cardiac rehabilitation cannot be made."[20] However, some noteworthy findings suggest that relatively low-cost interventions can be successful if tailored to patient barriers. For example, in trials targeting initial uptake of CR, mailed letters and patient navigation via telephone achieved 18-30% improvements[21-23], especially when reminder content addressed predictable obstacles and included motivational messages [24].

Non-adherence to treatment can be difficult to define has been described as either intentional or unintentional[25]; this framework is a useful starting point, but provides minimal insight regarding how best to specifically address treatment adherence. There is an increasing recognition amongst those developing health services interventions that the strategies used to support change should address underlying determinants of the targeted behavior(s)[26,27]. For instance, the Theoretical Domains Framework (TDF) synthesizes key theories of behavior and behavior change, and their underlying constructs, into 14 over-arching domains that have been used as a basis to investigate potential barriers and enablers to change[28,29]. In our recent qualitative work, a number of the TDF domains seemed

particularly important for understanding treatment adherence post-MI, including *beliefs about consequences* (concern regarding side effects and less certainty about benefits), *behavioral regulation* (the importance of developing a routine, and the utility of pill boxes and reminders), *social/professional role and identity* (taking medication as a change in how patients saw themselves and perceived that others saw them), *memory, attention and decision processes* (forgetting to take their medication), and *social influences* (the importance of healthcare provider and family advice and support)[30]. These qualitative findings point towards key factors to consider in selecting the strategies for an intervention that aims to address adherence post-MI.

The TDF does not provide insight into how these domains relate to one another; an explicit theory of behavior change is needed to explain the processes underlying changes in treatment adherence that are or are not observed. For instance, the Health Action Process Approach (HAPA) describes health-related behaviors (including adherence to treatment recommendations) as a function of key constructs such as risk perception, outcome expectancies, self-efficacy, intention (motivation), action and coping planning, and action control (including self-monitoring), with barriers/facilitators such as social support playing a key role throughout,[25,31-35] as illustrated in Figure 1.

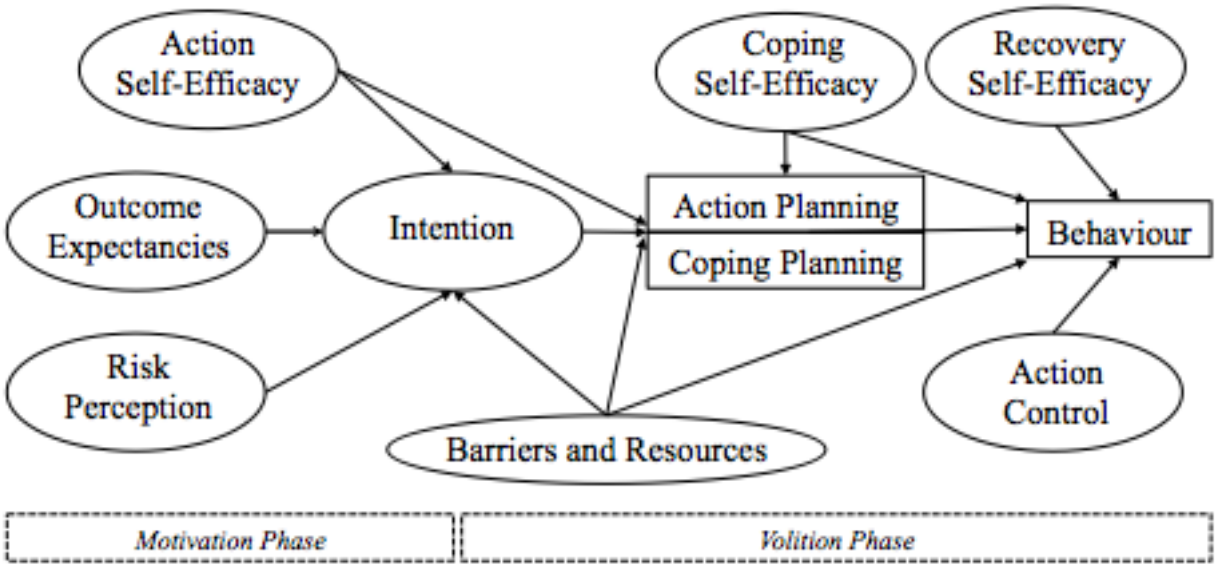

Figure 1. Health Action Process Approach (HAPA; Schwarzer 1992, 2008; Schwarzer & Luszczynska, 2015 [33-35])

Amongst patients who have had a recent MI, we have shown that HAPA constructs are associated with medication adherence[30]. HAPA builds upon previous studies demonstrating that adherence to treatment recommendations can be predicted (in part) by perceived need as well as perceived benefit (versus risks)[36,37] and self-efficacy for treatment[38,39,40]. HAPA also explains evidence suggesting the potential benefit of addressing unintentional non-adherence through prompts to aid memory and also through coping plans so that treatments can be fit into normal routines and foreseeable challenges managed (e.g., through incorporation of elements related to action control and/or activating social supports)[41]. Together, the TDF and HAPA provide complementary and promising theoretical lenses to inform intervention design and content to address treatment non-adherence. By using this approach and by evaluating the extent to which changes in TDF and HAPA-relevant constructs are related to intervention effectiveness, we hope to understand not only whether or not the intervention worked, but why, and how future interventions might be best designed[42].

We previously completed a single-center pilot trial of a Delayed Educational Reminder mail-out to patients to encouraged Long-term Adherence to cardiac medications (DERLA)[43]. The findings from that trial indicated a need to make the interventions more salient and to ensure the intervention content addresses determinants of treatment adherence[44]. This manuscript describes the next steps in our program of research to address adherence to treatment post-MI, demonstrating a hybrid implementation-effectiveness study design[45] to rigorously evaluate a suite of Interventions Supporting Long-term Adherence aNd Decreasing cardiovascular events (ISLAND).

Methods

Study design

ISLAND is a pragmatic, multi-center trial with embedded mixed methods process evaluation seeks to evaluate interventions that could be readily implemented by health systems or organizations wishing to improve long-term adherence to secondary prevention treatment recommendations post-MI. Eligible patients are randomized to one of three study arms (Figure 2):

- usual care (no standardized follow up interventions)
- usual care, plus a series of mail-outs with content specifically designed to target the determinants of medication persistence and completion of CR, including information for patients to share with their personal clinicians.
- usual care, plus the same mail-outs, plus automated reminder phone calls to identify any patients at risk of non-adherence and a trained lay health worker (LHW) to provide additional support and navigation for such patients via telephone.

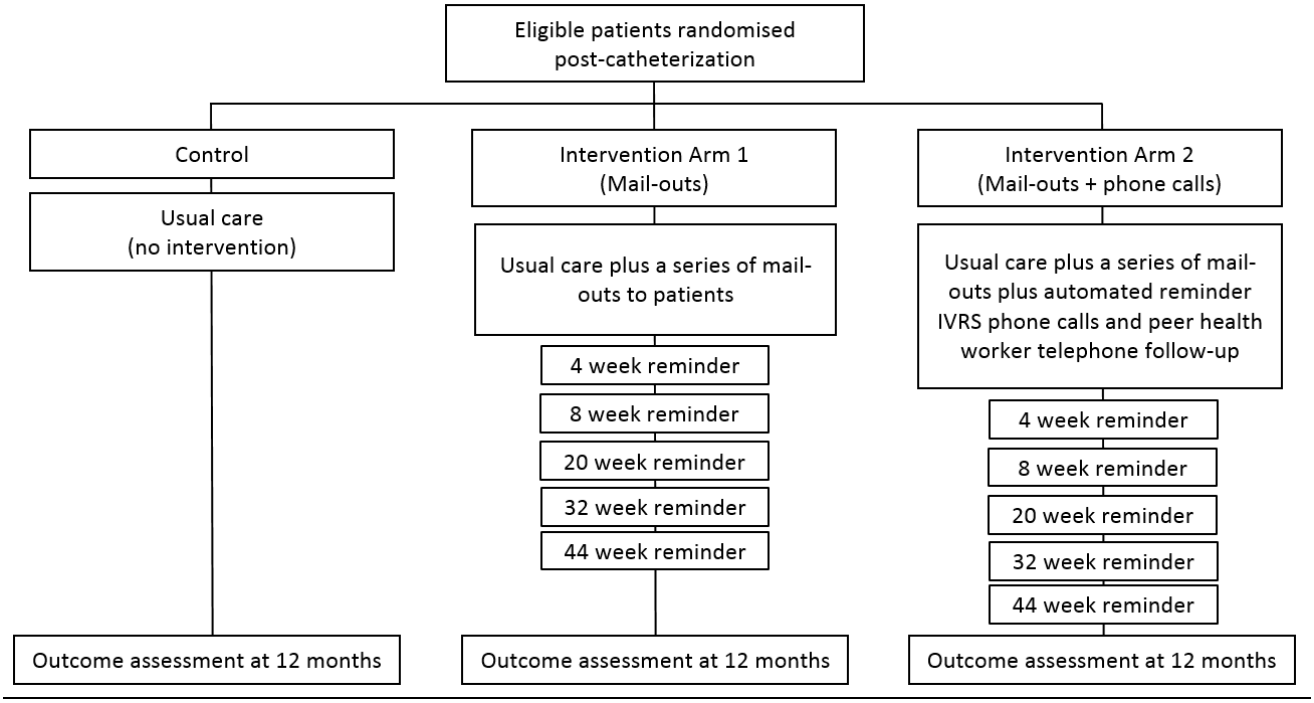

Figure 2. Trial design diagram (IVRS=interactive voice response system)

Setting

This study will take place in Ontario, Canada's most populous province. Healthcare in Ontario is financed through a single-payer (publicly administered) system. The cost of care provided in hospitals (including CR) is covered and there are no co-payments for visits to physicians. The cost of prescription medications is covered for persons 65+ years of age and those who qualify for social assistance, but other patients pay for medications out-of-pocket or through private insurance plans.

The Cardiac Care Network of Ontario (CCN) is funded by the Ontario Ministry of Health and Long-Term Care to coordinate, implement and evaluate cardiovascular care in the province[46]. At each of the 19 cardiac care centers in Ontario, CCN collects data regarding patient characteristics, indications and outcomes related to cardiac procedures. For example, for every patient requiring a cardiac catheterization, a representative at each cardiac center systematically completes standardized case report forms to allow CCN to conduct ongoing surveillance. CCN aggregates and de-identifies the data in a Cardiac Registry for use in health system planning. They also report data back to each cardiac center to facilitate local quality improvement.

Participants

Nine cardiac centers from across Ontario were engaged by the research team. To test the implementation of this intervention as an automated, health-system-level process, all eligible patients at each participating center were enrolled (see ethical considerations section regarding waiver of consent and opportunities to opt-out).

Eligibility criteria

In participating cardiac centers, eligibility criteria for patient selection were applied using routinely collected administrative data from the CCN Cardiac Registry.

Inclusion criteria:

- Ontario residents with a valid health card, aged 18 years and older, having a coronary angiography following an MI (ST-elevation or non-ST-elevation), with evidence of coronary artery disease (>50% blockage of left main and/or >70% blockage of ≥1 major coronary artery).
- Discharged from the cardiac center alive.

Exclusion criteria:

- Experience cardiogenic shock (Killip Class 4) at the time of their post-MI coronary angiography, due to their poor prognosis[47].
- Require a translator to receive services in English as recorded in the CCN referral form, as it is infeasible to offer the interventions in multiple languages at this stage.
- Have incomplete CCN Cardiac Registry data (i.e., data submitted within 4 weeks of their angiography), as they cannot receive the intervention as intended.

Allocation

Eligible patients are identified weekly by CCN. Patient lists are provided to each respective participating cardiac center, along with their demographic and procedural details; centers in turn securely transferred data to the Population Health Research Institute (PHRI), for integration into the study database. PHRI assigned a unique identifier to each participant and allocates participants 1:1:1

to one of the three study arms, stratified by cardiac center. An independent statistician generated the randomization schedule using a permuted block design with randomly varying block sizes. The allocation sequence was concealed from investigators, study team personnel, and study centers.

Usual care

In the usual care arm, patients receive no standardized communication from the project team or from the cardiology team that conducted the angiogram. Usual care may or may not include some contact between the admitting physician (generally not the interventional cardiologist) and the outpatient cardiologist or the primary care provider (generally the family physician). The quality of such communication and/or discharge summaries varies widely even within the same institution, and summaries frequently lack necessary information regarding long-term treatment recommendations[48]. A prescription for secondary prevention medications covering <60 days[14] is usually provided to patient and all patients are expected to receive a referral to CR prior to discharge. In keeping with the pragmatic nature of the trial, no attempt will be made to standardize the usual care arm[49].

Interventions

The recurrent, behavior change-focused interventions are coordinated and delivered by the project team at PHRI on behalf of the cardiology team at the hospital where the patient had their MI treated. Interventions are timed to correspond with likely need for prescription refills, as we have previously shown that these are vulnerable times for medication persistence[14]. Specifically, interventions are delivered by mail (and potentially by telephone depending on random allocation) at approximately 4, 8, 20, 32, and 44 weeks post-MI.

Interventions include behavior change techniques selected to address factors within the TDF and HAPA identified as determinants of the targeted patient behaviors (i.e., medication persistence, CR completion). The development team, including clinical experts as well as specialists in health psychology, human factors, communications, and knowledge translation, created content based on our prior work using HAPA to address risk perception, outcome expectancies, self-efficacy, and social support, as well as brief action planning and coping planning modules and action control prompts for self-monitoring[30]. Also, based on our prior work to identify determinants of adherence using the TDF with a similar patient population[30], we designed reminder elements to overcome unintentional non-adherence and created materials that encourage goal-oriented discussions with loved ones and the trusted health care professionals in the patient's circle of care[50]. We worked with a design firm[51] and employed a user-centred process with patients to optimize the design of the interventions. To maximize comprehensibility for those who may find health terms confusing, the interventions used plain language principles[52]. The iterative design process and resulting intervention content, including the specific behavior change techniques incorporated, are described in more detail in a separate manuscript[53].

<u>Intervention Arm 1 Mailed reminders</u>

Patients receive a series of mailed mini-booklets to encourage participation in CR and long-term adherence to secondary prevention medications. Content addresses predictors of intention to follow recommended treatments, including ongoing susceptibility to CV events and potential concerns with medications, as well as self-efficacy for adherence, highlighted with patient anecdotes[53,54]. Patients are prompted to develop action plans in their booklet, focusing on: i) discussion of treatment concerns with providers; ii) obtaining refills; iii) daily medication adherence; and iv) participation in CR. We adapted action plan and coping plan modules that have previously shown to improve adherence to CR[42]. The study team cannot directly communicate with family physicians or outpatient cardiologists,

as their contact information is not reliably captured in current databases. However, the first and second mail-outs include an enclosed letter for the patient to bring to their family physician, which provides evidence in support of CR and cardiac medication persistence, tips to address adherence, and a pre-filled referral form for the CR program closest to the patient's residence (to reduce paperwork for the family physician). Examples of the booklets have been previously published[53] and full materials are available upon request.

Intervention Arm 2: Mail-out reminders plus phone calls

In addition to the mail-outs as described above, patients receive automated phone calls using an IVRS, delivered by a company with extensive healthcare IVRS experience[55], 1-2 weeks after the letters have been mailed. The letters cue the patients to expect the call and the IVRS reminds patients to follow action plans emphasized in the letters. The IVRS responds to verbal answers and provides further content regarding next steps needed to achieve the behavioural targets based on a structured algorithm. For example, patients who report non-persistence with medications or CR are encouraged by the IVRS to discuss options with their health care providers to find a regimen that works form them. A sample of the IVRS algorithm is illustrated in Appendix I.

Patients who report suboptimal adherence to medications or CR, as well as those who report not receiving the mail-out reminder, those who haven't seen their family physician in the last 3 months, and those who did not complete their IVRS call, receive phone calls by an LHW. LHWs receive standardized training adapted for this project from the ongoing international HOPE 4 Study[56] [training manuals available upon request]. The LHWs identify barriers to adherence and attempt to address these with tailored advice, following structured scripts. They aim to develop rapport, to help patients identify options to overcome barriers, and to find ways to continue with their treatments, but they do not provide clinical recommendations. The LHW encourages the patient to discuss concerns or barriers with their own health care team and attempts to help the patient with reminder strategies such as implementing pill-boxes or developing specific action plans and coping plans to keep up with their CR. A sample of the semi-structured algorithms followed by LHWs when addressing non-adherence is illustrated in *Appendix II*.

Outcomes

Tables 1a and 1b list the primary and secondary outcomes, along with definitions and data sources.

Primary outcomes

Two co-primary outcomes will be assessed 12 months post-MI: (1) adherence to recommended cardiac medication classes (statins, anti-platelets, beta-blockers, and an angiotensin-agent), measured on an ordinal scale where 0=none and 4=to all classes, and (2) completion of CR. The trial has two primary outcomes because the intervention would be deemed a success by stakeholders if it increases adherence to either of these cost-effective treatment strategies.

Secondary outcomes

Secondary outcomes measured at 12 months include: health-related quality of life, health care utilization (e.g., outpatient visits, hospitalizations), cardiovascular events (e.g., revascularizations), mortality, extent of CR attendance, and individual measures from the composite medication adherence outcome. As an additional approach to measuring adherence, the proportion of patients with adherence to *all recommended* cardiac medication classes will be measured[57]. Moreover, a continuous variable will be created by determining the number of days missed in the week prior to assessment, and cumulating this for all recommended medication classes for a maximum adherence score of 28.

Adherence will also be explored using days missed in the 30 as a dichotomous measure (<6 days missed = adherent)[58]. In addition, we will assess medication persistence (active prescription at 12 months. Finally, we will assess medication possession ratio for cardiac medications amongst those over age 65 for whom such data are available from administrative databases[7]. Although guidelines recommend dual antiplatelet therapy[59] for 1 year, outcome assessment may occur just beyond this time point. Therefore, adherence to dual antiplatelet therapy will be measured as a secondary outcome.

Data collection

Data will be collected from two sources: patient self-report and administrative databases.

Patient-reported variables

Primary outcomes will be assessed via phone call 12 months post-MI by research staff blind to treatment allocation (case report forms available upon request). We will not use an IVRS to collect outcomes to avoid risk of response bias amongst particular subgroups[60].

Patients will be asked whether they participated in CR and whether they graduated/completed the program; patient report of CR participation in Ontario is highly concordant with program report[61].

Our team has conducted phone calls to assess medication persistence using open-ended questions (e.g., "list your current prescription medications") at the time of follow-up in two previous trials, finding high agreement with administrative records[43,62]. This has also been shown to have high agreement with data from dispensing pharmacies[63]. Patients listing a medication from the recommended class will be considered as 'persistent' for that class. Patients who have not missed any days in the last 7 (or <6 in the last 30) will be considered 'adherent' for that medication class; we will also assess number of days in the last 7 missed as a continuous measure[58,64,65]. An adapted version of the Brief Medication Questionnaire[66] will be used to inquire about missed pills, using an approach previously validated for statins against cholesterol levels[58] and for antihypertensive non-adherence against pill counts and pharmacy records[64].

Patients will also be asked about health-related quality of life using the Seattle Angina Questionnaire-7, a validated disease-specific health status instrument for coronary artery disease[67]. Finally, to enable exploration of differential effects across patient subgroups, we will collect self-reported data on smoking status, marital status[68], level of education attained, ethnicity, and insurance coverage for medications (especially relevant for those under age 65)[69-71].

Data from administrative sources

Baseline patient characteristics are obtained from CCN Cardiac Registry data collected by each cardiac center. This includes basic sociodemographic information (including address from which rurality can be ascribed and neighborhood income can be estimated), comorbidities, and the findings at the time of angiography. The variables in the CCN Cardiac Registry are thought to be highly accurate – they have recently been used as a reference standard for validation of other databases[72].

We will link CCN and patient-reported data to the population-level health administrative databases held at the Institute for Clinical Evaluative Sciences (ICES) through a unique identifier. Data will be compiled from the following databases: (a) the Ontario Drug Benefits database, covering all medications on the provincial formulary prescribed to persons in Ontario over 65 years of age[73,74], including statins, beta-blockers, and angiotensin-agents, but not aspirin; (b) the Canadian Institute for Health Information Discharge Abstract Database covering hospital discharge diagnoses, including

cardiovascular events[75] and its National Ambulatory Care Reporting System, which includes abstracted data on all emergency department visits; (c) the Ontario Health Insurance Plan database, covering physician billings for procedures and visits[76]; and (d) the Registered Persons Database covering demographic information including date of death. We have previously linked CCN data to these databases at ICES to identify gaps in persistence to cardiac medications post-angiography[14].

Table 1a. Definitions for primary and secondary outcomes collected by patient report

Outcomes	Definition
Primary	
Medication adherence	Number of cardiac medication classes with no missed tablets in last 7 days (ordinal)
Cardiac rehabilitation completion	Patient participated in at least some of the program components and had formal re-assessment at the conclusion of the program (dichotomous)
Secondary	
Quality of life	Seattle Angina Questionnaire-7
Smoking status	Point-prevalence, smoking any cigarettes in last 3 months (dichotomous)
Medication persistence	Active prescription for *all* recommended medication classes (dichotomous)
Medication persistence	Active prescription for *each* recommended medication class (dichotomous)
Medication adherence	Number of cardiac medication classes with <6 missed tablets in last 30 days (ordinal)
Medication adherence	No missed tablets in last 7 days for *any* recommended medication class (dichotomous)
Medication adherence	Number of days missed for *any* recommended cardiac medication classes in last 7 days (continuous)

Outcomes	Definition
Cardiac rehabilitation adherence	Proportion of total prescribed sessions attended
Cardiac rehabilitation enrolment	Attendance at ≥ one session (dichotomous)

Table 1b. Definitions for secondary outcomes collected from administrative databases

Outcome	Definition
Medication adherence	Medication possession ratio > 80% for *all* recommended medication classes in those 65+ (dichotomous)
Medication adherence	Medication possession ratio > 80% for *each* of the recommended medication classes in those 65+ (dichotomous)
Medication adherence	Mean medication possession ratio for *all* recommended medication classes in those 65+ (continuous)
Medication adherence	Mean medication possession ratio for *each* recommended medication in those 65+ (continuous)
Medication discontinuation	Inactive prescription for at least 20% of the length of time of the previous prescription, in those 65+ who filled a prescription for that medication class within 90 days of their MI (dichotomous)
Healthcare utilization	Outpatient visits, total and stratified by family physician versus specialist (count)
Healthcare utilization	Emergency Room visits not leading to admission, total and cardiovascular-specific (count)
Healthcare utilization	Hospitalizations, total and cardiovascular-specific, including repeat MI, stroke, heart failure, or revascularization (count)

Cardiovascular event	Repeat MI, stroke, revascularization with either coronary bypass surgery or percutaneous coronary intervention (count)
Mortality	Death during follow-up, total and cardiovascular-specific (count)

Notes: Guidelines recommend four medication classes in patients with MI and coronary obstruction: statins, aspirin, beta-blocker, and an angiotensin-agent. Administrative databases do not reliably capture aspirin so analyses using these databases will focus on only three cardiac medication classes. Clinical outcomes will be assessed using published, validated algorithms of International Classification of Diseases codes[77]. MI=myocardial infarction.

Statistical Analysis

Analyses will be performed on an intention-to-treat basis. No interim analyses are planned. Multiplicity issues arise due to dual primary outcomes and multiple comparisons of two intervention arms versus usual care. For each comparison of intervention versus usual care, the step-down Šidák procedure will be used to maintain the overall Type 1 error rate at 5%[78]. A data-driven ordering of the comparisons will be used, starting with the comparison that yields the smallest p-value. If the null hypothesis on any comparison is rejected (e.g., intervention arm 1 versus usual care), the analysis will proceed to the next comparison (e.g., intervention arm 2 versus usual care); otherwise, all remaining null hypotheses will be accepted.

For dichotomous outcomes, the absolute difference in proportions at 12 months for each intervention arm versus usual care will be calculated, together with 95% simultaneous confidence intervals. Random allocation stratified by center when the intra-cluster correlation coefficient is non-zero can lead to standard errors that are too high and a reduction in power[79]. Significance testing will therefore adjust for clustering (using Generalized Estimating Equations mixed-effects regression with center specified as a random effect) to potentially improve power. Ordinal logistic regression with a cumulative logit link function will be used to evaluate the effect of the intervention on number of recommended cardiac medication classes to which patients are adherent. The score test will be used to assess the proportional odds assumption. Time to medication discontinuation (in those age 65+) for any and each recommended cardiac medication class will be carried out using administrative data. Cox proportional hazards regression analysis will be used, with patients censored at the time of death.

To evaluate differences in secondary outcomes with low frequency of events (cardiovascular events, death), a composite outcome will be created and comparisons of times to event will be conducted using Kaplan-Meier analysis (1) for each arm, and (2) by pooling across intervention arms. Continuous secondary outcomes (e.g., quality of life) will be compared among groups, after suitable transformation if necessary, using mixed-effects regression. Healthcare utilization variables will be analyzed using Poisson or negative binomial regression analysis with correction for over-dispersion if required.

<u>Sample size</u>

The target sample size for the trial is 914 patients in each arm, for an overall total of 2,742 patients. This calculation is based on detecting a minimally important difference in at least one of the co-primary outcomes with minimum 80% power, accounting for multiple testing across two outcomes and a three-arm design maintaining the overall alpha level at 5% using the step-down Šidák procedure[78]. For CR, a usual care arm proportion of 35% is assumed and a minimally important difference of 9%; for medication adherence assumptions were made of proportions of 3%, 12%, 35%, and 50%

corresponding to ≤1, 2, 3, or 4 adherent medication classes respectively (based on data from the pilot study) and a minimally important odds ratio of 1.45. Assumed usual care arm proportions were informed by the pilot work[44]. With these assumptions, 685 analyzable patients per group are required for the CR outcome using a chi-squared test, and 635 per group for medication adherence using Whitehead's method for ordinal outcomes[80]. After adjustment for up to 25% loss to follow up, the target sample size is 914 patients per arm.

Subgroup and sensitivity analyses

Potential effect modification by patient socio-demographic factors (income quintile, age > 65, sex, rurality) will be explored by including interactions between these variables and treatment. Effect modification by clinical factors (prior medication use, history of prior MI or bypass surgery, type of MI, blood transfusion in hospital, renal dysfunction, history of smoking, heart failure, diabetes, chronic lung disease, mental health) will also be explored using administrative database records.

A planned sensitivity analysis will consider the assessment of medication persistence and adherence in a more lenient manner. Specifically, patients who report not taking a beta-blocker but without a known history of Left Ventricular Ejection Fraction ≤ 40% or with a history of asthma as denoted in the CCN Cardiac Registry, those patients not taking an angiotensin agent but without a history of Hypertension, Diabetes, and/or Left Ventricular Ejection Fraction ≤ 40% in the CCN Cardiac Registry, and/or patients with end-stage renal disease who are not taking an angiotensin agent, will be considered as appropriately 'adherent' to medication treatment recommendations.

Accounting for missing data

The strategy outlined herein follows state-of-the-art recommendations for dealing with missing data (e.g., Little et al., 2012)[81]. First, proactive steps to limit the extent of missing data will be taken, for example, by updating contact information using similar procedures across all study arms, and by asking permission to contact patients who opt-out for the purpose of assessing adherence at 12 months. This will preserve the ability to analyze the primary endpoints for all randomized participants in the arm to which they were allocated, in keeping with the intention-to-treat principle. Second, reasons for missing data will be documented, as we will attempt to identify variables that may be predictive of missing data. Third, the primary analysis will use multiple imputation under plausible assumptions about the missing data mechanism. Multiple imputation is the gold standard procedure for dealing with missing data; it has the advantage that it can incorporate auxiliary information about the missing data into the analysis to reduce bias and improve precision; it gives p-values and standard errors that account for missing data uncertainty. Fourth, sensitivity analyses will be conducted to assess robustness of the findings to alternative assumptions about the missing data.

Based on experience in the pilot study, three main causes of missing data are anticipated: a) deaths, b) participants opting-out during the trial or refusal at 12 months, and c) non-response (no contact) at 12 months. Multiple imputation will not be conducted for patients who have died, as measures of adherence are not meaningful in this case. To account for potential risk of bias due to differential deaths across the arms, the primary analyses will consider deaths as treatment failures (non-adherence). For the remaining categories, multiple imputation will be conducted under a primary assumption of Missing At Random, i.e., reasons for withdrawal or non-response are unrelated to the missing outcomes themselves. To make this assumption more tenable, the imputation model will include baseline sociodemographic and clinical characteristics such as age, rurality, income quintile,

indication, disease severity, ejection fraction, comorbidities, and smoking status. In sensitivity analyses, the assumption will be made that participants refusing or opting out are non-adherent.

Economic analyses

The cost and effect for each arm will be compared using trial data and data available from ICES. All costs associated with delivering the intervention will be included, plus health care utilization costs by patients within each study arm. The economic evaluation will be conducted using the net benefit regression framework[82] from the perspective of the Ontario public health care payer (i.e., Ontario Ministry of Health and Long-Term Care). The use of regression allows the adjustment of potential confounders. The main outcome of the economic evaluation is incremental net benefit of each arm compared to the usual care arm. Estimates of the following will also be done: (1) incremental cost per one more person adhering to medication, and (2) incremental cost per one more person completing CR. Statistical uncertainty will be characterized using 95% confidence intervals and a cost-effectiveness acceptability curve[83].

Process evaluation

An embedded process evaluation will be undertaken to understand the effects observed in the study. Descriptive data regarding intervention delivery (e.g., number and timing of patient-contacts with the LHWs and the issues addressed) will be recorded. Additionally, the mechanisms of action underlying the intervention and how the intervention strategies interacted with participant context(s) to contribute to medication adherence and CR use. The process evaluation involves both quantitative and qualitative components.

Quantitative process evaluation: theory-informed structured patient questionnaires

At the completion of the outcome assessment (12 months), participants will be invited to answer further questions on the telephone. Those agreeing will receive a questionnaire to assess constructs related to the underlying theoretical framework used to design the interventions. For instance, validated scales will assess intention, self-efficacy, outcome expectations, risk perceptions, social support, action planning and coping planning (questionnaires available upon request). We will explore whether changes in these determinants were associated with changes in treatment adherence and whether changes in these factors varied by intervention exposure and by patient characteristics. The target sample size for the process evaluations is 500 patients in total (i.e., 167 patients per arm). A comparison of outcomes between the process evaluation sub-sample and the remainder of the participants within groups will be conducted to explore whether findings in the process evaluation sub-sample are representative of the wider intervention sample.

Qualitative process evaluation: patient interviews

To better understand how future interventions supporting adherence to secondary prevention treatments might be optimized, an embedded qualitative process evaluation will also be conducted. Participants will be recruited from one academic (i.e., university teaching hospital) and one community center participating in the ISLAND study. Recruitment will be restricted to participants allocated to the second intervention arm to allow for exploration of the mail-out reminders as well as LHW phone calls as distinct components of the intervention, as well as the potential interaction between them. A stratified, purposive sampling approach will be used, seeking variation in sex, age, socioeconomic status, marital status, and ethnicity. In addition, we will seek input from three groups of participants, defined by engagement and adherence outcomes: (1) Engaged with Intervention, Adherence Outcome Positive; (2) Engaged with Intervention, Adherence Outcome Negative; (3) Did Not Engage with Intervention, Adherence Outcome Negative. Engagement will be defined as completion of all five

IVRS calls. Positive adherence outcomes are defined as no missed tablets in the preceding week for medications and completion of CR. Negative adherence for medications is operationalized as any missed tablet within the preceding week. Negative adherence outcomes for CR is operationalized as either failure to enroll in CR or partial attendance without completing the final assessment. Potentially eligible patients will be identified during outcome assessments.

Interviews will follow a semi-structured interview guide, informed by HAPA and the TDF. Data analysis of resulting transcripts will consist of six stages, as described by Braun and Clarke[84]: 1) familiarization with the data; 2) organization of initial codes derived from the research aims (i.e., capturing barriers and facilitators to adherence and experiences relating to the intervention); 3) iterative searching for themes, allowing the researcher to move back and forth between transcripts as new themes are established; 4) reviewing generated codes; 5) defining and summarizing themes using thematic mapping to explore relationships between themes; and 6) writing the report. Key themes, categories, and codes will be triangulated by comparing the qualitative results with the evolving program theory hypotheses (cross-syntheses) and the process evaluation survey results. A stepped analysis process whereby there is an initial independent review of the data (transcripts) by at least 2 reviewers who then meet to reach consensus around the common themes (reliability) will be employed[85,86].

The qualitative process evaluation sample size will be dependent on emergent findings (i.e., saturation); it is anticipated to be 13-15 participants per group[87]. Assuming a consent rate of 25% for Groups 1 and 2 (i.e., engaged with intervention), 60 participants meeting each of these criteria (120 total) will be invited to participate. A much lower consent rate for individuals who did not engage with the intervention (10%) is anticipated, and therefore 150 participants from Group 3 will be invited.

Ethical considerations

ISLAND meets all ethical principles for a deviation from the general principles of research consent. Specifically, the intervention under investigation involves no more than minimal risk for participants and is unlikely to adversely affect their welfare. As with advertisements or telephone solicitations, follow-up reminders can be ignored, thrown away, or hung-up on. The interventions explicitly avoid making specific treatment recommendations, but focus instead on supporting patients in adhering to treatments already recommended by the patient's own health care professionals. It would not be practicable to carry out the research and would be impossible to answer the question properly if prior consent was required, as many patients have only brief stays in cardiac centers before they are repatriated to local hospitals. Furthermore, typical consent procedures would likely create selection bias (i.e., patients likely to consent would probably be least likely to benefit from the intervention) and exacerbate the risk of a Hawthorne effect (i.e., patient awareness of treatment adherence monitoring may create a conservative bias). All participating research ethics boards approved waiver of consent with provision of multiple "opt-out" opportunities and a "debrief" at the time of outcome assessment[88,89].

Data for the CCN Cardiac Registry is already collected, analyzed, and reported back to cardiac centers for surveillance purposes without consent; an information sheet is provided to patients prior to the coronary angiography. Information about the ISLAND study and instructions to opt-out are appended to this CCN information sheet. At each study contact, patients will again be provided the option to opt-out. In the pilot study, which enrolled 900 patients following the same approach[44], this option was not exercised.

Discussion

The major strengths of this trial are the pragmatic nature of the intervention and study design. Many adherence trials implement complicated, expensive interventions; even if successful, sustainability of such interventions proves challenging. In contrast, this study builds upon pilot studies demonstrating feasibility[44] and tests the effectiveness and costs of theory-informed, sustainable interventions that better connect hospital-based cardiologists with patients, their informal caregivers, community-based pharmacists, and family physicians. The project will also be highly valuable even if the trial is negative; the process evaluation can inform the development of more effective interventions in the future.

However, we also acknowledge some limitations inherent in the study design. First, the study is not powered to assess changes in clinical outcomes. Still, the connection between treatment adherence and clinical outcomes in this population is well-established and this decision represented a need to bring results to stakeholders in a reasonable timeframe. Second, self-reported adherence to treatment may not represent a gold-standard approach (and socially desirable responding may bias toward a null finding), but as noted above, the measures chosen have been validated in other studies against clinical outcomes and we will also assess medication adherence using administrative data sources. These have their own limitations: the data may over-estimate adherence in those who fill but do not take their medications, or under-estimate adherence in those who pay privately, as is usually the case for aspirin. However, we do not anticipate the risk of misclassification bias to vary across trial arms. Similarly, the trial design protects against bias from relative contra-indications to specific treatment options since differential allocation across arms of such patients would not be anticipated; the planned sensitivity analysis will also examine the issue of clinical indications for specific medications. Finally, the intervention tested relies on printed materials and telephone calls rather than digital technology such as mobile phone applications or automated text messages. However, we believe that the traditional approaches are appropriate and feasible for the population whose outcomes we aim to improve and have some specific potential advantages related to the role of social supports. For example, printed materials can be shared with loved ones and members of their health care team, and LHWs can help patients navigate through barriers in a personalized way.

In conclusion, this manuscript describes in detail the underlying theory for an intervention to improve treatment adherence and a rigorous program evaluation to understand its effects. The provincial scope of the centrally-delivered intervention and the approach to waiver of consent are features that may be particularly interesting to others seeking to implement and rigorously evaluate large-scale quality improvement initiatives.

Trial status

2,742 patients were enrolled from nine cardiac centers between September 2015 and May 2016. Outcome evaluations initiated and expected to continue until June 2017.

Competing interests

No competing interests have been declared.

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Author's contributions

NMI, JDS, JMG, and MN together led the development of the protocol, obtained funding, and contributed to all aspects of the study design. NMI produced the first draft of the manuscript. MT developed the analytical plans. All other authors provided substantive contributions to the protocol. All authors read and approved the final manuscript.

Abbreviations

CAD: coronary artery disease
CCN: Cardiac Care Network of Ontario
CR: cardiac rehabilitation
HAPA: Health Action Process Approach
ICES: Institute for Clinical Evaluative Sciences
IVRS: interactive voice response system
LHW: lay health worker
MI: myocardial infarction
PHRI: Population Health Research Institute

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Appendix I – IVRS Script sample

[Insert selection from pdf 'ISLAND IVR Script V22.0 9Sept15']

Appendix II - LHW non-adherence script

[Insert pdf 'ISLAND LHW non-adherence script']

Supplemental files:
ISLAND LHW non-adherence script'
ISLAND IVR Script V22.0 9Sept15

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