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ASSESSING OUTCOMES OF ENHANCED CHRONIC DISEASE CARE THROUGH PATIENT EDUCATION AND A VALUE-BASED FORMULARY STUDY (ACCESS)

Study Protocol and Statistical Analysis Plan

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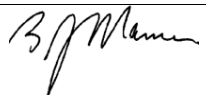
Signature:		Date:	Sept 15, 2022		
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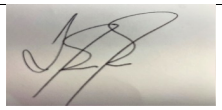
Signature:		Date:	Sept 15, 2022		
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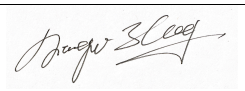
Signature:		Date:	Sept 16, 2022		

SAP Version	Date Approved	Section # Changed	Description and Reason for Change	Approver
1.0				
2.0	Sept 15, 2022	Section 6.1 (table only)	Minor changes to Admin codes used to define primary outcome (see justification provided). These changes were made prior to any analyses by group, and prior to unblinding of the data.	Braden Manns on behalf of the individuals noted above

Abbreviations and Definitions:	
Abbreviation/Acronym	**Meaning**

1. Introduction

Chronic diseases such as heart attack, stroke, and diabetes lead to significant morbidity, and cost the Canadian healthcare system over $93B per year (1). Although medications and lifestyle changes can improve outcomes, many do not receive them and therefore do not benefit. We have worked closely with Alberta health care decision makers since 2009 to design and implement a research program to optimize care for people with chronic disease. We first identified gaps in care for people with these chronic diseases in Alberta, including noting that 50% do not receive recommended cholesterol-lowering drugs (2). Secondly, with Statistics Canada, we surveyed nearly 2000 Western Canadians with chronic disease regarding barriers to optimal care. The most important barriers identified included *financial barriers* and *lack of patient knowledge***.** We identified that 20% and 30% of participants had financial and knowledge barriers, respectively (3,4) and that the odds of identifying a financial barrier were 3-fold higher in those whose out-of-pocket expenditures were >2% of household income (implying household income <$50,000). Patients with these barriers were 70% more likely to be hospitalized for their chronic disease and 50% less likely to use statins, suggesting these barriers are highly relevant.

We confirmed the need for the current study after presenting this evidence to Alberta Health and after completing systematic reviews of interventions to address these barriers. The systematic reviews assessed: 1) the effectiveness of reducing copayments for high-value drugs in people with chronic diseases and determined that reducing copayments may result in improved adherence to medical therapy (5); and 2) the impact of 11 quality improvement strategies for diabetes and determined that the most effective strategies were patient education and facilitated relay of information by patients to clinicians (6). Neither review could determine the impact of the interventions on clinical outcomes or costs – because available evidence consisted mostly of observational studies, or because trials were short-term and used surrogate endpoints.

2. Background and Rationale

What is the problem to be addressed?

Cardiovascular disease is the leading cause of death in Canada: Cardiovascular disease claimed over 69,500 lives in Canada in 2008 (7), most as a result of cardiovascular events, such as strokes and myocardial infarctions. Cardiovascular disease is also the leading cause of hospitalization for Canadians (8). Important risk factors for cardiovascular events include prior stroke or myocardial infarction, chronic kidney disease, heart failure, diabetes or hypertension (henceforth referred to simply as "chronic diseases"). These conditions lead to severe morbidity and cost the Canadian healthcare system over $93 billion per year (1).

Many patients with chronic diseases do not receive guideline-recommended therapy: Lifestyle modification (i.e. weight loss, exercise, healthy diet, and smoking cessation) as well as adherence with pharmacologic management are particularly important in the management of patients with chronic diseases (9–13). In Alberta, our group has documented that 50% of Albertans with these chronic diseases are not receiving guideline-recommended drugs (statins), due to a combination of patient, provider and health system level barriers (3). Our recent survey of nearly 2,000 Western Canadians suggests that patient-borne cost of prescription drugs as well as patient and provider-level knowledge gaps, are major barriers to optimal medical management (3).

Cost-related barriers to medication adherence are relevant in Canada: While the Canadian publicly funded health care system funds hospital and physician care, patients are responsible for many of the direct costs related to outpatient management of their chronic conditions. Canada is unique among OECD countries given that not all citizens have insurance coverage for outpatient medications (14,15), and even those with supplemental insurance are usually subject to cost-sharing (i.e., copayments or deductibles) (16). This requires that patients pay a portion of the cost at the time of medication dispensing; typically a copayment of 20-30% of the total cost of the prescription (17) or deductibles which may be as high as 5-20% of household income (18). This may represent a substantial financial barrier, since our recent survey noted that 64% of patients with chronic diseases had an annual household income <$55,000 (16). Furthermore, we found that the average self-reported annual out of pocket expenses on medications was $782 (95%CI $668-$897). In Alberta, government-sponsored drug insurance is provided to people on social insurance and those aged over 65. People who do not meet age or income criteria can pay a premium to receive the government insurance. All Albertans over age 65, and those who pay a premium to receive Blue Cross coverage pay 30% copayment for drugs.

While copayments are meant to reduce inappropriate medication use, they may have important negative consequences. Being faced with costs at the time of medication dispensing may discourage patients from filling prescriptions, including for important preventive medications. Recent Canadian studies estimated that up to 10% of people experienced cost-related medication non-adherence (19), and that 23% of Canadians with chronic conditions have either skipped medication or failed to fill a prescription due to cost (20). In our recent survey of Western Canadians with chronic diseases, 8-20% identified financial barriers to drugs; and patients with these barriers were 30-55% less likely to use statins (16). Studies suggest that

reducing copayments can improve adherence, though the impact on clinical outcomes is uncertain. One way to reduce the impact of these cost barriers is to provide full coverage for "high-value" medications (i.e., *defined as those medications that have been shown to confer important benefits in high quality studies, and/or provide good value for money*).

Other patient and provider-level barriers may also reduce appropriate medication use: Optimal management of chronic disease requires patient knowledge and a substantial degree of self-management (21) including adherence to outpatient medication regimens and lifestyle behaviour modifications. Our recent survey of Western Canadians suggested that 40% of chronic disease patients did not recall receiving counseling regarding lifestyle behavior modification, and of those who did, up to 70% of them did not follow the advice given (3). Part of this may relate to the format of the message, which (when crafted and delivered by health care workers) may be factually correct without effectively changing behaviour. Alternatively, patients might receive and understand messages about the value of certain health behaviors but require assistance from a health provider to implement the needed changes. A prior systematic review examining the impact of 12 different chronic disease management strategies for patients with diabetes noted that two of the most effective strategies for improving glycemic control and blood pressure were *patient education*, and *facilitated relay of information to clinicians* (22). *Facilitated relay* is defined as clinical information transmitted by patients to clinicians by means other than the existing medical record (22); the expectation is that clinicians act on the information to change patient management. In the ACCESS trial, the *facilitated relay* will involve patients providing personalized recommendations on the medications that should be used to treat their chronic diseases (provided to the patient within study educational materials) to their regular health care provider. Recommendations are based on contemporary clinical practice guidelines and use strategic marketing practices targeting patients not receiving guideline-concordant medications at study baseline.

3. Trial Objectives

Primary Objective:
To determine the effect of two novel interventions; (i) a value-based formulary which eliminates copayment for select high-value medications (proven to prevent heart attacks, stroke, and hospitalizations); and (ii) a comprehensive patient education program aimed at lifestyle modification and optimal drug use, combined with relay of information on medication use, on the risk of adverse clinical outcomes (mortality, heart attack, stroke, need for coronary revascularization, and chronic disease related hospitalizations) over three years.

Secondary Objectives:
To determine the effect of two novel interventions on medication adherence, overall quality of life, and health care costs.

4. Trial Methods

4.1. Trial Design

The ACCESS trial is a parallel, open-label factorial 2X2 randomized controlled trial with blinded end-point evaluation. Given the nature of these interventions, patient blinding is not possible.

4.2. Trial Interventions

1. **Elimination of copayments**: (reduction from 30% to 0%) for select high-value preventive medications by enrolling patients in a new Alberta Blue Cross drug coverage plan which was designed by the study team, including leaders at Alberta Health specifically for ACCESS (see letter of support, Evans). Since these patients either have or are at high risk of cardiovascular disease, the medications include statins, beta blockers, ACE-inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, anti-platelet agents, anticoagulants, oral hypoglycemics, insulin and smoking cessation aids (23) (see Appendix II). These formulary changes will be operationalized by transferring patients allocated to this intervention to a new government-sponsored Alberta Blue Cross formulary plan with updated payment rules.

2. **Patient education strategy on lifestyle modification and medication use** designed in collaboration with a leading marketing firm (see letter of collaboration, Emergence) and based on our recent survey of Western Canadians (3,4,24). The education program will be combined facilitated relay of information on patient medication use to their health care provider. Patients who are not using guideline-recommended therapy (including statins) at baseline will be given personalized recommendations to take to their usual clinician, aiming to increase the appropriate use of beneficial medications. Dissemination will occur by email invitations to access the personalized study website portal or regular post, depending on preferences of the participant (elicited at baseline). Personal health information will not be sent within emails. For any educational messages tailored to a specific patient's health information (as provided by them within baseline information forms), patients will be directed to log on to a secure password protected website.

Control patients for the two intervention arms will continue to receive all medications as per their usual coverage and/or will receive annual mailings of general educational materials about chronic disease.

4.3. Primary Outcomes

Outcomes of relevance to patients with chronic disease: When management of chronic disease is suboptimal for extended periods, patients may be hospitalized for complications (25). While myocardial infarction, stroke, and the need for revascularization are the classical complications (and are components of our primary outcome), hospitalization for chronic disease-related ambulatory care sensitive conditions are also relevant, since these complications can serve as a proxy for poor control of chronic disease. Ambulatory care sensitive conditions (ACSC) are those for which "timely and effective outpatient care, including use of appropriate medications, can help to reduce the risk of hospitalization by preventing the onset of an illness or condition, or managing a chronic disease" (26). While several agencies have examined what constitutes an ACSC for the chronic diseases

under study, the most applicable definition of ACSC for cardiovascular diseases, diabetes and hypertension using a Canadian context is from CIHI (2009). Since this does not include hospitalizations for CKD-related ACSC, this list was taken from a recent Canadian study (27). Importantly, these potentially preventable hospitalizations are clinically relevant to patients and represent an important economic burden for the system (28), which might be avoided through interventions which optimize patient management (29,30).

Primary Outcome: The primary outcome is the composite rate of any of the following: all-cause mortality, myocardial infarction, stroke, coronary revascularization (coronary artery bypass grafting, angioplasty, or coronary stenting), and hospitalizations for chronic disease-related ambulatory care sensitive conditions. Given that an individual may have multiple events during the follow-up period, we have chosen to use a rate outcome rather than a simple binary composite outcome.

4.4. Secondary Outcomes

1) each individual component of the primary endpoint
2) medication adherence for selected medications as defined below
3) overall quality of life as measured by the Euroqol EQ5D-5L
4) the cost of the interventions and other costs relevant to the health care system assessed in a concurrent economic evaluation.

4.5. Tertiary Outcomes (some to be reported in secondary manuscripts)

A) Body-mass index
B) Smoking status
C) Prescription of indicated medications
D) Treatment satisfaction
E) Medication Needs-Concerns
F) General barriers to care
G) Financial barriers to care
H) Health literacy
I) Self-reported general health
J) A1C (among those with diabetes)
K) Albuminuria
L) Serum Creatinine/estimated GFR
M) LDL-cholesterol

4.6. Timing of outcomes as assessments

The primary outcome data was ascertained through administrative health data held within the province of Alberta, including linked datasets such as: laboratory data, pharmacy dispensation data, acute care data, outpatient physician claims data, and demographic data. Participants were followed for a minimum of 2.5 years from the time of randomization through until March 30, 2021. This data will be available as of early 2022.

Self-reported outcome measures were obtained via electronic and paper-based surveys which were sent to participants 6-, 18-, and 33-months after randomization.

4.7. Randomization

The University of Calgary Clinical Research Unit developed the computer-generated randomization scheme within REDCap.

Randomization was completed using random small (<8) variable permuted blocks. This method will ensure robust allocation concealment. Randomization was stratified based on: age (</≥70 years); gender (man/woman); and low household income status (defined by household-size specific Low-Income Cut-offs).

4.8. Sample Size

Using the cohort of 170,000 Albertans described above, we estimated the annual event rate for this study reflecting the expected age distribution of enrollees. We found that this cohort of patients at high cardiovascular risk had a 26% risk of myocardial infarction, stroke, death or chronic disease-related hospitalization over a three-year observation period (Appendix VII). However, the endpoint in our primary outcome is not a binary event (many individuals had multiple events during the observation period), and so we have chosen to include recurrent events in our sample size calculation. In our administrative dataset, the rate of the primary outcome (MI, stroke, revascularization, death, or chronic disease-related hospitalization) is 14 per 100 participant years (Appendix VII).

We estimated the sample size required for Poisson regression analysis (31), using the following parameters: an annual event rate of 14 per 100 participant years, a minimal clinically important difference of a 12% relative risk reduction, α=5%, 80% power, allocation ratio of 1:1, average follow up of 3 years and presumed 1 percent per year loss to follow-up (32). The estimated total sample size required for the study was 4714 patients (4667 +1% of individuals who are expected to move out of province during the study) (Appendix VIII). Our sample size calculation assumed that there will not be an important interaction between our two interventions. To verify this assumption, we generated simulations using interactions of 25% and 50%. At both of these levels of interaction, with our current projected sample size, the effect on study power was negligible.

4.9. Framework

Two conceptual frameworks influenced the design of this study. First, the health belief model summarizes how and why people make health behaviour choices (33) and includes the constructs of perceived: susceptibility, severity, benefit, and barriers—many of which can be targeted by SMES. Second, the framework proposed by Campbell et al postulates

how financial barriers may affect clinical outcomes. These frameworks were used to inform the development of the interventions.

The overarching purposes of the interventions in the ACCESS study will be to:
(1) Increase initiation and adherence to medications that have been proven to reduce the risk of cardiovascular events in this population of high-risk patients, including HMG-CoA reductase inhibitors (Statins) (34) and renin-angiotensin-aldosterone system inhibitors (ACE inhibitors [ACEi] and angiotensin receptor blockers [ARBs]) (35).

(2) Encourage participants to make positive health behavior changes, including healthy dietary choices, engagement in physical activity, cessation of tobacco use, and increased adherence to all preventive medications.

4.10. Interim Analyses and Stopping Guidance

The trial interventions were deemed low risk to cause adverse events, so no DSMB or interim analyses were planned, or were possible given the use of administrative data to assess outcomes.

4.11. Timing of Final Analysis

The final analysis will be started in the summer of 2021, which will focus on the cleaning and preparation of the self-reported outcome data which were collected through the survey data.

We anticipate receipt of the administrative data from Alberta Health in early 2022, with data cleaning to follow and the final analysis to begin March 1, 2022, to be completed by July 1, 2022.

4.12. Timing of Other Analysis

Secondary analyses will be completed through the summer and fall of 2022, with further sub-analyses to be conducted thereafter.

4.13. Trial Comparisons

The impact of the two interventions will be conducted independently of one another. We will compare each intervention arm to those who did not receive that specific intervention.

5. Statistical Principles

5.1. Confidence Intervals and P-values

In all our analyses, we will calculate 95% Confidence intervals around all point estimates and will calculate p-values using appropriate statistical tests. We will consider our alpha value to be 0.05.

5.2. Adjustments for Multiplicity

For the secondary outcomes that are the individual components of the primary outcome, we will adjust for multiplicity using the Benjamini-Hochberg procedure (36). We will initially sort the primary outcome individual component secondary outcomes by p-value. Ranks will be assigned in ascending order of p-value. The Benjamini-Hochberg critical value will be calculated using the formula (i/m)Q, where:

- i = the individual outcome's p-value's rank,
- m = total number of tests,
- Q = the false discovery rate (25%).

We will then compare our original p-values to the critical value calculated. The largest p-value that is smaller than the critical value will be the last individual outcome that is considered statistically significant.

Given that the other secondary outcomes are exploratory, we will not make adjustments for multiplicity in these analyses (37).

6. Outcome Definitions

6.1. Primary outcome

Record of any of the following identified within the Discharge Abstract Database will be counted as one primary outcome. The number of composite outcomes will be used; therefore, any one individual may have multiple outcomes within the observation window.

The rates of the composite outcome will be calculated by generating the observation time, defined as the period from randomization to study completion, taking into consideration censoring for death or outmigration.

Changes made to this table are highlighted in red, with justification provided in last column

Outcome	Description	Classification Source	Codes included	Exclusions	Source	Justification for change
Myocardial Infarction	Acute myocardial infarction Subsequent myocardial infarction	ICD-10	I21.X I22.X	None	Quan et al. (38), Austin et al. (39)	No change
Stroke	Central retina artery occlusion	ICD-10	H34.1 I63.X	None		No change

	Cerebral infarction Stroke, not specified as hemorrhage or infarction Intracerebral hemorrhage Subarachnoid hemorrhage Transient cerebral ischemic attacks		I64.X I61.X I60.X G45.X		Kokotailo and Hill (40)	
Coronary Revascularization	Coronary Angioplasty Coronary endarterectomy/excision Coronary local pharmacotherapy Coronary Artery Bypass	Canadian Classification of Health Interventions (CCI)	1.IJ.50 1.IJ.57 1.IL.35 1.IJ.76		CIHI	No change
Death	Death (all-cause)	Vital Statistics				No change
Ambulatory Care-Sensitive Hospitalization for Diabetes	Type 1 DM with coma Type 1 DM with acidosis Type 1 DM with hypoglycaemia Type 1 DM without (mention of) complication Type 2 DM with coma Type 2 DM with acidosis		E10.0^^ E10.1^^ E10.63 E10.64 E10.9^^ E11.0^^ E11.1^^	None	CIHI	10.64, 11.64, 13.64, &14.64 added to CIHI definition of ACSC for diabetes since 2015

	Type 2 DM with hypoglycaemia Type 2 DM without (mention of) complications Other specified DM with coma Other specified DM with acidosis Other specified DM with hypoglycaemia Other specified DM without (mention of) complication Unspecified DM with coma Unspecified DM with acidosis Unspecified DM with hypoglycaemia Unspecified DM without (mention of) complication	ICD-10	E11.63 E11.64 E11.9^^ E13.0^^ E13.1^^ E13.63 E13.64 E13.9^^ E14.0^^ E14.1^^ E14.63 E14.64 E14.9^^			

Outcome	Description	Classification Source	Codes included	Exclusions	Source	Justification for change
Ambulatory Care-Sensitive Hospitalization for Chronic Kidney Disease	Type 2 diabetes mellitus with ketoacidosis Type 1 diabetes mellitus with ketoacidosis Type 2 diabetes mellitus with ketoacidosis with lactic acidosis Type 1 diabetes mellitus with ketoacidosis with lactic acidosis Type 2 diabetes mellitus with coma		E11.10 E10.10 E11.12 E10.12 E11.00	None	Gao et al. (41)	No change

	Type 1 diabetes mellitus with coma Hyperosmolality and hypernatremia Hyperkalemia Fluid overload Malignant hypertension Heart failure Hypertensive heart disease Hypertensive heart and renal disease Hypertensive heart and renal disease Ischaemic cardiomyopathy Dilated cardiomyopathy Other restrictive cardiomyopathy Alcoholic cardiomyopathy Cardiomyopathy due to drugs and other external agents Other cardiomyopathies Cardiomyopathy, unspecified	ICD-10	E10.00 E87.0 E87.5 E87.7 I10.1 I50.x I11.0 I13.0 I13.2 I25.5 I42.0 I42.5 I42.6 I42.7 I42.8 I42.9			
Ambulatory Care-Sensitive Hospitalization for Hypertension	Benign hypertension Malignant hypertension Hypertensive heart disease		I10.0 I10.1 I11	See below	CIHI	No change

Outcome	Description	Classification Source	Codes included	Exclusions	Source	Justification for change
Ambulatory Care-Sensitive Hospitalization for Heart Failure	Rheumatic heart disease, unspecified		I109.9	See below		CIHI excludes procedures when estimating rates of heart failure. Two of the most common administrative codes for heart failure were inadvertently left off our list - J81 I50. These 2 codes are part of the CIHI definition of heart failure
	Hypertensive Heart Disease		I11.0		CIHI	
	Hypertensive Heart and Renal Disease and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease		I13.0			
	Hypertensive heart and chronic kidney disease without heart failure, with stage 1		I13.10			

	through stage 4 chronic kidney disease, or unspecified chronic kidney disease Hypertensive Heart And Renal Disease and with stage 5 chronic kidney disease, or end stage renal disease		I13.2 J81 I50			
Ambulatory Care-Sensitive Hospitalization for Coronary artery disease	Angina pectoris Other current complications following acute myocardial infarction Acute coronary thrombosis not resulting in myocardial infarction Other forms of acute ischemic heart disease Acute ischemic heart disease, unspecified		I20 I23.82 I24.0 I24.8 I24.9	See below	CIHI	No change

* Excludes hospitalizations with one of the following cardiac procedure codes:
CCP: 47^^, 480^–483^, 489.1, 489.9, 492^–495^, 497^, 498^
ICD-9-CM: 336, 35^^, 36^^, 373^, 375^, 377^, 378^, 379.4–379.8
CCI: 1HA58, 1HA80, 1HA87, 1HB53, 1HB54, 1HB55, 1HB87, 1HD53, 1HD54,

1HD55, 1HH59, 1HH71, 1HJ76, 1HJ82, 1HM57, 1HM78, 1HM80, 1HN71, 1HN80, 1HN87, 1HP76, 1HP78, 1HP80, 1HP82, 1HP83, 1HP87, 1HR71, 1HR80, 1HR84, 1HR87, 1HS80, 1HS90, 1HT80, 1HT89, 1HT90, 1HU80, 1HU90, 1HV80, 1HV90, 1HW78, 1HW79, 1HX71, 1HX78, 1HX79, 1HX80, 1HX83, 1HX86, 1HX87, 1HY85, 1HZ53 rubric (except 1HZ53LAKP), 1HZ55 rubric (except 1HZ55LAKP), 1HZ56, 1HZ57, 1HZ59, 1HZ80, 1HZ85, 1HZ87, 1IF83, 1IJ50, 1IJ55, 1IJ57, 1IJ76, 1IJ86, 1IJ80, 1IK57, 1IK80, 1IK87, 1IN84, 1LA84, 1LC84, 1LD84, 1YY54LANJ

6.2. Definition of Medication Adherence

Data extracted from the Pharmacy Information Network will be used to calculate the Proportion of Days Covered (PDC): "number of days dispensed"/"number of days between prescription renewals" (42,43) using drug data in the ICDC Chronic Disease Repository. Patients with medication supplies to cover ≥80 % of observed treatment days are considered adherent (44,45).

We will calculate PDC for each participant in the initial 12-month period that they were in the trial for both Statins and ACEi/ARBs. For those switching between statins or agents within the ACE/ARB class, ANY dispensed medication in the class will be included in the analysis.

6.3. Definition of Quality of Life

The Canadian-specific EQ5D index score will be the primary quality of life measure. For patients who die during the study, subsequent index scores will be given a score of 0, consistent with usual EQ-5D convention (scale is anchored at zero and 1, with zero being dead and 1 being perfect health).

Mixed models will be used to compare EQ-5D index scores over time between the treatment groups for each intervention.

In secondary analyses of EQ-5D index scores, to assess the impact of missing data, we will consider two alternate methods using imputation. Firstly, we will impute missing variables using multiple imputation as noted in section 10.3. We will then use this data to compare the area under the curve of index scores across each intervention group (equivalent to comparing a "QALY" profile for each participant). Secondly, we will used last observation carried forward to impute missing values, and then similarly compare the area under the curve of index scores. Both approaches will test the impact of missingness of data.

7. Trial Population

7.1. Recruitment

Throughout the 30-month enrollment period, a variety of recruitment strategies were used to identify eligible participants for the ACCESS trial, which we have classified into five overarching strategies and 14 sub strategies (Table 1). Participants who called the survey

unit were asked an open-ended question to determine how they learned about the study. Responses to this question were allocated to one of the 14 sub strategies.

From November 2015 until study completion a total of 12,342 people called the survey unit (Fig. 1). Of these potential participants, 4768 were randomized.

Recruitment for ACCESS was time-consuming and costly, but ultimately successful. We used 14 sub strategies to recruit the first 4013 participants into the study, at a cost of $354,330 CAD, which was approximately 20% of the overall study operating expenditures during this period. Despite eventual success, there was a lack of adequate planning and budgeting at the beginning of the study to successfully reach the target number of participants. Initial planning set out 12 months for recruitment, with only $20,000 CAD set aside as a dedicated recruitment budget to contact pharmacies, which was to be the sole recruitment strategy. As recruitment continued, the timeline had to be extended and considerably more resources had to be put towards recruitment—all the other strategies developed once it became clear that the initial plans for recruitment were going to be inadequate. No single strategy appeared to succeed in recruiting typically under-represented groups; rather, the strategies differed in their ability to recruit various types of people (46,47).

7.2. Baseline Characteristics

Baseline characteristics will be reported in a Table using descriptive summary statistics. These will be stratified by group assignment, and t-tests/Chi2 tests will be used to examine for inter-group differences in these characteristics.

8. Data Sources

The main data source for the trial will be the ACCESS trial RedCAP database. This contains participant group assignments and all patient reported measures from baseline, 6-month, 18-month, and 33-month surveys. It also contains individuals' unique provincial health number which will permit deterministic linkage to administrative health databases held by Alberta Health (including Alberta Precision Laboratory data, Pharmacy Information Network Data, Practitioner Claims data, Discharge Abstract Database, National Ambulatory Care Reporting System data). All PHNs were verified at the time of study enrollment to be sure that they were accurate and active. In cases where a deterministic linkage is not possible, probabilistic linkage using name, date of birth, and postal code will be used.

9. Interventions (s)

9.1. Handling of Withdrawn Participants

A small proportion of ACCESS trial participants contacted the study coordinating centre and requested to be withdrawn from the trial.

Where individuals requested full withdrawal of all study data, they will be excluded entirely. However, in most cases, those requesting withdrawal simply wanted to receive no further contact from the study but did not specifically ask to have their data withdrawn.

For the outcomes relying upon administrative data, we will use outcome data for all withdrawn participants. For the patient-reported outcomes we will use the responses provided to the time of withdrawal and will using multiple imputation methods for the missing datapoints thereafter (See 10.3).

10. Analysis Methods

10.1. Covariate Adjustment

Consistent with usual practice, we will only adjust the primary analysis for stratified variables (age (</>70; sex and low-income status) (48).

Assuming that randomization has worked, and we have approximately equal distribution of sociodemographic and clinic characteristics between randomization groups, we will not adjust our analyses for covariates, as this should have been dealt with through the process of randomization. If there is imbalance in important covariates between randomization groups, a sensitivity analysis will be conducted statistically adjusting for these imbalanced covariates through the modelling process.

10.2. Distributional Assumptions and Outlying Responses

There is the potential that some participants will have had repeated hospital encounters and excessive costs. If the number of these participants is imbalanced between the randomization groups, these outliers have the potential to skew results. In order to address this potential concern, we plan to conduct a secondary analysis in which the participants in the top 1% of encounters/costs will be excluded.

10.3. Handling Missing Data

Given that our primary outcome is determined using administrative data, we anticipate minimal missing data for our principal analysis. Therefore, we will use intention-to-treat principles for this analysis.

However, our secondary outcomes rely on self-reported data and therefore there may be considerable missing data points. For the analyses of these outcomes, we will undertake the following procedures for handling missing data:

We will first check the degree and patterns of missingness in the data, based on which we will consider optimal ways of handling missing data to minimise the bias potential. In the presence of missing at random (MAR) given the observed data, we will use methods such as multiple imputation or full information direct maximum likelihood to analyze the missing data.

If the MAR assumption is in doubt, then we will also conduct sensitivity analyses to assess the potential impact that missing not at random (MNAR) may have on the analytic results. Exploration of the sensitivity of conclusion to the MAR assumption may include models which allow for missingness that is not random. These models will include variables that we find to be related to missingness as well as those potentially related to the outcome (including age, sex, baseline medication adherence, comorbidities, household income).

If loss to follow-up is related to the level of the outcome being analyzed, then results obtained under the assumption of independent loss to follow-up may be biased; and in this situation, we will investigate the magnitude of this problem by using measurements taken at previous visits to predict loss to follow-up, and include variables that are determined to predict loss to follow-up in our predictive models in order to satisfy the conditions for the data to be considered MAR, with maximum likelihood techniques being used to estimate parameters. If necessary, we will also examine other approaches in consideration of how robust the results will be and whether they provide appropriately conservative estimates for the outcome analyses.

10.4. Analysis Methods- Primary Outcome

Consistent with an intention-to-treat analysis, we will categorize all participants by their randomization group, regardless of compliance (intention-to-treat), in our primary analysis. For those participants who are no longer actively receiving the self-management intervention or completing follow-up surveys, as permitted by CHREB, we plan to use available health administrative data until the time of death or outmigration from the province.

A Poisson model will test the main effects of the impact of the interventions on the rate of the primary outcome. This technique was chosen as individuals may experience multiple outcomes prior to the end of the study period, therefore we will account for both number of events and varying observation time within the Poisson model (by using an offset to account for losses to follow-up). The likelihood ratio test will test a negative binomial regression model within the Poisson model to examine for the presence of overdispersion. If present, negative binomial models will be used.

10.5. Analysis Methods- Secondary Outcomes

Medication adherence is a binary variable and will be analyzed using log binomial regression (generalized linear models with a log link)—given the likely high prevalence of non-adherence.

EQ5D index scores are continuous and will be analyzed using linear regression.

Medication self-efficacy and concerns will be dichotomized and analyzed using logistic regression.

10.6. Analysis Methods- Exploratory Outcomes and Analyses

In addition to the primary analysis, we will conduct time-to- first event analysis and will use cox regression models to calculate Hazards Ratios separately for each of these outcomes:

- Mortality
- MACE: Non-fatal MI, Non-fatal Stroke, CV death
- ACSC hospitalization

10.7. Safety

Given the low-risk nature of our interventions, and since our outcomes will be assessed using administrative data (with a one-year lag to receipt of data), there will be no external data safety and monitoring board. This study is considered low risk since patients' physicians remain ultimately responsible for managing patients' medical treatments and any complications that may arise as part of their treatment.

10.8. Planned Subgroup Analyses

We have a priori specified particular subgroup analyses, considering the biological plausibility for subgroups. We will conduct analyses stratified by subgroup, as described in the primary and secondary outcomes sections. We will provide effects with confidence intervals for subgroups (rather than p-values), as tests of interactions for subgroups can fail to detect important effects. These will be presented in a forest plot (49,50).

The subgroups of interest include:

Gender: Men vs Women (self-reported), likely exclude gender diverse
Age: >70 years vs 65-69 years
Income group: <30,000 vs >30,000
Financial barriers: Present vs Absent
Condition type: Diabetes // CKD // ASCVD // Risk factors only
Multimorbidity: 1-2 vs 3-4 indicated conditions
Primary Care Relational Continuity: Low/Medium vs High
Specialist Involvement in the year prior to randomization: Yes vs No
On statin at baseline: Yes vs No
On ACE/ARB at baseline: Yes vs No
Living environment: supported living vs. Independent living
Baseline medication adherence: >80% PDC for all covered meds vs <80% for any covered med

10.9. Sensitivity Analyses

Sensitivity analyses will be conducted as follows:
- Excluding those who have admissions/costs in the top 1% of all participants
- Excluding participants who resided in the same household as another participant.

- We will also conduct a complete case analysis to examine the effects of the missing data, where relevant (ie. Self-reported outcomes).

11. Interaction between intervention arms

Given the factorial design of the trial, we will assess for multiplicative interaction. Because each of our two interventions was designed to address very different patient barriers to medication adherence (financial barriers vs. Knowledge/motivation), we don't anticipate major multiplicative interaction effects.

12. Health Economic Analysis

The primary outcome will be mean total 3-year in-study health care costs for patients receiving copayment elimination (or not) and those receiving MOXIE (or not), adjusting for co-intervention received. We will include costs for hospitalization and ED visits, physician claims (specialist and primary care physician visit and procedure billing costs), prescription medications (including those subject and not subject to copayment elimination), nonphysician ambulatory costs (day medicine and day surgery clinics), and outpatient diagnostic imaging and laboratory costs. The total costs will be calculated as the sum of these costs. Alberta Health uses Canadian Institute of Health Information case-mix grouper methods to estimate hospital costs and ambulatory-case costing methods to estimate outpatient costs.

Physician claims will be based on the amount paid by Alberta Health. The cost of medications will be estimated by combining a database containing a comprehensive list of medications dispensed to all Alberta residents with a price list from Alberta Blue Cross, including dispensing fee. Diagnostic imaging and laboratory costs will be based on estimates provided by Alberta Health Services. All costs will be reported in 2021 Canadian dollars.

Assuming a non-gaussian distribution of costs, we will use established methods to enable comparisons of mean total costs, as these are easily interpretable and relevant to health care payer. We will use non-parametric bootstrap estimates to derive standard deviations and 95% confidence interval (95% CI) and mean cost differences between the treatment arms as we have done. We will use 1000 bias-corrected bootstrap replications, and sample with replacement from the original data, we will estimate the distribution of a sampling statistic to derive 95% confidence intervals. To allow us to control for stratified variables (age (</>70; sex and low-income status), we will also use generalized linear models to compare total costs across groups, using a gamma distribution and log-link function.

13. Statistical Software

We will conduct all the analyses using SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina), and Stata, version 17 (Stata Corp, College Station, Texas).

14. Differences to the protocol

None

Commented [DC1]: Dave to confirm

15. References

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