Study Title: Electronic Health Record augmented LDL-Cholesterol Optimization and Control via Active Lipid Engagement (EHR-LOCALE): A Quality Improvement Implementation Study

Short Title: EHR-LOCALE

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Study Synopsis

Title	Electronic Health Record augmented LDL-Cholesterol Optimization and Control via Active Lipid Engagement (**EHR-LOCALE**): A Quality Improvement Implementation Study
Objectives	To determine if a centralized, electronic health record augmented, lipid optimization pathway can improve quality of care and clinical outcomes after an acute coronary syndrome (ACS)
Trial Design	Pragmatic, individually randomized evaluation of a province-wide quality improvement intervention embedded within routine care.
Number of Participants	2000
Population	Individuals discharged from hospital with an acute coronary syndrome who have undergone coronary angiography in Alberta, Canada (Population 4.8 million)
Intervention	Centralized, electronic health record (EHR) augmented lipid optimization pathway which consists of: - Electronic identification of individuals discharged with an ACS - Automated identification of individuals who have achieved lipid targets - Referral to a centralized, pharmacist-led, telephone clinic for optimization of dyslipidemia management
Control	Usual care
Outcomes	*Primary outcome:* 1. Proportion of individuals who achieve guideline recommended low-density-lipoprotein (LDL) cholesterol target of <1.8 mmol/L at 6-months *Secondary outcomes:* 2. Proportion of individuals with repeat lipid panel testing at 3-months and 6-months 3. Proportion of individuals who undergo escalation or addition of new of

	lipid lowering therapies 4. Absolute difference in lipid values (LDL-C, high-density lipoprotein-cholesterol [HDL-C], non-HDL cholesterol, triglycerides) at six-months 5. Composite of all-cause mortality, hospitalization for myocardial infarction, hospitalization for stroke and unplanned coronary revascularization at one-year and five-years *Tertiary outcome:* 6. Cost-effectiveness of a centralized, EHR-augmented dyslipidemia management pathway following an ACS

BACKGROUND AND RATIONALE

ASCVD is a major public health priority and represents one of the most common causes of death in Canada. In Alberta (Population 4.8 million), the incidence of ASCVD is ~554 per 100,000 individuals with approximately 10,000 new cases annually (1). Patients presenting with an acute coronary syndrome (ACS) represent a high-risk population, with one third of patients experiencing a second major adverse cardiovascular event (MACE - myocardial infarction, stroke or death) within the next 5 years (2). While this residual risk is composed of many contributing risk factors (age, smoking, diabetes, hypertension, inflammation), residual cholesterol risk represents one of the most established and prevalent components (3). Despite established clinical benefits of lipid lowering in the ACS setting and international guidelines recommendations (4-6), only 20-45% achieve a low-density lipoprotein-cholesterol (LDL-C) target of <2.0 mmol/L (7-9). Individuals with have experience an ACS and do not attain guideline-recommended targets (≤1.8 mmol/L) are at particularly high-risk, with1 in 2 experiencing an additional MACE within the subsequent 3.5 years (10).

Barriers to residual, cholesterol-related risk management include clinical inertia, access to lipid lowering therapy and adherence/tolerance of lipid lowering therapy (11). The use of electronic health records (EHR) offers an opportunity to mitigate clinical inertia by identifying patients with persistent cholesterol risk despite efforts as part of routine follow-up (12). In Alberta, pharmacists have privileges that allow them to order investigations (such as lipid panels) and prescribe medications within their scope of practice (including lipid lowering therapies). When coupled with a pharmacist-led, remote intervention to assess compliance, side effects, current therapies, medication coverage and eligibility for dose adjustment or additional lipid lowering therapies, there is an opportunity to provide improve guideline recommended care in this high-risk population (13).

HYPOTHESIS

Following an ACS, the adoption of a centralized, EHR-augmented, pharmacist-led strategy will improve metrics of quality of care (repeat cholesterol testing), improve attainment of LDL cholesterol targets, increase the use of intensified lipid lowering therapies and improve cardiovascular outcomes in a cost-effective manner compared to usual care.

OBJECTIVES

Primary Objective: To determine if a centralized, EHR-augmented, pharmacist-led strategy will improve the proportion of individuals who achieve LDL-cholesterol targets following an ACS compared to usual care.

Secondary Objectives: To determine if a centralized, EHR-augmented, pharmacist-led strategy will improve:

- Rates of repeat cholesterol measurement
- Absolute differences in lipid parameters – LDL-cholesterol, HDL-cholesterol, triglycerides, total cholesterol
- Dose escalation or intensification of lipid lowering therapies
- Cardiovascular outcomes – composite of all-cause mortality, hospitalization for myocardial infarction or stroke at one-year

Tertiary Objective: To determine the cost-effectiveness of a centralized, EHR-augmented, pharmacist-led strategy compared to usual care.

STUDY DESIGN:

This pragmatic assessment of a quality improvement initiative will be evaluated in a randomized fashion across the province of Alberta that captures 4.8 million individuals, 3 cardiac catheterization laboratories and 106 acute care hospitals.

Study Population:

Inclusion Criteria:

1. Adults over the age of 18
2. Resident of Alberta
3. Individuals hospitalized with an acute coronary syndrome and have undergone coronary angiography.
4. Able to participate in follow-up contact if randomized to the intervention arm

Exclusion Criteria:

1. In-hospital mortality

OUTCOMES:

Primary Outcome:

- Proportion of participants who achieve LDL-cholesterol target of <1.8 mmol/L at 6-months

Secondary Outcomes:

- Proportion of participants with repeat lipid panel testing at 3-months
- Proportion of participants with repeat lipid panel testing at 6-months
- Absolute difference between LDL-cholesterol at baseline and 6-months
- Absolute difference between HDL-cholesterol at baseline and 6-months
- Absolute difference between triglycerides at baseline and 6-months
- Absolute difference between total cholesterol at baseline and 6-months
- Absolute difference between non-HDL cholesterol at baseline and 6-months
- Proportion of participants who underwent dose escalation or intensification of lipid lowering therapy 6-months
- Composite of all-cause mortality, hospitalization for myocardial infarction, hospitalization for stroke and unplanned revascularization at 1-year and 5-years

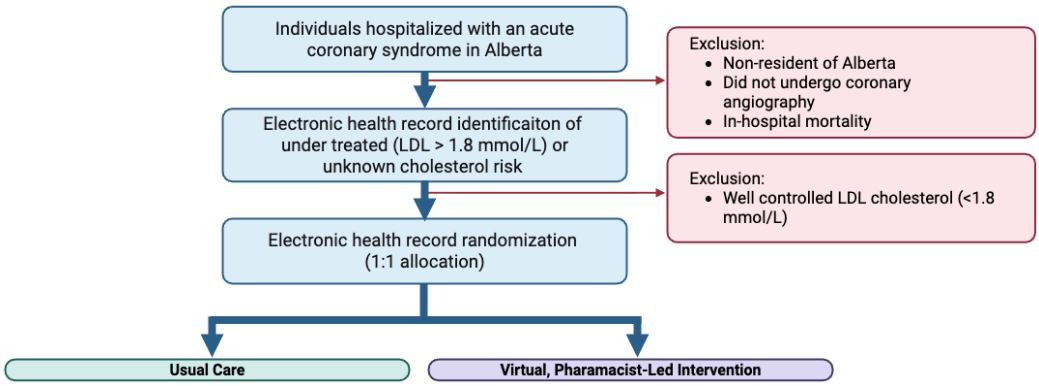
Tertiary Outcomes:

- Cost effectiveness of the quality improvement initiative

STUDY PLAN

On a daily basis the EHR build will be used to identify individuals who have been discharged from hospital with an acute coronary syndrome and have undergone coronary angiography. At 30-days post-discharge the EHR system will identify those who are not at their LDL target (>1.8 mmol/L) or have not undergone a lipid panel assessment. These individuals will undergo randomization to usual care or invited to participate in this quality improvement initiative. If randomized to the intervention arm, an Alberta Health Services pharmacy team member (in their clinical role) will contact the patient, inform them that their cholesterol level is above the recommended target and determine their interest in hearing more about the study. If they agree, they will be played an audio recording of the verbal consent script. They will have the option of

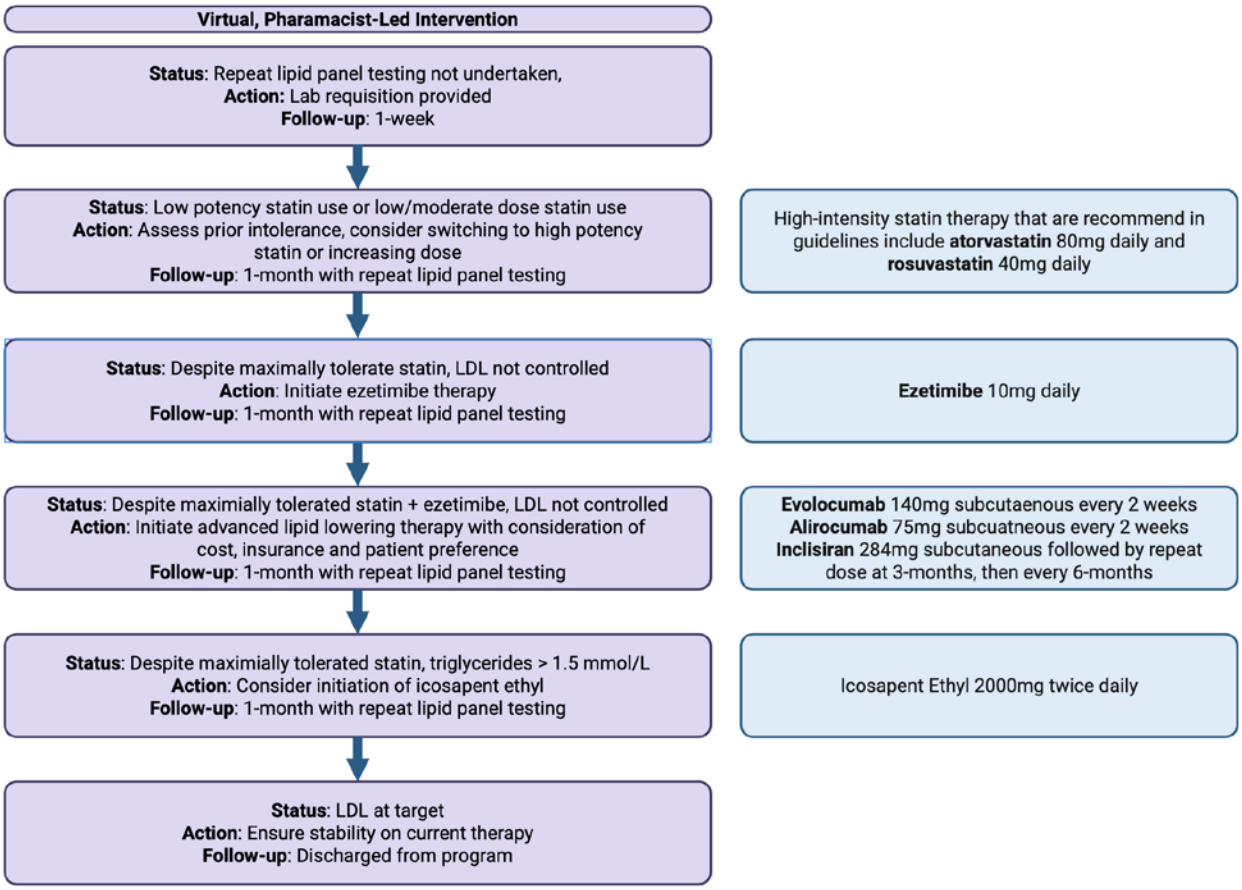
agreeing, not agreeing or getting more information. If they would like to hear more about the study or agreed, contact details as well as the participants' provincial healthcare number will be collected from the patient by the Alberta Health Services pharmacy team member to be passed on to the study team to be used for two factor authentication. This conversation will be audio recorded.



Control: Usual care will involve continued care with follow-up with cardiologists, family physicians and cardiac rehabilitation as per national guidelines.

Usual care + Quality Improvement Initiative:

1. Participants who have not undergone repeat lipid panel testing will be provided a lab requisition to have this undertaken and followed up the subsequent week.
2. Participants who are not at LDL- cholesterol targets will be assessed for compliance and discuss treatment escalation as per national guidelines (Figure), followed by repeat lipid panel testing in one-month.
3. Participants will exit the program once their LDL is at target, no further changes in lipid lowering therapies are expected or if they no longer wish to participate.



Informed Consent

This study uses individual randomization with a waiver of informed consent prior to randomization paired with post-randomization verbal consent for individuals' allocated to the intervention arm.

We are requesting a waiver of individual informed consent for randomization and for the use of routinely collected health data in the usual care arm. Participants randomized to the intervention arm will be contacted and provided with clear information about the program, and their verbal consent to participant in the program will be documented and audio recorded.

This approach aligns with the proportionate and context-sensitive approach to consent in the Tri-Council Policy Statement 2 (TCPS2; 2022), as well as with international ethical guidance on pragmatic and embedded health system research (14). TCPS2 (2022), article 3.7A, allows an REB to approve an alteration of consent if the following conditions are met, for which this study

satisfies all five criteria.

Minimal Risk - This quality improvement initiative is considered minimal risk. The study involves no investigational products and is instead assessing a quality improvement initiative to change in how we deliver dyslipidemia care in the post-ACS setting which adheres to national guideline recommendations (4). The use of all lipid lowering therapies in this study are considered safe and follow national guideline recommendations. No invasive or additional procedures, beyond what is recommended in national guidelines will be undertaken. Pharmacist interventions are within their regulated scope of practice. The risks that participants may be exposed to related to lipid lowering therapies are no greater to what they may be exposed to in usual practice as both are expected to follow national guidelines.

Unlikely to adversely affect participants welfare - Participation does not affect treatment or components of usual care for all participants. Those randomized in the intervention arm are contacted by a pharmacist, receive clear information about the program, may refuse participation without impact on their clinical care and may withdraw at any time. No patient is denied access to standard therapy and a waiver does not negatively affect participants' rights, dignity or welfare.

Research cannot practically be carried out without the waiver – The TCPS2 (2022) explicitly acknowledges certain types of research, including embedded health system and quality improvement evaluations, may be impracticable without consent modification. This program aims to target > 6000 ACS hospitalization annually, covers a geographically large, demographically diverse population, relies on EHR-based case identification and administrative data linkages. Obtaining prospective informed consent would be logistically infeasible, create systematic exclusion of rural, elderly, socioeconomically disadvantaged and acutely ill populations and is in direct tension with RCPS2's emphasis on justice and inclusiveness.

Participants will be provided with additional information where appropriate – The program aims to ensure transparency, even when consent is waived. In this study, all participants will be informed about the program during pharmacist contact and will be given contact information for

further questions. Additionally, all cardiac catheterization laboratories in Alberta (Mazankowski Heart Institute, Royal Alexandra Hospital, Foothills Medical Center) will share with patients that they may be contacted regarding optimization of their cholesterol, with information about the program provided to patients.

Participants may withdraw their data where feasible – Participants will be provided with the opportunity to opt out of further contact and may request that their data not be used in research analyses where feasible.

Randomization

Blinded simple randomization will be performed through an automated system. Randomization sequence will be concealed. Participants will be randomized to either usual care or the quality improvement initiative in a 1:1 ratio. Due to the nature of the intervention, only study statisticians will be blinded to treatment allocation when assessing outcomes.

Adverse events

Due to the nature of the quality improvement initiative adverse event collection is not feasible in the usual care group. Serious adverse reaction in both groups will be ascertained through administrative health data wherever possible. In the intervention arm, patient-reported adverse events, therapy discontinue due to intolerance and serious adverse drug reactions will be captured.

Data Collection

Participants in the quality improvement arms will have details of the intervention recorded in an electronic case report form (eCRF) in the REDCap system. Data will be entered by a study team member using web-based electronic data transfer. All other data will be extracted from the EHR using standardized definitions for variables of interest.

Statistical Analysis

Sample Size Calculations

An increase of 10% in the proportion of patients achieving LDL target of <1.8mmol/L was felt to

be clinically significant. Prior studies have demonstrated that in usual care LDL of <1.8mmol/L target is achieved in ~30% (7-9). Prior small-scale studies have demonstrated that pharmacist-led initiatives may double the rate LDL target achievement (15).

With an inclusion of 477 patients per arm (954 in both arms), the study will have a 90% power to detect a 10% increase in the proportion of patients achieving an LDL target of <1.8mmol/L at 6-months from 30% in usual care to 40% in the EHR-augment lipid lowering initiative arm, with a 5% significance level of the test. With adjustment for a loss to follow up rate of 10%, a total sample size of n=1060 patients (530 per arm) will be randomized (Appendix A).

The sample size calculations above represent at a minimum what would be required to detect a meaningful increase in the proportion of patients who achieve their LDL cholesterol targets. However, a primary goal of this project is to determine feasibility and sustainability of continuing this program long-term. As a result, it was felt the program would need to continue for a minimum of one-year to gain an understanding of the long-term resource requirements that would allow sustainability of this program.

Statistical Analysis

Analyses will be performed by Canadian VIGOUR Centre. The primary analysis will be performed after the last participant accrued completes 6-months of follow-up. Unless otherwise specified, all analyses will be performed on an intention-to-treat basis, and statistical tests will be conducted against a two-sided alternative hypothesis at a significance level of 0.05.

For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, inter-quartile range) and for discrete variables, frequency counts and percentages will be reported by treatment group.

For the primary outcome (achievement of LDL-C < 1.8mmol/L), odds ratio (and the 95% confidence interval) of achieving LDL-C threshold of <1.8 mmol/L at 6 months, comparing the EHR-augmented lipid lowering group to usual care will be estimated from a fit of a logistic regression model for a binary outcome. The model will be adjusted for LDL-C level at baseline.

The odds ratio, two-sided 95% confidence interval for the odds ratio, and p-value based on the fitted model will be reported. If the p-value based on a two-sided test for EHR-augmented lipid lowering strategy versus usual care at 6-months is < 0.05 and the corresponding odds ratio is greater than 1, statistical significance in favor of EHR-augmented lipid lowering strategy is declared.

Cost-Effectiveness Analysis

A cost-utility analysis (CUA) and will be performed in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) and Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines. (16, 17) Recent systematic reviews of modelling-based economic evaluations of lipid-lowering therapies for secondary prevention of cardiovascular disease will be used to inform the methodological choices relevant to this analysis (18-20). Based on these insights, we will develop a state-transition microsimulation model in TreeAge Pro 2023.9 from the perspective of a publicly funded healthcare system. The model will simulate lifetime clinical and economic consequences of secondary lipid-lowering strategies in 10,000 individuals with established ACS and an LDL-C above the Canadian Cardiovascular Society (CCS) Guidelines on Dyslipidemia threshold (≥1.8 mmol/L). Two strategies will be compared:

1. Standard of Care (SOC): Usual care for achieving LDL-C <1.8 mmol/L in patients with ACS, consistent with the 2021 CCS guidelines. These recommend initiation with a maximally tolerated statin, with intensification using non-statin therapies (e.g., ezetimibe, PCSK9 inhibitors) if thresholds are not achieved. Hospital setting primary care and specialist providers are expected to follow these guideline-based standards of care.
2. EHR-LOCALE (Electronic Health Record–augmented LDL-Cholesterol Optimization and Control via Active Lipid Engagement): A clinical decision support intervention that identifies patients discharged with an acute coronary syndrome (ACS) diagnosis and LDL-C ≥1.8 mmol/L. The program enhances provider and patient engagement through EHR and patient portal communication, coupled with monthly, pharmacist-led virtual assessments that include repeat lipid profile testing, treatment intensification, or the addition of lipid-lowering therapies as required.

The model will be used to predict subsequent cardiovascular events and cardiovascular- or non-cardiovascular-related mortality as a function age, sex, LDL-C level, and cardiovascular (CV) event history. Health states will include non-fatal myocardial infarction, non-fatal ischemic stroke, other ASCVD (e.g., peripheral artery disease revascularization, carotid endarterectomy, or abdominal aortic aneurysm repair), CV and non-CV death. Coronary revascularization will be included as a procedure and not as a separate health state because it is assumed it does not affect long-term cardiovascular event risk and quality of life. Markov models assume that a patient is always in one of the predefined health states, and patients can transition between health states over time. Each health state is assigned a (time-dependent) utility and cost. The long-term expected health effects and costs of each strategy can be calculated by multiplying the total time spent in each state by the utilities and costs corresponding to these states, respectively. Costs and utilities will be discounted annually at a rate of 1.5%. The principal outcome is a cost per quality-adjusted life-year (QALY), expressed as the incremental cost-utility ratio (ICUR). Other outcomes reported will include cumulative and disaggregated costs in 2025 CAD dollars, cumulative and disaggregated life-years (LY), cumulative and disaggregated quality-adjusted life-years, and cost per LY.

Targeted Population: The simulation model will be populated with a hypothetical cohort of 10,000 patients discharged from an Alberta hospital with a primary diagnosis of MI (STEMI and NSTEMI) and LDL-C $\geq$ 1.8 mmol/L.

Model Inputs: The planned trial will provide observed 1-year data on the baseline ASCVD event rates, coronary revascularization rates and the treatment efficacy data (hazard ratios), pharmacotherapy patterns (baseline and post-intervention distributions and mean doses), LDL-C levels (baseline and post-intervention proportion reaching LDL-C target levels and mean values), and discontinuation rates. Long-term cardiovascular event rates will be estimated by combining trial data with evidence from the Cholesterol Treatment Trialists' (CTT) meta-analyses, which provide hazard ratios for major cardiovascular events per 1 mmol/L reduction in LDL-C over longer-term follow-up (21). Annual rates will be converted into transition probabilities. Mortality from non-cardiovascular causes is assumed to be the same as that of the general population and will be extracted from Canadian national life tables. Costs for non-fatal MI, non-fatal ischemic

stroke, other ASCVD events, and revascularization will be estimated using Alberta Ministry of Health administrative data, incorporating both hospitalization and ambulatory care costs (via the standard hospital stay methodology). Patient monitoring (general practitioner/pharmacist visits, and laboratory tests) and pharmacotherapy utilization and costs will be determined from the trial, published literature and administrative health databases. All costs will be inflated to 2025 CAD dollars using the Consumer Price Index. A pragmatic literature search will be performed to identify Canadian utility values.

Model Validity: Model validity will be established by comparing the expected cardiovascular time-to-event data from the planned trial (1-year follow-up data) to the predicted cardiovascular events from the microsimulation model. We will also validate that the model reproduces consistent mean age, distribution of LDL-C, and proportion achieving LDL-C targets with the trial participants. To ensure the model produced stable estimates, we will examine outcomes when varying the number of individuals simulated from 2,000 to 10,000.

Sensitivity Analyses: Assumptions and uncertainty in the base-case analysis will be assessed by conducting a series of sensitivity analyses. One-way and 2-way sensitivity analyses will vary key model parameters independently and jointly, respectively, over a range of plausible values while holding all other parameters constant. We will also perform a probabilistic sensitivity analysis (PSA) to assess uncertainty in model parameters by drawing 1,000 random samples for each model parameter from prespecified distributions and repeating the simulation for each parameter set (22). We will use beta distributions for probabilities and utilities, lognormal distribution for relative risks, and gamma distributions for costs. The distributions will use published or calculated standard errors and 95% CI when available; otherwise, input parameters will be varied by 20%. Cost-utility acceptability curves will also be constructed from the PSA results to summarize the uncertainty in estimates of cost-utility.

Subgroup analysis

All subgroup analysis will be considered exploratory and tested via interaction terms. Pre-specified subgroups of interest include:

1. Age ≥ 65 years versus < 65 years

2. Sex
3. ACS type (STEMI vs NSTE-ACS)
4. Diabetes
5. Current or history of heart failure
6. Chronic kidney disease (estimated glomerular filtration rate of <60 ml/min/1.73m^2)
7. Revascularization status – medical management, coronary artery bypass surgery, percutaneous coronary intervention
8. Systemic inflammation hsCRP >2 mg/L
9. Lp(a) > 50 mg/dL
10. Frailty using the Hospital Frailty Risk Score

Data Management

All data transferred to the eCRF and any process derived from the eCRF will be handled anonymously. This will ensure that the identity of the individual will be protected.

Patients' health records will be accessible only to research study personnel who are appropriately trained and delegated to work on the study. Patients will be assigned a unique identifying code in the REDCap system and thus the eCRF will contain no private identifying information. Only trained and delegated study personnel/study monitors will have access to the eCRF and each will be provided his/her own unique logon and password. In the event of a data privacy breach (anticipated to be very unlikely) the University of Alberta HREB will be notified.

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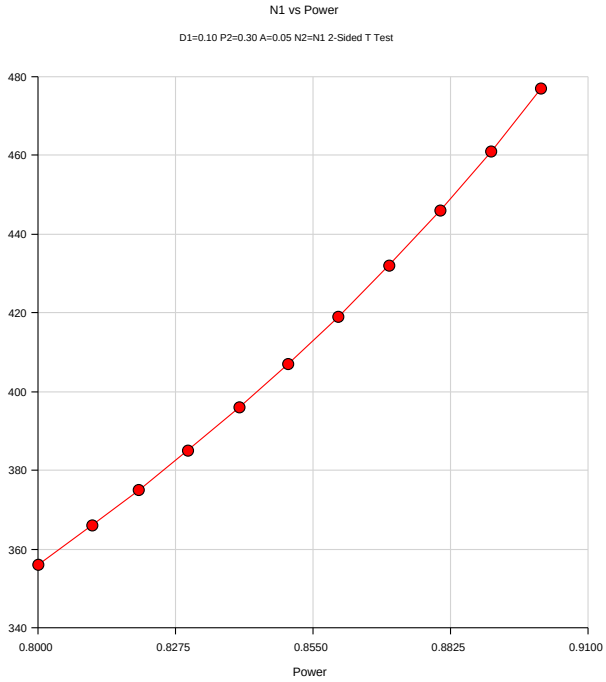
Appendix A – Power analysis

Two Independent Proportions (Null Case) Power Analysis

H0: P1 - P2 = 0. H1: P1 - P2 = D1 ≠ 0. Test Statistic: T-test

Power	N1	N2	N1 adjusted	N2 adjusted
0.90	477	477	530	530
0.85	407	407	453	453
0.80	356	356	396	396

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