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The OPTIMIZE trial: Rationale and design of a randomized controlled trial of motivational enhancement therapy to improve adherence to statin medication

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ABSTRACT

Background: Statins are a class of medications that are particularly effective for lowering cholesterol and reducing cardiovascular morbidity and mortality. Despite a range of benefits, non-adherence to statin medication is prevalent with 50% to 75% of patients failing to adhere to treatment within the first 2-years. A previous review on interventions to improve adherence to cholesterol lowering medication concluded that rigorous trials were needed with emphasis on the patient's perspective and shared decision making. Motivational interviewing (MInt) is a promising patient-centered approach for improving adherence in patients with chronic diseases. This manuscript describes the rational and design of a randomized controlled trial (RCT) testing the efficacy of MInt in improving adherence to statin medication.

Methods: Patients filling their first statin prescription will be recruited to complete a 6-month observation run-in period (phase-1) after which medication possession ratio (MPR) will be assessed. Patients meeting criteria for non-adherence (MPR ≤ 60%) will be invited to participate in the trial. 336 non-adherent new statin users will undergo a fasting lipid panel, complete baseline questionnaires, and be randomly allocated to receive four sessions of adherence education delivered using MInt (EdMInt) or to an education control (EC) delivered at 3-month intervals. Final assessments will occur 12-months after the first EdMInt or EC session. The primary outcome is change in MPR adherence to statin medication from baseline to 12-months. Secondary outcomes include within-patient change in self-reported medication adherence, stage of change and self-efficacy for medication adherence, motivation to adhere to statin medication, and lipid profile.

1. Introduction

Statins are a class of medications that lower low-density-lipoprotein cholesterol (LDL-C) levels by as much as 50% [1–3] and have cholesterol-independent cardioprotective effects [4,5]. Statins reduce ischemic heart disease events by 60% [6], vascular events by 35% [1,7], all-cause mortality by 10% [8], and were credited with 24% of the reduction in coronary deaths in the U.S. between 1980 and 2000 [9].

Despite the benefits associated with statin therapy, approximately 50% of patients treated using statins discontinue their use within their first year of treatment [10–14]. Further, only 25% of those treated with statins for primary prevention will persist with therapy after 2 years [10,12,15–17].

There are several factors associated with statin non-adherence. A meta-analysis of 67 studies reported that risk factors for statin non-adherence included: new statin users, use for primary prevention and low income [12]. Smoking [18], depressed mood [10,19], perception of a financial barrier [20], adverse statin-related effects [14], poor self-efficacy for taking medications [21], and older age [22] are additional predictors of non-adherence. Further, expert opinion [23] suggests that patients

Abbreviations: EC, education control; EdMInt, education delivered using motivational counseling; MInt, motivational interviewing; MPR, medication possession ratio; RCT, randomized controlled trial.

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are less likely to adhere to medications if they do not believe statins to be of benefit, fail to understand the risks associated with hypercholesterolemia, or have poor adherence motivation.

A recent (2010) Cochrane review of interventions to improve adherence to lipid lowering medication identified 11 randomized controlled trials (RCTs) [24]. Eight RCTs (n = 6449) focused on statin medication and were associated with improvements in adherence between 2.3% and 24% with a mean of 7.4% [25–32]. Interventions generally used education [30,31], or patient reinforcement/reminders [25–29,32], which improved adherence by 7.8% and 7.2%, respectively. The review noted that several trials were limited by low methodological quality and risk of bias and concluded that rigorous trials were needed with emphasis on the patient's perspective and shared decision making. Shared-decision making is a form of patient-centered care that seeks to foster and support patient autonomy by involving the patient in every aspect of the decision making process and reaching a mutually agreed upon consensus about the treatment to implement [33]. Patients who are involved in treatment decisions are more likely to feel autonomously motivated (as opposed to extrinsically motivated) to change their behavior [34]. Fostering patient confidence and autonomy are particularly important in chronic care where patients' are often required to make complex behavior changes and actively carry out the treatment [35]. Attesting to the importance of patient involvement and shared-decision making, patient ratings of provider communication and involving patients in decisions accounted for an absolute difference in adherence to oral hypoglycemic medications of 15% [36].

Motivational interviewing (MInt) is a non-judgmental, collaborative, person-centered counseling style for strengthening a person's motivation and commitment for change by exploring and resolving ambivalence between present behavior and future goals or values [37,38]. MInt encompasses principles and techniques drawn from various theoretical paradigms, including the provision of patient-centered counseling [39]; fostering self-efficacy [40], enhancing autonomous motivation [41,42], focusing on patient readiness for change [40], and helping to clarify goals, overcome barriers, and commit to behavior change. Meta-analyses reported that MInt is efficacious for improving health-related behaviors (e.g., reducing smoking, dietary sodium, and total cholesterol) [43–46]. MInt significantly improved clinical outcomes in three out of four studies, with comparable effects for medical outcomes (72%) and psychological outcomes (75%) [46]. Further, several RCTs have demonstrated that MInt can be used to improve adherence to medication [47–49]. Despite encouraging results, the impact of MInt on chronic preventive medications like statins, where baseline adherence is low, is not well understood.

This manuscript details the rationale and design of an RCT evaluating the efficacy of education delivered using MInt (EdMInt) versus education control (EC) in improving 12-month adherence to statin medication among new statin users.

2. Methods

2.1. Study design

This study is a double-blind, parallel-group RCT adhering to the CONSORT guidelines for non-pharmacological RCTs [50]. Fig. 1 depicts a flow diagram of the study design. Approximately 1008 patients who have filled their first statin prescription will be screened for eligibility and enrolled in a 6-month observation period (phase 1). Following observation, patients meeting criteria for non-adherence will be invited to participate in phase 2 of the study. After eligibility has been confirmed, patients will be randomly assigned to one of two groups: education delivered using a motivational counseling style (EdMInt) or EC. Individuals in the EdMInt group will receive usual care plus four sessions of education delivered using a motivational counseling style at 3-month intervals while individuals in the EC group will receive four sessions of education delivered at 3-month intervals. Recruitment will continue until our desired sample of 336 patients (168 per condition) is reached. The primary outcome will be statin adherence 12 months after baseline assessment. Statin adherence will be measured using % medication possession ratio (MPR) measured with pharmacy refill records. The secondary outcomes are baseline to 12-month within-person change in LDL-C, self-reported adherence to statin medication, stage of change for medication adherence, self-efficacy for medication adherence, and motivation to adhere to statin medication.

2.2. Study setting

A community sample of patients newly prescribed statin medication will be recruited for a 6-month medication adherence observation period (phase 1). Advertisements for a research study examining lipid control in patients newly started on cholesterol-lowering medication will be placed in family medicine clinics and community pharmacies in Calgary, AB.

2.3. Patient eligibility

2.3.1. Inclusion criteria

At least 18 years of age, prescribed their first (i.e., no previous statin prescription within the preceding 6-months) statin or combination medication including a statin, and fluent in the English language.

2.3.2. Exclusion criteria

Deemed unable to comply with protocols (e.g., unwilling to participate, unable to attend testing sessions, relocating within the upcoming year, sporadic out of town work schedule); diagnosis of cognitive impairment (e.g., dementia); severe psychopathology (e.g., schizophrenia); history of drug and/or alcohol abuse; terminal condition with low likelihood of 12-month survival; residing in a long-term care facility; previous prescription of a lipid lowering agent.

2.4. Procedure

2.4.1. Patient screening, recruitment, and enrollment

Patients will be recruited from family medicine clinics and community pharmacies in Calgary, AB. Study information will be provided to patients through pamphlets placed in family medicine clinics and community pharmacies, and through active promotion by allied healthcare professionals (e.g., pharmacists, physicians). Patients who are interested in participating can: 1) contact the study team directly, 2) sign a consent form allowing the study team to contact them directly, or 3) be directly enrolled by their healthcare professional. Interested patients will undergo a telephone screening interview during which they will be asked to provide informed consent, both verbal and written, to participate in the study and to contact their pharmacy to obtain medication information for all medications prescribed from the date of the first statin prescription to the end of the trial. In order to be as inclusive as possible, patients can provide written informed consent via e-mail, fax, scan, or in person. Patients who have filled their first statin prescription will be re-contacted and informed that if they agree to participate, they will be followed for 6-months (phase 1) after which time they may be eligible for phase 2, which involves random assignment to one of two conditions designed to evaluate lipid management. MPR will be assessed following the observation period (refer to Section 2.5.1) and patients deemed adherent (MPR > 60%) will be given education material on cholesterol adapted from the Heart & Stroke Foundation of Canada's website while patients deemed non-adherent (MPR < 60%) will be invited to join phase 2 and schedule a time to attend a baseline appointment. Recruitment efforts will continue until we identify 336 non-adherent patients. Given consistent findings of a mean 12-month statin adherence measured using MPR of 56% [51], and that discontinuation is greatest in the first 3-months, we expect that one third of patients completing the observation period will be eligible for the study.

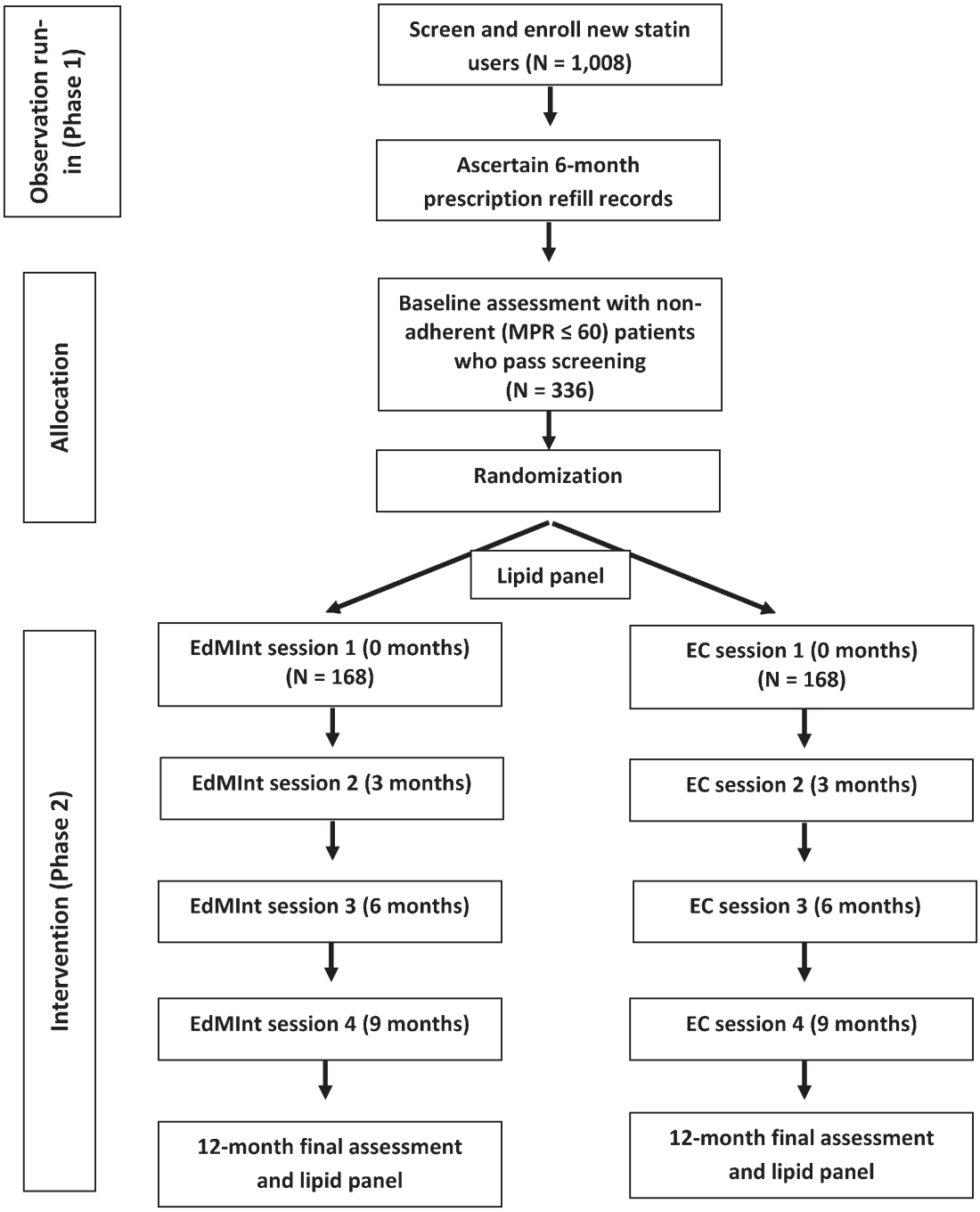

Fig. 1. Flow diagram depicting anticipated participant flow through the motivational interviewing (MInt) and education control (EC) arms of the trial.

Thus, we conservatively estimate having to recruit approximately (336 ∗ 3) 1008 patients in order to identify 336 who are not adherent following phase 1.

Following careful consideration, we elected to target all new statin users rather than patients with an existing history of non-adherence. The rationale for this decision is three-fold. First, we have concerns about the feasibility of recruiting patients who are already non-adherent and anticipate there would be minimal interest to participate. Second, the majority of new statin users are expected to have less than perfect medication adherence at 12-months, making this a reasonable group to target. Third, one key tenet of any behavioral trial is that the behavior of interest is present at the onset of the trial [52].

We anticipate that there will be 678 new statin users each month in Calgary. We extrapolated from the population-based report of new statin users in British Columbia (BC) [53]. There were 239,911 new statin users in BC between January 01, 1997 and June 30, 2004. This equates to (239,911 new users/91 months) 2636 new statin users each month. BC has 4.6 million residents meaning that there are (2636 new users each month/4.6 million populous) 573 new statin prescriptions filled each month per 1 million residents. Calgary has a population of 1.2 million, suggesting that there are (573 ∗ 1.2) 678 new statin prescriptions filled each month. Using a conservative estimate, if our recruitment efforts reach 10% of prescribing physicians and pharmacies then we can expect to identify 68 new statin prescriptions per month.

2.4.2. Observation run-in period

Patients will visit Calgary Laboratory Services (CLS) within 14-days prior to the baseline assessment for a fasting lipid panel. A 14-day

timeframe was chosen to ensure that the researcher has the results of the blood lipid panel prior to the baseline assessment. Patients will then visit the Behavioural Medicine laboratory at the University of Calgary to undergo baseline assessment.

2.4.3. Baseline assessment

Patients will complete a demographics questionnaire and study measures (refer to Section 2.5) and the first EdMInt or EC session will then be scheduled to take place within the following 7-days.

2.4.4. Randomization and blinding

A research assistant (RA) not affiliated with the proposed study will use Research Randomizer (http://www.randomizer.org/) to generate lists of randomly sequenced numbers for assigning patients to condition in a manner consistent with CONSORT [50]. Central randomization stratified by prevention setting (primary or secondary) will be performed using a 1:1 allocation schedule with random block sizes of 4, 6, and 8. Randomization will be stratified by prevention setting (primary or secondary) because the benefits of statins are greater [54] and adherence rates are higher [55,56] in secondary prevention. The allocation sequence will be concealed from the researcher using sequentially numbered, opaque, and sealed envelopes. In order to protect against expectation effects and biases, the RA delivering EC will be unaware that they are delivering a control condition, participants will not know what condition they have been assigned to, and an RA not affiliated with this study will complete the outcome assessment without being aware of participant condition. Adequacy of blinding will not be formally evaluated given the lack of evidence for, and concern against conducting such an assessment [57].

2.4.5. Education delivered using a motivational counseling style (EdMInt)

Patients randomized to this condition will receive four individual, in-person sessions (with the option of receiving up to two additional sessions, see below) lasting approximately 15–30 min each. All sessions will be delivered at the Behavioural Medicine Laboratory located at the University of Calgary. The initial session will be longer (30 to 45 min) in order to establish therapeutic rapport, which is critical in MInt [38,58]. Sessions will be delivered at 0, 3-, 6-, and 9-months.

In order to ensure that the interventionist remains MInt compliant and to ensure the reproducibility of the intervention, the treatment will be manualized but not standardized. The manual includes various MInt protocols and tools that can be selected based on patient presentation and deviated from where appropriate, thus adhering to the fundamental principles of MInt. One strength of MInt is that it is an individually tailored and flexible intervention that need not be delivered in a pre-determined order over a prescribed number of sessions [38,58]. As such, strategies used from session to session may differ according to the clinical status, stage of change, and objective of the patient.

Our intervention was designed with the following criteria: *four to six*, 15–30 min *sessions delivered one-to-one over a* 12-month *period.* We based our intervention design on previous meta-analytic results [44–46,59] that have reported: 1) sessions lasting between 15–60 min were efficacious in changing health behaviors in 64–81% of studies [46], 2) the magnitude of the effects increases with the number of sessions, with 87% of studies showing an effect with ≥5 sessions, compared to 40% (10/25) of studies with one session [46], 3) MInt is equally effective as a stand-alone or additive intervention [59], 4) MI has stronger effects when delivered individually rather than by telephone or in group format, and 5) strict adherence to a manual detracts from MInt outcomes [44,59].

EdMInt sessions will employ the four processes of MI (engaging, focusing, evoking, and planning) within a framework that is both sequential and recurring throughout the interaction [38]. The interventionist (a MInt trained doctoral level Clinical Psychologist) will review the education material outlined in Section 2.4.6 while conducting MInt to (i) facilitate collaborative tone, (ii) assess motivation for change, (iii) elicit positive self-motivational statements about their adherence behavior, which will be supported by reflective statements about change, (iv) use an empathy-based approach to providing feedback about laboratory results, (v) and, if ready, negotiate personal goals and a behavioral plan for change.

The flexible, non-scripted, individualized nature inherent in the delivery of MInt makes it a suitable technique for addressing both intentional and unintentional non-adherence. For example, if a patient is intentionally non-adherent then the intervention might focus on recognizing ambivalence, weighing the costs and benefits of statin medication, rolling with discordant statements, and strategically guiding patient's to overcome ambivalence using clinical skills, such as reflections and reframing. Given that there is a presumption that unintentional non-adherence is a passive process which is less strongly associated with a patient's beliefs and cognitions [60], if a patient endorses unintentional non-adherence then the intervention may focus more on the ask-provide-elicit elements of MInt. For example, the interventionist might elicit the patient's reasons for poor adherence and strategies that they think might be helpful before asking permission to provide education about helpful methods to overcome unintentional non-adherence (e.g., use of memory aids, establishment of a routine, blister packing medication). Finally, the interventionist would elicit the patient's feedback about the strategies discussed before asking what strategy the patient might try.

A Cardiac Risk Profile adapted from the Drinker's Check-Up [61] will be used when providing feedback. The patient will be given a written record of their plan and a copy will be retained in the research file. While the education material provided in Section 2.4.6 was designed to provide incremental knowledge from one session to the next, the interventionist will be flexible and cover the education material that best addresses the needs of the patient that arose while setting a collaborative agenda. It will be up to the interventionist and the patient to decide together if more than four sessions are needed to achieve statin adherence goals. Allowing a certain degree of flexibility more accurately reflects clinical reality, and is viewed as a strength in such studies [38,58].

2.4.5.1. Treatment fidelity and integrity. All EdMInt sessions will be performed by a doctoral level clinical Psychologist with training in MInt, who will also receive a 2-day workshop for trial-specific MInt training, as well as ongoing supervision with an MInt expert (TC). While the existing evidence suggests that MInt is a teachable, learnable skill that might be appropriate for a variety of healthcare providers (e.g. nurse, pharmacists, physicians), previous trials with inadequate or uncertain interventionist training background along with a failure to assess treatment fidelity have often produced null results, making it difficult to disentangle the efficacy of the intervention from proper delivery [62]. The use of a Clinical Psychologist to deliver the intervention will allow assessment of the efficacy of EdMInt for improving medication adherence when the intervention is delivered under optimal circumstances. This is a pre-requisite step to an effectiveness trial that is recommended by the NIH funded Obesity Related Behavioral Intervention Trials (ORBIT) Intervention Development Model for Behavioral Trials [63] to better understand the appropriate use of EdMInt on adherence and ultimately develop an empirically-validated intervention delivered by health care providers as part of routine clinical care. All sessions will be audio taped and fidelity to the techniques of MInt will be assessed using 30% of audio recording drawn at random. Threshold for treatment integrity will follow guidelines of the Motivational Interviewing Treatment Integrity (MITI) code [64]. Competency is defined by a global therapist rating of 4/5, reflection to question ratio of 2, 70% open questions, 50% percent complex reflections, and 100% MInt adherence. Frequencies will be computed by a trained graduate student upon study completion to determine whether the MInt tapes meet or exceed these cut-offs.

2.4.6. Standard education control (EC)

Patients will attend 4 individual sessions (delivered at 0-, 3-, 6-, and 9-months) located at the Behavioural Medicine Laboratory that span approximately 15–30 min each where they will receive education that is similar in content to the most rigorous RCTs using education to improve patient adherence to statin medication [25,30,32,65]. Patients will receive education about the measurement of cholesterol, the risks associated with elevated LDL-C, dietary information, and about influences known to impact medication adherence (e.g., motives for medication adherence, barriers to medication adherence, and intentions to persist). Further, patients in both conditions will have their 10-year Framingham Risk Score (https://www.cvdriskchecksecure.com/FraminghamRiskScore.aspx) and heart age (http://www.newswire.ca/en/story/1109369/are-you-young-at-heart-heart-age-calculator-helps-canadians-stay-heart-smart) explained to them. All sessions will be audio taped and 30% of audio recordings will be drawn at random and assessed to ensure that the there is no contamination between EC and EdMInt (i.e., to ensure that the interventionist is not delivering MInt).

2.4.7. Final evaluation

Final evaluations will be performed 12-months following the baseline assessment. Patients will visit CLS for a fasting lipid profile within 14-days preceding their final evaluation. Next, patients will meet the RA and complete the study measures (refer to Section 2.4). At this time, the RA will fax the pharmacist a request form for the patient's pharmacy refill records.

2.5. Measures

Table 1 shows the measures taken at each assessment study visit.

2.5.1. Primary outcome

Statin medication adherence will be measured using prescription refill records. We chose this method of assessment because one of the most objective measure of adherence is failure to refill a prescription (relative to pill counts which are vulnerable to patient tampering) [66], and because prescription refills have been associated with clinical outcomes, such as elevation of LDL-C among diabetic dyslipidemia

Table 1
Schedule of assessments.

Testing variables	Phone screen	6–month run–in	Adherence check	Randomization	Within 14–days prior baseline	Baseline	Within 14–days prior final assessment	12–month post–intervention
Inclusion & exclusion criteria	X							
Sociodemographics						X		
Medical history						X		
Statin adherence								
Pharmacy refills			X					X
Self–report						X		X
Adherence motivation								
TSRQ						X		X
Adherence Self–efficacy								
MASES						X		X
Stage of change								
SCAQ						X		X
Fasting lipid panel					X		X	
Intervention/contact evaluation (manipulation check)								
Usefulness						X		X
Pertinence						X		X
Enjoyableness						X		X
Expectancy to change adherence						X		X
Motivation to adhere to medication						X		X

MASES = Medication Adherence Self–Efficacy Scale; SCAQ = Stages of Change for Adherence Questionnaire; TSRQ = Treatment Self Regulation Questionnaire

patients [67]. There are drawbacks to using prescription refill records to measure adherence (e.g., the need for a closed pharmacy system, not equivalent to ingestion of a pill). All statin medication is prescribed on a dose by frequency method. Our measure is based on an equation that has been used extensively in previous research [68–70]. Prescription refill records will be obtained by accessing the patient's individual pharmacy records through their local pharmacy and used to calculate MPR. Specifically, patient signed 'consent to access pharmacy records' forms will be faxed to all pharmacies that the patient reports. In order to ensure prescription refill records are accurately capturing medication use, patients will be asked to self-report pills in their possession at each laboratory visit (e.g., free samples and prescriptions filled at different pharmacies). MPR is defined as the percentage of days that the patient has pills available [66], and calculated using the formula [(# of refills at the pharmacy * number of pills per prescription) / (# of days the patient is expected to be taking the medication)]. Statin medication is prescribed daily meaning that the denominator will remain stable at 365 at 12-months. A modified 6-month MPR will be used to calculate baseline adherence. As prescription days are always based on what is prescribed, and statins are administered daily, we can easily account for change in medication or change in dose. Change from one statin to another will be considered adherence with statin therapy.

We are targeting a mean improvement in adherence of 14%. Our reason for this target was twofold. First, one previous RCT assessing adherence to antihypertensive medication [49], along with previous RCTs examining adherence to corticosteroids [71] suggests that EdMI could improve adherence by 14%. Second, a 14% improvement in adherence is clinically relevant based upon previous research reports that an improvement in adherence to statin medication of 16.3% reduced LDL-C by 0.40 mmol/L [67]. Further, while the association between LDL-C and cardiovascular disease (CVD) may not be linear, extrapolating data from previous studies suggests that a reduction in LDL-C of 0.40 mmol/L would equate to an 8% reduction in risk of CVD and a 3.6% reduction in all-cause mortality [72].

2.5.2. Secondary outcomes

The secondary outcomes are within person change in lipid profile, self-reported medication adherence, stage of change for medication adherence, self-efficacy for medication adherence, and motivation to adhere to statin medication. Patients' complete assessments at baseline and 12-months, and within-patient change are computed as the difference in the score between baseline and final assessment.

2.5.2.1. Within-person change in lipid profile. Patients will visit CLS twice during the research project to receive a fasting lipid panel (within 14 days preceding baseline assessment and final assessment). LDL-C will be calculated using the Friedewald equation [LDL-C = total cholesterol − high density lipoprotein cholesterol − (triglycerides / 5)] [73,74].

2.5.2.2. Within-person change in self-report adherence. Self-report medication adherence will be assessed using the *Morisky Medication Adherence Scale* (MMAS-4), a 4-item questionnaire developed to assess medication compliance [75] that has been found capture medication adherence among statin users in primary care [76]. Items are rated on a 5-point Likert scale with anchors 1 = very often and 5-never. Representative items include: "Do you ever forget to take your medicine?" and "Sometimes when you feel worse when taking your medicine, do you stop taking it?" The MMAS-4 has excellent reliability ($\alpha = 0.83$) and was both sensitive (93%) and specific (53%) in the measurement of adherence to antihypertensive medications [77]. Self-report questionnaires of medication adherence have been found to correspond with direct and indirect measures of adherence [75,78–80], and predict clinical outcomes [80,81].

2.5.2.3. Within-person change in stage of change for medication adherence. Within-person change in stage of change for medication adherence will be measured using the *Stages of Change for Adherence Questionnaire* (SCAQ), a 2-item scale that was specifically designed to assess stage of change in medication adherence [82], according to the Transtheoretical Model of behavior change [83]. In medication adherence studies, the SCAQ predicted adherence as measured by electronic monitoring in a population of HIV positive patients over 30 days and self-report of adherence in an international hypertension study as measured by the Medical Outcomes Study Questionnaire ($N = 731$, Chi square = 441.3, $p < 0.001$) [82].

2.5.2.4. Within-person change in self-efficacy for medication adherence. Within-person change in self-efficacy for medication adherence will be assessed using the *Medication Adherence Self-Efficacy Scale* (MASES), a self-report questionnaire designed to identify situations in which patients have low self-efficacy in adhering to prescribed medications [84]. Respondents are asked to rate 26 situations with regards to how sure they are that they can take their medications all of the time using a 3-point scale: not at all sure, somewhat sure, very sure. The MASES has excellent psychometric properties including high reliability ($\alpha = 0.95$) and validity in measuring self-efficacy for adherence to anti-hypertensive medications [84].

2.5.2.5. Within-person change in autonomous motivation. Within-person change in autonomous motivation will be measured using the *Treatment Self-Regulation Questionnaire* (TSRQ), a questionnaire assessing the degree to which one's motivation for a particular behavior is relatively autonomous or self-determined [85,86]. Respondents are asked to rate 15 responses to the question "I would take my statin medication as prescribed because…" using a 7-point Likert scale where 1 = not at all true and 7 = very true. The TSRQ yields four motivation subscales (i.e., external, introjected, identified, and integrated). A relative autonomy index will serve as the index of autonomous motivation and is calculated by weighting the external subscale −2, the introjected subscale −1, the identified subscale +1 and the integrated subscale +2. This scale has been found reliable (α 0.62–0.82) [87] and valid in assessing patient motivation to adhere to prescription medication [88] and engage in the treatment of different chronic illnesses [89].

2.5.3. Covariates

2.5.3.1. Symptoms of depression. A meta-analysis by DiMatteo et al. reported that depression is a predictor of non-adherence to medical recommendations with an odds ratio of 3 [90]. Symptoms of depression will be assessed using the *Center for Epidemiological Studies - Depression scale* (CES-D), a reliable (α 0.84–0.90 among patients and non-patients) and well validated 20-item self-report scale that will be used as a screening measure for depression symptoms [91]. Items are summed to yield a continuous scale of depression ranging from 0 to 60 with a threshold of 16 or greater indicative of depression. The CES-D has been used widely in populations with chronic medical conditions [92], including CVD [93]. An elevated score does not ensure a diagnosis of depression, but further assessment may be warranted, therefore patients reporting elevated CES-D scores will be given community referral information for support with depression.

2.5.3.2. Medical comorbidity. Medical comorbidity will be assessed using a self-report version of the *Charlson Comorbidity Index* (CCI) [94]. The CCI is a validated and widely used weighted-index designed to evaluate the longitudinal risk of mortality attributable to co-morbid disease [95]. Higher scores on the CDI represent greater comorbidity-related risk of mortality.

2.5.3.3. Literacy in medicine. The World Health Organization (WHO) and other reviews have documented low health-related literacy as a reason

for medication non-adherence [23,96,97]. Literacy in medicine will be assessed using the *Rapid Estimation of Adult Literacy in Medicine* (REALM), a screening instrument used to assess an adult's ability to read common medical words and lay terms for body parts and illnesses [98]. The REALM has high 1-week test-retest reliability ($r = 0.99$) and is highly correlated with widely used measures of adult literacy and academic achievement [e.g., Wide Range Achievement Test ($r = 0.88$), Peabody Individual Achievement Test-Revised ($r = 0.97$), Slosson Oral Reading Test-Revised ($r = 0.96$)], attesting to its concurrent validity [98].

2.5.4. Manipulation check

Impressions of the intervention (EdMInt and EC) will be assessed at baseline and immediately following the final session by having patients rate the perceived usefulness, pertinence, enjoyableness, expected likelihood of intervention to change adherence behavior, and motivation to adhere to medication using 10 cm visual analogue scales (VAS's) with anchors "not at all" and "extremely".

2.6. Data analysis

2.6.1. Statistical analysis plan

An intent-to-treat analysis will be performed [99] according to CONSORT recommendations [50,57]. Intent-to-treat analyses provide an assessment of the practical impact of a treatment. *Primary Analysis*: EdMInt will improve adherence to statin medication relative to EC intervention as measured by MPR. Using the general linear model (GLM) function in SPSS, the analytic strategy is a mixed models Analysis of Covariance (ANCOVA) with time (baseline, 12-months) as the within subject factor, treatment condition (EdMInt, EC) as the between subject factor and sex, age, baseline depressed mood, number of medications, number of comorbidities, and length of time prescribed statin medication at study initiation as covariates. Given that randomization is expected to eliminate selection bias and equate groups on relevant baseline characteristics [100], rather than include all possible covariates, an a-priori decision was made to include only covariates with a strong empirically established association with the dependent variable. Based on previous literature, statin adherence is a relatively "well-behaved" variable with respect to the assumptions of a general linear model. Even so, prior to conducting any analyses, preliminary examination of the assumptions of the GLM will be conducted [101]. In particular, the homogeneity of regression assumption will be closely examined. Should the data indicate that this assumption is violated, we will model the corresponding interaction term(s). Heteroscedasticity of errors and nonlinearity will also be evaluated using standard approaches [101]. Should these assumptions be violated, appropriate transformations will be made [101]. Any missing data will be handled using multiple imputation [102] in accordance to Harrell's guidelines. *Secondary Analyses*: The effects of the intervention on within-subject change in LDL-C, self-report medication adherence, stage of change, treatment motivation and treatment self-efficacy from baseline to 12-months will be evaluated in a manner analogous to that described above.

2.6.2. Sample size calculation

We powered our trial and based our sample size calculation on the number of patients needed to assess our primary outcome of 12-month statin adherence determined using prescription refills. We selected the Dilorio et al. [47] MInt for antiretroviral therapy RCT to base our sample size calculation because it is similar to the proposed trial. The common elements between this trial and our own include: MInt sessions delivered in 3-month intervals, a 12-month duration, and the use of an education control condition. In this previous trial, MInt was found efficacious in reducing the rate of 12-month non-adherence relative to usual care (10% adjusted difference; a standardized mean difference Cohen's $d = 0.33$ which is a small-to-medium effect size) [47]. In the proposed trial, we anticipate a change in adherence as a result of our EC condition of 7% (the average improvement reported by RCTs using education as a means of improving adherence to statin medication), and we expect EdMInt to result in an adjusted improvement, after adjusting for all relevant a-priori covariates, in adherence to statin medication by a similar amount to that reported in the best RCT assessing MInt for adherence to antihypertensive medications [49], 14%. Calculations were performed using open access software designed to calculate sample size estimates for parallel group clinical trials that was published by Dr. David Schoenfeld. Setting power at 80%, $\alpha = 0.05$, and two-tailed hypothesis testing, 292 patients (146 per group) would be needed to detect a covariate adjusted increase of +7% ($d = 0.33$) in statin adherence in the intervention vs. control group (using a 2 group pre-post intervention comparison design). In order to preserve power and account for potential attrition of 15%, a total sample of 336 patients (168 per group) will be recruited.

2.7. Research ethics

The protocol for the full trial will be submitted to the Calgary Conjoint Health Research Ethics Board (CHREB). A pilot trial assessing feasibility of the intervention and recruitment strategy has been reviewed and approved by the Calgary CHREB.

3. Discussion

Data from this study will provide information about the efficacy of MInt in improving adherence to statin medication in patients prescribed their first statin medication. MInt has gained increasing attention in recent years and is showing promising results in helping people initiate and sustain health behavior change [43–46,103–105]. Further, a recent review reported that MInt had significant effects at improving adherence among primary care populations [104]. Several RCTs have evaluated the effects MI for improving adherence to a variety of medications, including antihypertensive medication [49], osteoporosis medication [106], antiretroviral medication [47], antidepressant medication [48], and inhaled corticosteroids [71]. The results have been equivocal and are difficult to interpret due to methodological differences and limitations (refer to [62]). Only one previous RCT has evaluated the use of MInt to improve adherence to statin medication and reported no effect of MInt relative to usual care [107]. This trial had a number of limitations, including concerns over treatment fidelity, recruitment of patients who may not have had problems with adherence, and poor patient attendance to MI sessions with a mean 1.15 sessions attended over 18-months (refer to [108] for elaboration).

In general, adherence rates for prescribed medications are poor with an average of about 50% [97,109]. Moreover, approximately half of interventions intended to improve medication adherence are not successful and this includes interventions reported in the most rigorous RCTs with the lowest risk of bias [110]. It has been acknowledged that many interventions to improve medication adherence lack sound theoretical foundations and the development of successful interventions may depend upon comparing and contrasting theoretical models and their components [111]. This study should shed light on the potential mechanisms through which MInt exerts its effects on behavior change. Specifically, we will test the mediating effects of important constructs such as self-efficacy and autonomous motivation on medication adherence.

The proposed research aims to provide a definitive answer regarding the efficacy of EdMInt to improve adherence to statin medication. Our intervention will also inform the discussion on patient centered approaches to improve medication adherence with the potential to highlight the importance of improving communication skills, and enhancing intrinsic motivation and patient responsibility for their own health. As outlined above, an efficacy trial of this nature is a necessary prerequisite to conducting a "translation II trial [63]," which is aimed at improving the utilization of proven therapies in clinical practice and

community settings. If proven efficacious when delivered under optimal circumstances then the intervention can be tested in an effectiveness trial with the ultimate goal of demonstrating successful integration into routine practice and delivery by a range of healthcare providers to improve standards of care

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