CANADIAN HEART RESEARCH CENTRE

259 Yorkland Road, Suite 200
North York, Ontario, Canada M2J 0B5

TITLE Guidelines Oriented Approach to Lipid lowering Quality Enhancement Research Initiative (GOAL QuERI) International

STEERING COMMITTEE

1. Anatoly Langer, MD (Chair) langera@chrc.net
2. Khalid Al Faraidy, MD (King Fahad Military Medical Complex, Saudi Arabia) kalfaraidy@yahoo.com
3. Mousa Akbar, MD (Sabah Hospital, Kuwait) mousaakbar@hotmail.com
4. Wael Almahmeed, MD (Cleveland Clinic, Abu Dhabi) wmahmeed@gmail.com
5. Marco Antonio Alcocer-Gamba, MD (Mexican Society of Cardiology, Mexico) marco.alcocerg@gmail.com
6. Otavio Berwanger, MD (Albert Einstein Hospital) otavioberwanger@gmail.com

ACADEMIC COORDINATING CENTRE

Canadian Heart Research Centre, Toronto, ON, Canada
Protocol CHRC2019-GOAL INT

INVESTIGATOR SPONSORED STUDY LEAD

Anatoly Langer, MD, M.Sc, FRCP(C,) FACC
☎ 416-999-6264; Fax 866-562-9769
E-mail: langera@chrc.net

SUPPORT Amgen Inc.

PROJECT LEADER

Caroline Spindler, CCRP
☎ 416-977-8010 x 224; Fax 416-977-3606
E-mail: spindlerc@chrc.net

STATISTICIAN

Mary Tan, MSc, CCRP
☎ 416-977-8010 x 233; Fax 416-977-8020
E-mail: tanm@chrc.net

PROTOCOL SIGNATURE PAGE

Study Titile: Guidelines Oriented Approach to Lipid lowering Quality Enhancement Research Initiative (GOAL QuERI) International

The signature below consitutes the apporval of this protocol version dated January 28, 2019 and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and accoriding to local, legal and regulatory requitments and applicable regulations.

A. Langer

Anatoly Langer, MD, MSc, FRCPC, FACC
Chair, Canadian Heart Research Centre

28/01/2019

Date (Day/Month/Year)

INVESTIGATOR'S AGREEMENT

I have read this protocol (version dated January 28, 2019) and agree that it contains all the necessary details for carrying out the study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol (version dated January 28, 2019) and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of this study.

Investigator's Signature Date (Day/Month/Year)

Name of Investigator (Printed)

Name of Institution (Printed)

Executive Summary: Guidelines Oriented Approach to Lipid lowering (GOAL) Quality Enhancement Research Initiative (QuERI) International.

Background	This Quality Enhancement Research Initiative (QuERI) is a knowledge translation medical practice activity based on decision making support through feedback to physicians on their management of dyslipidemia in order to achieve guidelines recommended LDL-C levels in high risk patients. Physician interaction has three distinct components: 1. Capture of data as reported by participating physician; 2. Highlight (by providing feedback) where management may be optimized based on guidelines or recommendations; 3. Identify challenges faced by physicians resulting in the care gap. Current European and US Guidelines recommend the use of maximal statin therapy in patients with established cardiovascular disease or those with familial hypercholesterolemia and addition of ezitimibe or PCSK9 inhibitor, or both when the LDL-C levels remain higher than recommended level. GOAL Canada is an ongoing medical practice activity of approximately the same size as GOAL International enrolling approximately 2000 Canadian patients with clinical vascular disease or familial hypercholesterolemia (FH) and LDL-C > 2.0 mmol/L (77 mg/dl) despite maximally tolerated statin therapy. As part of an interactive knowledge translation component, physicians are asked to indicate their next steps in lowering of LDL-C and are then asked whether they will be following the guidelines and if not why not.
Project Overview	The GOAL QuERI International will engage approximately 115 health care practitioners (HCP) who will enroll up to 2500 patients with management observations based on four visits by the patients in an outpatient setting. The timing of the visits will be baseline, 6±2 months, 12±2 months, and 18±2 months during which patient management by their physician

	will be captured using the electronic data capture form (DCF). The DCF will be created and managed by the CHRC.
Study Design	Observational in relation to best practices management and therapy as specified by country specific practice guidelines. Educational intervention is delivered as a reminder where practice is not consistent with country specific practice guidelines.
Objectives and End points	**Objectives:** 1. To assess the proportion of patients who achieve LDL-C target after 18 month final visit. 2. To describe and characterize high risk cardiovascular patients who do not achieve recommended LDL-C target despite optimal statin therapy (with or without ezetimibe). 3. To identify opportunities where further combination therapy,may be of help to physicians in managing their high risk patients in order to achieve guideline-recommended LDL-C levels. **End Points:** **Primary** Proportion of patients achieving country specific guideline-recommended LDL-C levels after 18 month final visit or last available observation during follow up visits. **Secondary** 1. Relative and absolute reduction of LDL-C with lipid lowering medications added during the observation period. 2. Proportion of patients not achieving recommended LDL-C level based on high risk inclusion sub-group (e.g. FH), co-morbid conditions (diabetes mellitus), baseline treatment or baseline lipid profile. 3. Proportion of patients not achieving recommended LDL-C level at each of the follow up visits according to physician responses as to why country specific recommendation for LDL-C lowering opportunities was not followed. 4. Proportion of patients achieving LDL-C and non-HDL level across participating countries.

Methods	**Patients:** Inclusion criteria: 1. Adults ≥ 18 years old 2. High risk for cardiovascular morbidity and mortality such as prior history of clinical cardiovascular disease and/or history of familial hypercholesterolemia 3. LDL-C within the past 6 months above recommended level despite maximal tolerated statin therapy ± ezetimibe for the past 3 months. Exclusion criteria: 1. Current treatment with PCSK9 inhibitor 2. Current participation in investigational study 3. Prior participation in the GOAL program
Expected Timelines	**Project Start Date:** Q2 2019
	Duration: 36 months
	Project End Date: Q2 2022
Sample Size **Statistical Analysis** **Concomitant Medications**	The sample size of 2,500 participants is based on the previous experience and success of recruitment in the DYSIS registry in Canada as well as more recent experience with lipid lowering quality enhancement research initiatives. This sample size will also allow meaningful comparison across participating countries assuming an average 10% difference in the proportion of patients achieving the recommended LDL-C level (90% power, 95% confidence level).
	Descriptive analysis of demographic variables, co-morbid conditions, physical exam, medical history and treatment profile will be performed for baseline and each observation as appropriate.
	Patients will be prescribed commercially available medications by their physicians according to a treatment strategy which their physician believes is in the best interest of the patient.
Methods and Procedures for Data Collection	Canadian Heart Research Centre will enable the use of the electronic data collection form by the participating physicians. Data collected will be managed according to the applicable laws and regulations of privacy and according to the applicable parts of GCP regulation. Patients will be prescribed commercially available medications by their physicians according to a treatment strategy which they believe is in the best interest of the

	patient. Therefore, no specific requirement is anticipated beyond the usual clinical practice. If a safety event occurs related to any marketed Amgen product that the subject may be taking as part of standard of care, this must be reported to the local authority in accordance with pharmacovigilance requirements in participating countries.

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1. Introduction

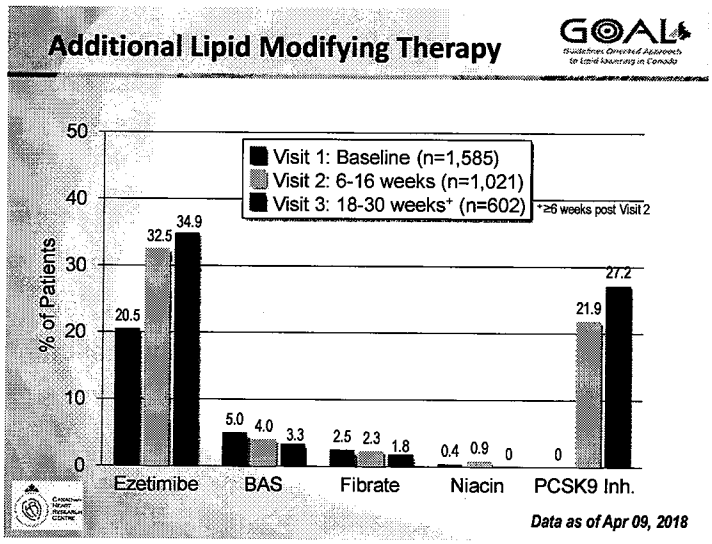
Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor for cardiovascular (CV) disease and there is considerable evidence that lowering LDL-C reduces the risk of both cardiovascular events and mortality in patients with, or at high risk for, vascular disease (1). Nonetheless, strategies for lowering LDL-C are poorly adopted in clinical practice, and many patients fail to reach guideline-recommended levels (2-10). Thus, patients in routine practice may not receive the same benefits in cardiovascular risk reduction observed in clinical trials.

Although statins remain the mainstay of dyslipidemia management, attainment of the recommended LDL-C targets can be difficult without the use of combination therapy (11).

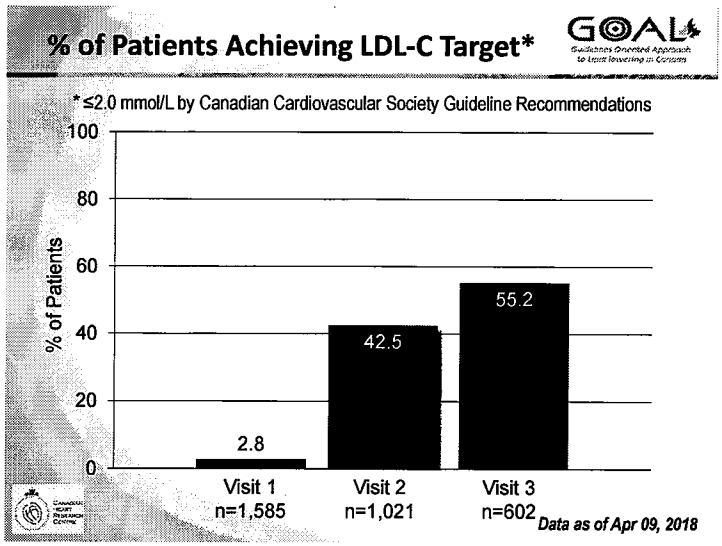
In the recently conducted Canadian Heart Research Centre DM-SCAN survey (12), only 57% of high CV risk patients with diabetes achieved the guideline-recommended LDL-C target ≤ 2.0 mmol/L (77 mg/dl). Similarly, in the Canadian cohort of the DYSlipidemia International Study (DYSIS Canada), only 63% of all high CV risk patients were at recommended LDL-C levels (13).

The clinical implications of this type of care gap are significant and have been reported previously (14), highlighting the importance of following the guidelines. Current US and European Guidelines recommend LDL-C levels of < 70 mg/dl (1.8 mmol/L) in patients with atherosclerotic cardiovascular disease (ACVD) or familial hypercholesterolemia (FH) (15,16) and addition of PCSK9 inhibitor based on documented improved cardiovascular outcome (17, 18).

In an ongoing Canadian GOAL program (21) additional lipid modifying therapies during follow up (shown below) were chosen by managing physicians



These additional therapies used as per Canadian Guidelines resulted in over 50% of patients achieving recommended LDL-C levels as shown below.



Thus, the use of evidence based therapies including PCSK9i was associated with significant reduction in the care gap and indicates that programs like GOAL can help overcome treatment inertia.

2. Program Objectives and End-points

2.1 Objectives

1. To assess the proportion of patients who achieve LDL-C target after 18 month final visit.
2. To describe and characterize high risk cardiovascular patients who do not achieve recommended LDL-C target despite optimal statin therapy (with or without ezetimibe).
3. To identify opportunities where further combination therapy, may be of help to physicians in managing their high risk patients in order to achieve guideline-recommended LDL-C levels.

2.2 End Points

2.2.1 Primary

Proportion of patients achieving country specific guideline-recommended LDL-C levels after 18 month final visit or last available observation during follow up visits.

2.2.2 Secondary

1. Relative and absolute reduction of LDL-C with lipid lowering medications added during the observation period.
2. Proportion of patients not achieving recommended LDL-C level based on high risk inclusion sub-group (e.g. FH), co-morbid conditions (diabetes mellitus), baseline treatment or baseline lipid profile level .

3. Proportion of patients not achieving recommended LDL-C level at each of the follow up visits according to physician responses as to why country specific recommendation for LDL-C lowering opportunities was not followed.

4. Proportion of patients achieving LDL-C and non-HDL level across participating countries.

3. Overview and Design

3.1 Overview

This program is a Quality Enhancement Research Initiative (QuERI) defined as a knowledge translation medical practice activity based on feedback to physicians on their management of dyslipidemia to support their decision making and choice of therapy in order to achieve the guideline-recommended LDL-C level in high risk patients (15,16).

This prospective study utilizing a clinical decision-making support platform will be based on four visits by patients in an outpatient setting (see Section 4: Program Procedures for timing of the visits). Patient management will be captured using the electronic case report form (e-CRF). The e-CRF is created and managed by the CHRC.

The e-CRF is interactive and has three distinct components:

1. Capture of data as reported by participating physician;
2. Highlight (by providing feedback) where management may be optimized based on guidelines or recommendations;
3. Identify challenges faced by physicians resulting in the care gap.

3.2 Program Participants

The program population will consist of up to 2,500 study patients at approximately 115 health care provider (HCP) offices across five regions:

- 600 pts Saudi Arabia (KSA) / 30 HCPs
- 500 pts Kuwait (KWT) / 25 HCPs
- 400 pts United Arab Emirates (UAE) / 20 HCPs
- 500 pts Mexico (MEX) /20 HCPs
- 500 pts Brazil (BRA) / 20 HCPs

HCP participation will be by invitation only and will be approved by the coordinating centre. All participating HCPs will be required to sign a memorandum of understanding outlining their role and compensation prior to their start of the program procedures.

3.3 Inclusion Criteria

1. Adults ≥ 18 years old
2. High risk for cardiovascular morbidity and mortality (at least one of the following):
    1. Atherosclerotic Cardiovascular disease
        - Coronary Artery Disease (CAD): history of ACS/MI, CABG, PCI, coronary stenosis >50% and stable angina
        - Cerebrovascular Disease (CeVD): history of CVA/TIA, carotid surgery
        - Abdominal Aortic Aneurysm (AAA): history of surgery/intervention
        - Peripheral Arterial Disease (PAD): history of surgery/intervention
3. Familial hypercholesterolemia defined as LDL-C > 5 mmol/L (200 mg/dl or ≥190 mg/dl as per Grundy SM, et al 2018 Cholesterol Clinical Practice Guidelines) prior to lipid lowering therapy and one of:
    - typical physical findings (stigmata) such as tendon xanthomata, xanthelasma, and arcus corneae
    - personal history of early cardiovascular disease
    - family history of early cardiovascular disease or of marked hyperlipidemia
4. Receiving optimal (maximal or maximal tolerated) statin therapy for at least 3 months prior to patient enrolment
5. LDL-C within the past 6 months above recommended level according to the most up-to-date Guidelines despite maximally tolerated statin therapy +/- ezetimibe (or other lipid lowering therapy)
6. Desire and ability to participate in the program.

3.4 Exclusion Criteria

1. Current treatment with PCSK9 inhibitor
2. Current participation in an investigational study
3. Prior participation in the GOAL program

3.5 Program Timelines

The program is expected to start in Q2 of 2019.

The program is expected to close in Q2 2022 with the overall duration of 36 months (6 months start up, 12 months of enrolment and 18 months of follow up).

4. Program Procedures

4.1 The program data points to be collected are summarized in the Table below.

Program Data Points				
Evaluation	**Visit 1 Time: 0 Baseline**	**Visit 2* Time: 6±2 months**	**Visit 3* Time: 12±2 months**	**Visit 4* Time: 18±2 months Final**
1. Eligibility verification	X			
2. Informed consent if needed	X			
3. Demographics (age, gender)	X			
4. Co-morbidities (CAD, CeVD, AAA, PAD, FH,)	X			
5. Medical history (cancer, CKD, liver)	X			
6. Risk Factors (HT, DM, smoking)	X			
7. Prior Lipid lowering therapy (drug and duration)	X	X	x	x
8. Other cardiometabolic	X			
9. Vitals (BP, Wt, Ht, waist)	X	x	x	x
10. Cholesterol panel (obtained prior to each visit)	X	x	x	x
11. Calculation of the LDL-C	X	x	x	x
12. Dyslipidemia Medication Prescription	X	x	x	x
13. Physician feedback and interaction	X	x	x	x
14. Prescription dispensation	X	x	x	x
15. Ascertainment of coverage/insurance	X	X	X	X

* Visits 2 through 4 are anticipated as part of routine clinical care including cholesterol panel when appropriate based on changes in lipid lowering medications or other clinical indicators during the prior visit.

4.2 Physician feedback and interaction

The two levels of feedback will be worded in a specific format consistent with country specific guidelines for management and availability of lipid lowering therapies. The intent of the feedback will be similar across participating countries as follows:

Feedback 1: Will be provided if lipid lowering treatment chosen is not consistent with current recommendations such as examples provided below based on US or EU guidelines:

1) if patient is on optimal statin therapy (atorvastatin 40 mg or 80 mg or rosuvastatin 20 mg or 40 mg), consideration of addition of lipid lowering therapy according to the country specific guideline recommendations will be studied; or

2) if patient is on optimal statin therapy and Ezetimibe, participating physician will be asked to consider whether other therapies should be used to reach recommended LDL-C level based on the country specific guideline recommendations.

Expected possible responses:

a. "Change my management" in which case treatment options will be shown again, or

b. "I would like to continue with my management". In this case Feedback 2 will be shown.

Feedback 2: Will aim to ascertain reasons why physician is not following country specific recommendations?

Expected possible options:

1. Patient Refusal
2. Patient intolerance (this answer implies that tretament was prescribed)
3. Social constraints (e.g. patient is not able to administer the treatment)
4. Medical constraints (co-morbidities)
5. I believe my management is appropriate/ I disagree with the recommendations
6. Cost

If treatment chosen is consistent with recommendations no Feedback will be shown. If treatment chosen is not consistent with recommendations then Feedback 1 will be shown and any change in treatment will be re-captured. If treatment chosen is still not consistent with recommendations then Feedback 2 will be shown.

5. Ethics

This program is to be conducted according to globally accepted standards of Good Clinical Practice (GCP) (International Conference on Harmonization (ICH) guidelines, May 1996), US 21 CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards, the Declaration of Helsinki, and all local regulations.

5.1 Ethics Approval

This protocol and any amendments will be approved by a properly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) in agreement with applicable regulatory requirements, for formal approval of the program conduct. The decision of the IEC/IRB concerning the conduct of the program will be made in writing to the Investigator and a copy of this decision will be provided to the CHRC before commencement of this program.

5.2 Monitoring

The patient enrolment and program procedures will be monitored on-line to ensure e-CRF completion.

5.3 Informed Consent Form (ICF)

Where required, patients will be provided with sufficient information in the form of an Informed Consent. This document will be submitted for approval to the IEC/IRB along with the protocol. A statement of approval must be provided to the CHRC before commencement of the program.

The formal consent of all patients must be obtained according to local regulations before any program-specific procedures are initiated.

The ICF will be approved by the same IEC/IRB that approves this protocol. Each ICF will comply with participating country specific regulations and local regulatory requirements. Patients will receive a copy of their signed informed consent form; the original shall be kept on file by the participating physician.

5.4 Protocol Modifications

Any modification to the protocol that may affect the conduct of the program or patients' safety, including changes of program objectives, program design, patient population, program procedures, or significant administrative aspects, will require a formal amendment to the protocol.

Administrative changes to the protocol are minor corrections or clarifications that have no effect on the way the program is to be conducted. The CHRC and the Lead Investigator will agree upon these administrative changes. The IEC/IRB may be notified of administrative changes at the discretion of the Lead Investigator.

6. Safety

6.1 Documentation and Reporting of Adverse Events (AE)

Patients will be prescribed commercially available medications by their physicians according to a treatment strategy which they believe is in the best interest of the patient. Therefore, no specific requirement is anticipated beyond the usual clinical practice.

If a safety event occurs related to any marketed Amgen product that the subject may be taking as part of standard of care, this must be reported to the local authority in accordance with pharmacovigilance requirements in participating countries.

In addition, the following submissions will be made to Amgen:

Safety Data	**Timeframe for submission to Amgen**
Adverse Events considered Related to Amgen drug	**Per contractual agreement,** sent to Regulatory Agency only at the time of Sponsor awareness.

Please also note the following requirements for aggregate reports (if applicable):

Safety Data	**Timeframe for submission to Amgen**
Annual Safety Report (if applicable, and as per local regulations)	**Annually**
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	**At time of ISS sponsor submission** to any body governing research conduct (eg, regulatory agencies, ethics committees, etc)
Final (End of Study Report, including): • Reports of unauthorized use of a marketed product	**At time of ISS sponsor submission** to any body governing research conduct (eg, regulatory agencies, ethics committees, etc) but not later than 1 calendar year of study completion

7. Statistical Analysis

7.1 Program Population

Analysis will be based on treated population, defined as all enrolled patients whose laboratory and treatment data is recorded for Visit 1.

7.2 Data Analysis

7.2.1 Validation procedures

The data entered will be validated according to a pre-specified validation plan as part of quality assurance/ quality control.

7.2.2 Interim analysis

An interim analysis will be carried out after 25% of patients have been enrolled or after six (6) months after first patient in, whichever is earlier. If the patient enrolment at the time of the interim analysis is less than 100 patients/month then modifications to the protocol may be undertaken.

7.2.3 Statistical analysis

No formal hypothesis will be tested. Data analysis is expected within six months of database lock.

Descriptive analysis of demographic variables, co-morbid conditions, medical history and treatment profile will be used to describe the population of patients enrolled. For continuous variables, descriptive summary statistics will be presented with mean (and standard deviation) or median (and interquartile values) where appropriate. For the description of categorical variables, absolute and relative frequencies will be used.

Proportion of patients achieving the LDL-C target (15) after the last follow-up will be summarized. The proportion of patients who received PCSK9 and of those, the proportion who achieved target will also be summarized. Additional measures of the study will be used to determine the proportion of patients who achieve and do not achieve the LDL-C target in each of the followings: (1) receive statin by dose (moderate vs. low dose); (2) receive combination therapy (statin + another one or two lipid lowering agents); (3) have prior cardiovascular disease; (4) have FH.

In each of these measures, the outcome variable, LDL-C, will be presented with mean and standard deviation. The proportion of patients achieving target LDL-C and receiving PCSK9 will be summarized by the above measures and sex, age (<65 and

>=65), presence of co-morbidities, insurance type, and other lipid lowering treatment received.

The association between continuous LDL-C as the outcome at the end of follow-up (after last visit) and the above mentioned measures will be assessed using multivariable linear regression model. This model will also be adjusted by other demographic covariates such as gender, age, BMI that may deem to be clinically important. Colinearity between covariates in the model will be assessed. We will perform a backward elimination of independent covariates using an inclusion criteria of α=0.05 to obtain the best fit model. Regression coefficient associated with covariates that are significant in the multivariable model will be provided.

Logistic regression will assess the proportion of patients who achieve LDL-C target after visit 4 using the above measures, PCSK9 use, as well as sex, age, BMI. Odds ratios from covariates that are significant at α=0.05 will be retained and presented.

Incomplete data entry is prevented by the design of the eCRF. Missing data may occur in patients lost to follow up or those missing protocol mandated visit. In cases of missing data when visits other than baseline have been completed analysis will be based on the last observation carried forward approach.

7.3 Sample size and power calculations

The sample size of 2,500 participants is based on the previous experience (and success of recruitment) in the DYSIS registry in Canada (13) as well as more recent experience with lipid lowering quality enhancement research initiatives (19, 20, 21). This sample size will also allow meaningful comparison across participating countries assuming an average 10% difference in the proportion of patients achieving the recommended LDL-C level (90% power, 95% confidence level).

7.4 Limitations

The design of our data set acquisition cannot exclude the bias of physician selection, patient selection, or in particular the Hawthorne effect. Furthermore, lack of comparator arm limits the strength of the conclusions with respect to the effect of the educational intervention.

8. Records, Reports and Policy

8.1 Records Retention

The participating physician must retain sufficient source documents/records about the identity of the patients so that health authorities and/or the CHRC may access this information if needed.

The investigator will retain copies of all pertinent information for 5 years or longer as required by local regulations after the CHRC notifies the investigator that the program is completed.

8.2 Use of Information and Publication

Information derived from this program shall not be disclosed to others without prior consent from the CHRC.

8.3 Reports and Record Management

8.3.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs and recorded data from automated instruments. All source documents pertaining to this program will be maintained by the participating physician and made available for direct inspection by the CHRC if requested.

8.3.2 File Management at the Program Site

The participating physician will ensure that the program binder is maintained as required by applicable local regulations and measures are in place to prevent accidental or premature destruction of these documents.

8.4 Quality Control and Quality Assurance

8.4.1 Monitoring

Monitors from the CHRC may visit the physician office during the program to ensure ICH/GCP Guidelines have been followed to protect patient confidentiality or may ask written questions that require clarification of the data entered.

8.4.2 Auditing

The CHRC may conduct program site audits in person or online. Audits will include, but are not limited to, presence of required documents and comparison of eCRF with source documents. The physician agrees to participate with audits.

8.5 Confidentiality

All information generated in this program will be considered highly confidential and will not be disclosed to anyone not directly concerned with the program without the CHRC's prior written permission. However, authorized regulatory officials and CHRC personnel (or their representatives) will be allowed full access to inspect and copy the program records.

Patients will be identified only by a unique program number in the e-CRF. Their full names may, however, be made known to a regulatory agency or other authorized officials if necessary, and consistent with pertinent IRB policies.

9. References

1. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.

2. Pearson TA, Laurora I, Chu H, Kafonek S. The Lipid Treatment Assessment Project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low density lipoprotein cholesterol goals. Arch Intern Med 2000;160:459-67.

3. Waters DD, Brotons C, Chiang CW, et al. Lipid Treatment Assessment Project 2:Amultinational survey to evaluate the proportion of patients achieving low-density lipoprotein cholesterol goals. Circulation 2009;120:28-34.

4. Saposnik G, Goodman SG, Leiter LA, et al. Applying the evidence: Do patients with stroke, coronary artery disease, or both achieve similar treatment goals? Stroke 2009;40:1417-24.

5. Hackam DG, Leiter LA, Yan AT, et al. Missed opportunities for secondary prevention of cardiovascular disease in Canada. Can J Cardiol 2007; 23:1124-30.

6. Yan AT, Yan RT, Tan M, et al. Contemporary management of dyslipidemia in high-risk patients: targets still not met. Am J Med 2006;119:676-83.

7. Banegas JR, Vegazo O, Serrano P, et al. The gap between dyslipidemia control perceived by physicians and objective control patterns in Spain. Atherosclerosis 2006;188:420-4.

8. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high risk elderly patients: the treatment-risk paradox. JAMA 2004;291:1864-970.

9. Petrella RJ, Merikle E, Jones J. Prevalence and treatment of dyslipidemia in Canadian primary care: a retrospective cohort analysis. Clin Ther 2007;29: 742-50.

10. Rapezzi C, Biagini E, Bellis P, et al. Exploring the gap between National Cholesterol Education Program guidelines and clinical practice in secondary care: results of a cross-sectional study involving over 10 000 patients followed in different specialty settings across Italy. J Cardiovasc Med 2008; 9:878-87.

11. Martineau P, Gaw A, de Teresa E, et al. Effect of individualizing starting doses of a statin according to baseline LDL-cholesterol levels on achieving cholesterol targets: the Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST) study. Atherosclerosis 2007;191:135-46.

12. Leiter LA, Berard L, Bowering K, et al. Type 2 Diabetes Mellitus Management in Canada: Is It Improving? Can J Diabetes 37 (2013) 82e89

13. Goodman SG, Langer A, Bastien NR, et al. Prevalence of dyslipidemia in statin treated patients in Canada: results of the Dyslipidemia International Study (DYSIS). Can J Cardiol 2010;26:e330e5.

14. Grima DT, Leiter LA, Goodman SG, et al. How Many Cardiovascular Events Can Be Prevented With Optimal Management of High-Risk Canadians? Can J Cardiol 2008;24(5):363-68.

15. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA. Guideline on the Management of Blood Cholesterol. Circulation. 2018;000:e000–e000. DOI: 10.1161/CIR.0000000000000625).

16. Catapano AL, Graham I, De Backer G, et al 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. European Heart Journal (2016) 37, 2999–3058.

17. Sabatine MS, Giugliano RP, Wiviott SD, et al for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events. March 15, 2015, at NEJM.org. DOI: 10.1056/NEJMoa1500858

18. Schwartz GG, Steg PG, Szarek M, et al for the ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. DOI: 10.1056/NEJMoa1801174

19. Teoh H, Mendelsohn AA, Goodman SG, Jaffer S, Chen RYY, Tjia S, Theriault L, Langer A, Leiter LA, on Behalf of the Guidelines Based Undertaking for Improvement in Dyslipidemia Related Events (GUIDE) Investigators. Usefulness of Statin–Ezetimibe Combination to Reduce the Care Gap in Dyslipidemia Management in Patients With a High Risk of Atherosclerotic Disease. Am J Cardiol 2009;104:798–804

20. Katz PM, Mendelsohn AA, Goodman SG, Langer A, Teoh H, Leiter LA, Use of a Treatment Optimization Algorithm Involving Statin-Ezetimibe Combination Aids in Achievement of Guideline-Based Low-Density Lipoprotein Targets in Patients With Dyslipidemia at High Vascular Risk Guideline-Based Undertaking to Improve Dyslipidemia Management in Canada (GUIDANC). Can J Cardiol 2011;27:138–145.

21. Langer A, Wills C, Tan M, Spindler C, Goodman SG, Spindler C, Lin P, Mancini G, Dufour P, Gregoire J, Leiter LA. Guidelines Oriented Approach To Lipid Lowering (GOAL) Medical Practice Activity (MPA) To Achieve Low Density Lipoprotein Cholesterol (LDL-C) Targets. Can J Cardiol 2018;34(10);Supplement 1, S88–S89.