Title

An Educational Intervention to Improve Physician Effectiveness in the Detection, Treatment and Control for patients with Hypercholesterolemia and high Cardiovascular Disease (CVD) risk in low-resource settings in Argentina

IAS – **Pfizer Grant 11526941** - Full Proposal – Submission

Abstract

In Argentina, the National Risk Factor Surveys conducted by the Ministry of Health (MoH) indicate that between 2005 and 2009 the prevalence of hypercholesterolemia increased from 27.9% to 29.1%, whereas the rate of non-optimal LDL-C,is 28.0%. The rate of high cholesterol awareness is 37.3 and the percentage of those who are under pharmacological treatment is dismally low: only 11.1%. Furthermore, only one of every four subjects with a self-reported diagnosis of CHD is taking statins and most individuals with coronary heart disease (CHD) who are on statins have sub-optimal LDL-C levels. Until now, the MoH has provided drugs free-of-charge for the treatment of different cardiovascular risk factors. Nevertheless, statins havenot been included to date in the list of covered drugs. As of 2014, statins (simvastatin) will be incorporated into the package of drugs provided free-of-charge for patients with high cholesterol, according to CVD risk stratification. The goal ofthisstudy is to test whether a multifaceted educational intervention targeting physicians and nurses improvesdetection, treatment and control of hypercholesterolemia among uninsured patients with moderate-high cardiovascular risk in Argentina. This randomized cluster trial will enroll 350 patients from 10 public primary care clinics who will be assigned to receive either the intervention or the usualstandard of care. The interventionprogram will target the public primary care system through clinician education for implementation of a Clinical Practice Guideline to improve management of dyslipidemias. This study, strongly supported by the Argentine Lipid Society and the MoH, is timely and necessary to address CHD risk in vulnerable populations in Argentina.

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1. Overall Goal & Objectives

1.1. Hypercholesterolemia is a major global public health challenge

Hypercholesterolemia, a major cause of disease burden in both the developed and developing world, is estimated to cause 2.6 million deaths annually (4.5% of all deaths) andone third of ischemic heart diseases, and result in29.7 million DALYs.[1]Globally, mean total cholesterol levels changed little between 1980 and 2008, falling by less than 0.1 mmol/L per decade for both men and women. In 2008, the global prevalence of elevatedtotal cholesterol among adults was 39% (37% for males and 40% for females).[2]Although a higher serum lipid seems to be an inevitable consequence of economic development, urbanization, westernization, and nutritional transition, these determinants can be offset through healthier diets and pharmacological interventions. Consequently, statins and other lipid-lowering drugs are increasingly used in high-income countries[3,4], but there is still low coverage of screening and treatment in low and middle-income countries.[5,6]Data from CARMELA, a population-based cross-sectional study conducted in 7 cities in Latin America, found a prevalence of hypercholesterolemiabetween 5.7% in Barquisimeto to 18.7% in Buenos Aires and 20.2 % in Quito. [7]

1.2. Blood cholesterol is continuously associated with risk of CVD and lifestyle modifications and statins are the preferred treatment for high cholesterol and sub-optimal LDL cholesterol levels (LDL-C)

Observational studies show that there is a continuous positive relationship between Coronary heart disease (CHD)and blood cholesterol concentrations.[8] The Cholesterol Treatment Trialists' (CTT) Collaboration reported a meta-analysis[9] of individual datafrom 90,000 individuals in 14 randomized trialsof statintherapy versus control. Statin regimensresulted in a mean difference of about 1.0 mmol/L in LDL-C and a proportionalreduction of 20% in major vascular events (definedas coronary death, non-fatal myocardial infarction,coronary revascularization, or stroke). A recent meta-analysis showed that trials comparing less intensive vs. more intensive statin regimens produced further reductions in major vascular events. [10-13]

1.3. The prevalence of hypercholesterolemia in Argentina is high and awareness, treatment, and control are low

In Argentina, the National Risk Factor Surveys conducted by the Ministry of Health indicate that between 2005 and 2009 the self-reported prevalence of hypercholesterolemia rose from 27.9% to 29.1%. Of these, only 54.8% received some treatment and of whom only 56.3% were prescribed lipid-lowering drugs (the rate of those receiving treatment was less than 20% among uninsured subjects, including subjects with more than 3 risk factors).[14]Recent baseline results are available with blood samples from the CESCAS I study, which is a population-based prospective cohort study for detection and follow-up of Cardio Vascular Disease (CVD) and risk factors in 8,000 adults from four cities in Argentina, Chile and Uruguay. This study, which is conducted by our group[15],foundthat the prevalence of hypercholesterolemia in Argentina is **23.1% in men and 25.6% in women**, and according to the Framingham coronary disease risk measure,the prevalence of non-optimal LDL-C is 28.0%. On the other hand, the percentage of subjects with hypercholesterolemia who are aware of their condition is 37.3%[95%CI:32.8-41.9] and the percentage of those who are under pharmacological treatment is dismally low: only 11.1%. Furthermore, only one in every four subjects with a self-reported diagnosis of CHD is taking statins and most of those with CHD who are on statins have sub-optimal LDL-C levels*(Rubinstein et al. personal communication. Data not yet published*).This is especially relevant because hypercholesterolemia accounts for 25% of the burden of CHD in Argentina, as we have shown recently in another study.[16]

1.4. Use of Evidence-based Clinical Practice Guidelines (CPG) improve effectiveness and quality of treatment forpatients with dyslipidemia

Because CHD is common and lipid-loweringdrugs, particularly statins, areamong the most frequently prescribed drugs, lipid treatment guidelines have importantimplications both for population health and for healthcareresources.[17]The International Atherosclerotic Society (IAS) has recently issued a CPG for the management of sub-optimal LDL-C, recommending statins as first-line therapy, choosing the type of statin based on availability and costs, and adjusting the dose according to patient's CVD risk. [18] More recently, the 2013 ACC/AHA panels have recently updated their blood cholesterol guidelines, recommending the prescription of high-intensity statin therapy (lowering LDL–C ≥50%) or moderate-intensity therapy (lowering LDL–C by approximately 30% to <50%), based on the presence of CVDLDL-C levels,type 2 diabetes, age, and the estimated 10-year risk of CVD. Because of a lack of evidence from randomized control trials regarding the efficacy of titrating statins to reduce CVD, the guidelines no longer recommend this treatment to meet specific LDL-C or non-HDL-C goals. [13]However, the publication of a CPG does not ensure its application in clinical practice, and therefore effective implementation plans that are tailored for the organizational context for which the CPG is intended, must be designed.

1.5. Interventions to address barriers toCPG implementation improve clinical outcomes

Despite the availability of evidence-based practice guidelines, multiple barriers hinder the appropriate management of hypercholesterolemia in the primary care setting. These can be organizational barriers withinprimary care clinics; confusing and conflicting guidelines from external sources; errors and omissions by primary care doctors; communication problems at the interface between secondary and primary care[19],multiple competing demands on physicians' time, and lack of reimbursement for preventive counseling.[20]Other barriers are related to:(1) the health care system such as lack of access, medication cost, and poor insurance coverage; (2) health care providers, such as lack of adherence to guidelines, willingness to accept elevated high cholesterol, and failure to prioritize this issueamong multiple chronic medical issues; and (3) patients, such as reluctance to take medication.[19]Among the interventions that have been effective in dealing with barriers related to clinical practice are multifaceted educational outreach visits (EOVs)[21],and audit and feed-back.[22]EOVs havethe potential to change health professionalpractice, particularly the prescribing patterns of physicians. The termEOVor "academic detailing"is used to describea personal visit by a trained person to health professionals in theirown settings. Some key principles of this approachinclude surveys ofpractitioners to determine barriers forappropriate practice and thesubsequent development of an intervention tailored toaddress those barriers using simple messages; targeting of practitionerswith low compliance; and the delivery of the interventionby a respected person. The intervention often includes feedbackon existing practices.[23]EOVs with or without the addition of other interventions has been effective in improving practice in the majority of circumstances; for studies with dichotomous healthprofessional outcomes, such as proportion of patients treated in accordance with the guideline, the improvement was 5.6% and for studies with continuous outcomes, such as mean number of prescriptions, it was at least 20%. [21]A recent Cochrane review indicates that patient re-enforcement and remindersseem to be the most promising interventionsto increase adherence to lipid-lowering drugs. Other interventions associated with increased adherence were simplification of the drug regimen and patient information and education. [24]

1.6. Overall goal and specific aims of the study

The overarchinggoal of the proposed study is to test whether a multifaceted educational intervention targeting physicians and nurses improvesdetection, treatment and control of hypercholesterolemia among uninsured patients with moderate-high cardiovascular risk in Argentina. The intervention will target the public primary care system through healthcare

provider education aboutimplementation of a CPG to improve management of dyslipidemias in these patients.

Thespecific aims are as follows:

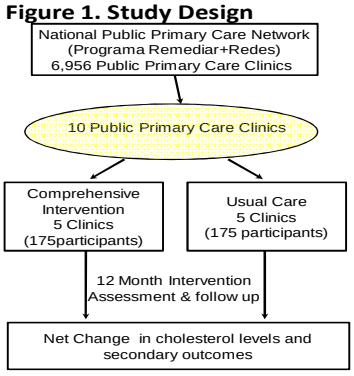
1. To test whether a multifaceted educational intervention programlowers cholesterol levels and CVD risk in moderate-high cardiovascular risk patients.
2. To test whether this intervention program improves physician compliance with clinical practice guidelines
3. To test whether this intervention program improves patient care management and adherence.
4. To estimate the cost-effectiveness of this comprehensive intervention program compared to the usual standard of care.

2. Technical approach

2.1. Current Assessment of need in target area

As described in a previous section of this proposal, prevalence of CVD and risk factors in Argentina arehigh, and awareness, treatment, and control, particularly for hypercholesterolemia are dismally low. The Program Remediar+Redes (R+R) is a program from the National Ministry of Health that provides free ambulatory drugs to vulnerable people without health insurance who attend public primary care centers (PCCs) in Argentina.[25]The program covers almost 7,000 PCCs (>90% of all public clinics) in the country.R+R uses the WHO package for the assessment and management of cardiovascular risk in low-resource settings.[26]Interventions delivered by the program include: 1) identification and enrollment of the uninsured population inthe catchment area served by PCCs; 2) screening to identify persons at risk of CVD in order to refer them to aPCC; 3) CVD risk stratification and classification of subjects by primary care physicians, including lab and other ancillary tests; 4) treatment with generic drugs as needed for hypertension, diabetesor for subjects with moderate-high CVD risk (10 year risk ,≥10%); and 5) regular follow-up forpatients with moderate and high CVD risk. To date, R+R hasprovideddrugs for the treatment of different cardiovascular risk factors such as antihypertensives, antidiabetics, and low-dose aspirin. Nevertheless, statins havenot been included in the list of drugs delivered by the Program. *As of 2014, statins (simvastatin) will be incorporated in the package of drugs delivered free-of-charge for patients with high cholesterol, according to CVD risk stratification.* Although inclusion of statins is a critical step to reduce CVD in vulnerable, uninsured subjects with high cholesterol and moderate-to-high risk, a recent study that analyzed prescriptions to hypertensive patients seen in public clinics in Argentina reported that only 57% of hypertensive patients covered by the R + R program were treated. Of those who were treated, almost 75% of patients received medication for less than 4 months/year and only 12% received it for ≥9 months/year.[27] Thus,a comprehensive intervention aimed to changing practice styles in professionals and improving adherence to drugs in patients, is key to achieve the expected goal of reducing CVD through lowering cholesterol levels. This study is timely because not onlywill statins be introduced in 2014 into the national list of ambulatory drugs to be provided free-of-charge at public primary care clinics in Argentina, but also because there is no CPG in place in public PCCs aimed at specifically addressing the management of dyslipidemia and statins by health providers.

Figure 1. Study Design



2.2. Study Design and Methods:

2.2.1. Rationale for using a cluster randomized controlled trial design

Cluster trials are an important method forevaluating educational outreach and related interventions. Randomisation by group (PCC) is preferable because it avoids thepotential contamination that could occurif randomization were to be done at individual level (e.g. the cholesterol treatmentsfor patients in one clinic aremore similar to each other than topatients from another clinic) and the effect of the intervention can be assessed in the natural practiceenvironment. [28]

2.2.2. Overview of study design

The proposed studyis designed as a proof-of-concept intervention to test whether a multifaceted educational program targeted at theprimary care team *improves processes and outcomes of carein uninsured patients with hypercholesterolemia and moderate-high cardiovascular risk*.We propose to conduct a cluster randomized controlled trial (cRCT),recruiting 350 patients with high cholesterol and moderate to high CVD risk among 10 public PCCs in Argentina; 5 clinics will be assigned to receive the intervention program and 5 clinics will receive usual standard of care (usual care)(figure 1).All clinics will providestatinsas prescribed. The educational programwill be focusedonthe implementation of a CPG to improve management ofdyslipidemiasin high CVD risk patients.This program will be supported by innovative tools including: 1) mobile phone (mHealth) applications to provide decision aids to physicians and nurses;2) electronic medical records (EMRs) accessed via Internet by administrative personnel and health professionals; and 3) a web-based platform to send tailored SMS messages to patients. The study will recruit 35 study participants from each clinic. Eligible patients will be enrolled and will have 12 monthsof follow-up. CVD risk factors as well as physical and blood measures, including a lipid profile, will be measured at baseline and at 6 and 12 months of follow-up using standardized methods.

2.2.3. Eligibility criteria for the PCCs:

There are 6,956 PCCs affiliated with the R + R program. We will work with the coordinatingunit of the program to select 10 PCCs for the proposed study.The main criteria for their selection will be the motivation and performance of the PCC, operative capabilities,and the number of patients enrolled to date with high CVD risk.Other selection criteria will include prior participation in research studies or activities and their geographical location, in order to ensure a balanced representation of the major sub-regions of the country. The research team will invite the selected PCCs to participate in the trial after an audit visit to determine final eligibility.

Inclusion criteria for PCCs:

- The clinic is affiliated with the R+ R program.
- The clinic is located in a poor urban area according to 2010 census data.
- The clinic has ≥800 outpatient adult visits each month, to ensure that a sufficient number of participants can be recruited.
- Physician visits and statins are available free of charge to patients at the point of care
- The minimum distance between PCCs is 10 kilometers (different catchment area) and they do not share health professionals (to minimize the risk of contamination of the intervention).
- Good performance of the PCC (and their pharmacy) within the R +R program.

2.2.4. Recruitment and randomization of the PCCs

Recruitment: Each PCC will recruit 35 eligiblepatients for the proposed study over a 12 month period.Given that each PCC has ≥800 outpatient visits each month, and over 20% of patients havehypercholesterolemia, there should be a large pool of potential participants for the proposed study at each eligible PCC.

Randomization: The 10 selected PCCs fulfilling the inclusion criteria will be randomized to either the intervention or the control group: 5 PCCs to the intervention and 5 to the control group.Randomization will be conducted at the data management unit at the Institute for Clinical Effectiveness and Health Policy (IECS).

2.2.5. Eligibility criteria for study participants

Patients aged ≥40years who received primary care from the participating PCCs will be eligible if they have one of the following criteria:

- Arteriosclerotic cardiovascular disease (ASCVD): defined as acute coronary syndrome; history of myocardial infarction, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack presumed to be of atherosclerotic origin, and peripheral arterial disease or revascularization.
- Moderate-High CVD risk according to the WHO chartsadapted by the National MoH (estimated 10-year CVD risk ≥ 20%)[29]
- LDL-C level ≥ 190 mg/dL
- Type 2 diabetes in patients between 40 and 75 years of age

Patients that are already receiving statins, pregnant women, bed-bound, and patients who cannot give informed consent will be excluded.The research nurses will review their clinic's appointment schedules daily and identify eligible patients who will be invited to participate in the study and make an appointment for the screening/baseline visits.

2.2.6. Referrals

We will work closely with staff (physicians, nurses, and pharmacists) at each participating clinic in order to optimize the referral of potential eligible patients to our study nurse. The study brochures will be displayed in waiting areas, physicians' offices, and pharmacies within each clinic. The studyteam has substantial experience with recruitment for both clinical and population-based research and access to a large pool of potential participating PCCs and eligible patients.

2.3. Intervention program

Irrespective of the assignment of the clinic to the intervention or control group, all physicians from participating PCCshave received previous training on cardiovascular risk management. In addition, all clinics will receive resources for patient education, such as informational brochures for patients and educationalposters to be displayedat the PCCs, including charts with the CPG on management of dyslipidemia.

2.3.1. Educational program forphysicians

The intervention will include the 3 components, as follows:

1) Workshops: at the start-up of the program, an intensive 2-day workshop will be provided for all adult primary care doctors from the 5 intervention clinics that will be given by respected opinion leaders. Workshop session topicswill include global cardiovascular risk assessment and management; epidemiology, diagnosis, treatment and monitoring of patients with dyslipidemia;the chronic caremodel; and management of adherence issues in patients with chronic diseases. One of the sessions will be devoted to the learning and practice of the use ofthe studyCPG for the management of dyslipidemias.

2) Educational Outreach Visits (EOVs): Specialists from the Argentine Lipid Society (ALS) will conduct baseline on-site EOVsafter the workshop that will be tailored to the needs of individual practitioners at the clinics as well as to the barriers for change that prevent appropriate prescribing (e.g., side effects of statins). The EOVs will include GPC practice exercises; prescribing audit andfeedback using selected charts from high CVD risk patients;use of web-based EMR reminders that prompt users to perform clinical actions; and suggested changes forimprovingpracticeadministration/procedures such as support for systematiccase

identification, particularly for complex patients with low adherence. Reinforcement through subsequent visits to the clinic will be provided 3, 6 and 9 months from enrollment of the clinic.
3) E-learning modules: the first EOV will be followed by two online practice modules that will be provided 2-weeks apart through an online platform for virtual learning. The online modules will include supplementary information to reinforce the topics covered during the workshop, exercises, and patient cases to be discussed in an online forum.

2.3.2. Educational program fornurses

At each EOV, registered nurses inintervention clinics will be trained and reinforced in case-management strategies to identify patients with cardiovascular disease, low adherence, or those with special needs (e.g. in need of home visits).Nurses will also receive online practice training modules focused on case-management after the EOVs.

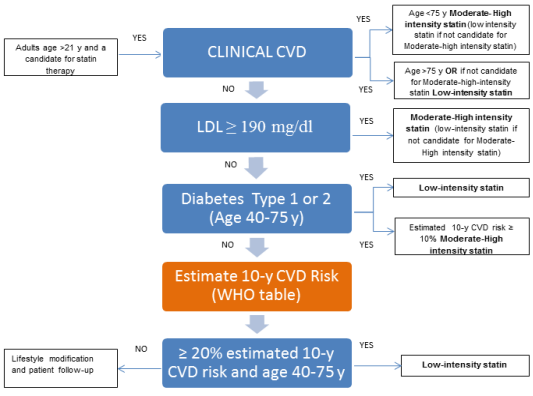
2.3.3. Educational intervention support tools

a) mHealth applications for physician's and nurse's smartphones will be developed to provide evidence-based and guideline-driven decision aids for physicians and nurses to improve patient management. It will use SANA framework (http://sana.mit.edu), a highly customizable, open-source, android-based mHealth information system. Our research team has experience in developing applications for smartphones
b) A centralized, web-based EMRwill be developed using OpenMRS to be used by administrative personnel and health professionals in each PCC. The EMR will allow them to create a patient registry, identify and schedule referrals for patients with high risk of CVD and help physicians with prompts and reminders to improve CPG use.
c) A web-based platformthat is tailored to send SMS messagesfor lifestyle modification, and prompts and reminders for clinic appointments will be used toimprove medication adherence forparticipating patients that are recruited in the intervention clinics

2.3.4. Treatment algorithm

The algorithm for the use of statins in the treatment of high cholesterol according to CVD risk will be adapted from the new ACC/AHA Guideline on the Treatment of Blood Cholesterol to reduce Atherosclerotic Cardiovascular Risk in Adults[13]and the WHO CVD risk charts.[29]Physicians will prescribe statins in moderate-high intensity (simvastatin 40 mg) or low intensity (simvastatin 20 mg) doses, as can be seen in figure 2below.

Figure2. Treatment algorithm



Low intensity: simvastatin 20 mg
Moderate-high intensity: simvastatin 40mg.

2.4. Evaluation design

All data collection and measurements will be performed by trained nurses not participating in the study intervention. After identifying eachpotentially eligible participant, a research physician/nurse will explain the goals and scope of the study, and will invite her/him to participate, and if accepted, to sign a written consent form approved by an independent Internal Review Board (IRB). A research nurse will administer a questionnaire and will perform the physical and biochemical measurementsat baseline, 6 and 12 months of follow-up (Table 1).

2.4.1. Data collection and study measurements

a) Forms and questionnaires: The study nurses will administer general information forms and questionnairesto participants at baseline and follow-up visits, gathering information on history of CVD disease and risk factors, and health behaviours (e.g., smoking, diet, and physical activity) and utilization patterns. Adherence to chronic medications will be assessed with the Morisky Green questionnaire, which is being validated in Argentina.[30]

b) Blood pressure: Three blood pressure (BP) measurements will be obtained at each clinical visit by trained independent study staff. BP will be measured according to a standard protocol recommended by the American Heart Association.An automatic device (OMRONHEM-705-CP)[31-34]will be used and one of four cuff sizes (pediatric, regular adult, large or thigh) will be chosen on the basis of each participant's arm circumference. Systolic and diastolic blood pressure will be recorded.

c) Anthropometric measures**:** At the clinic visit, trained staff will take anthropometric measurements on individuals in light clothing without shoes using a standard protocol. *Body weight* will be measured to the nearest 0.1 kg on a dedicated scale; *Body height* will be measured to the nearest 0.1 cm with a free-standing stadiometer; *Body mass index* will be calculated as an index for overall obesity;*Waist circumference* will be measured (at the smallest circumference between the ribs and iliac crest) in centimetres to the nearest 0.1 cm. To minimize measurement error, the Gulick II tape measure (Gays Mills, WI) with a no-stretch, retractable tape and tensioning device will be used.

d) Biochemical measures**:** a fasting capillary blood sampling will be obtained by fingerstickat the baseline visit with aCholestech LDX analyzer (Point of Care Diagnostics, Sydney, NSW). Practice staff will be trained to use the device, and an internal quality control will be conducted. Each PCC participating in the intervention arm of the trial will be provided with a *Cholestech LDX* and LDX Capillary Plungers to measure: total cholesterol (TC), calculated LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG),and glucose.Point of care testing with this device has been validated in several studies.[35-38]

Table 1. Data collection schedule

Measures	BV	Follow-up and termination visits, months	
		6	12m (TV)
Informed Consent	X		
Medical history and questionnaires	X	X	X
Physical Measurements	X	X	X
Delivery of statins	X	X	X
Clinical Lab	X	X	X
Assessment of outcomes		X	X

BV=screening/baseline visits; TV=termination visits at month 12

2.4.2. Follow-up and termination visit

Follow-up visits will be scheduled at 6 and 12 months (termination visit)from the baseline visit. We will try to arrange these visits to coordinate with patients' regular clinic visits in order to reduce time burden for patients. BP,anthropometrics measures, biochemical measures and updated information on the use of medications, cigarette smoking, alcohol drinking, diet, physical activity, and costs of treatment will also be obtained.

2.4.3. Data management (DM), quality assurance (QA) and quality control (QC)

Trained nurses will use tablets for data gathering and will regularly transfer the information via internet to the Data Management Unit at IECS. The quality assurance and control process will be employed at every step of the study.

a) Developing the manual of procedures (MOP): The MOP will describe the procedures forthe educational intervention program; participant recruitment; instructions for all forms and procedures; measurements, use of *Cholestech LDX*, and SMS delivery; and other operational aspects of the study.
b) Training and certification: All study personnel will be required to participate in a study training session prior to the initiation of any study procedures. The training sessions will include all aspects of the protocol and MOP with regard to recruitment, follow-up visits, intervention protocol, and measurement procedures. Periodic retraining sessions will be conducted subsequently to maintain standard application of all study-related procedures.
c) Quality monitoring and reporting: A QC subcommittee will review the QC data regularly, including timeliness and completeness of study visits and data collection, intervention protocol adherence, and data quality. Reports on data QC will be sent to each clinic monthly.

2.5. Study Outcomes

The **primary outcome** is net change in LDL-C levels from baseline to month 12 between intervention and usual care groups among all study participants.
The **secondary outcomes** are:

- Net change in 10-year-CVD Framingham risk score before and after the implementation of the program.
- Proportion of patients withmoderate-high CVD risk who have reduced 30% and 50% of their LDL-C, respectively.
- Proportion of patients with moderate-high CVD risk (through a validated risk assessment questionnaire used by the Ministry of Health)[39]who are correctly classified with a risk-prediction algorithm at the PCC.
- Proportion of patients with high CVD risk who are on statins, and are receiving an appropriate dose according to the CPG.
- Annual number of follow-up visits to the PCC for high CVD patients.
- Annual Rate of prescription refills at the clinic pharmacy among treated patients
- Cost-effectiveness of the interventionprogram

2.6Statistical power and data analysis

2.6.1. Power and detectable differences

The proposed study will use a cluster randomized design; 5 clinics will be assigned to intervention and 5 to control groups. The intervention and follow-up will last for 12 monthsand the primary outcome is the difference in LDL-C levels from baseline to month 12 between intervention and usual care groups among all study participants.The proposed trial is designed to provide 90% statistical power to detect a 0.7 mm/l reduction in LDL cholesterol level at a significance level of 0.05 using a 2-tailed test, assuming an intra-cluster correlation coefficient (ICC) of 0.06. An 85% follow-up rate will be assumed and the cluster design will be takeninto consideration in the power calculation.The sample size calculation used the formula developed

by Donner and Klar[40,41] and was implemented in the Power Analysis and Sample Size (PASS 2008) software (NCSS, Kaysville, UT). The estimated sample size for each cluster (PCC) is 35 and totals 350 for each group (10 clusters) based on these assumptions. The above power calculation is based on a two-sample t-test using cluster design. We will utilize mixed-model regression analysis which should increase statistical power because of inclusion of multiple repeated measurements.This sample size ensures adequate power for testing our secondary outcomes as well.

2.6.2 Data analysis plan

Intention-to-treat analyses will be conducted, in which the primary and secondary outcomes will be compared between participants according to their randomization assignment, regardless of their actual adherence to the intervention. Baseline characteristics of patients (demographics, clinical variables, lifestyle factors, anthropometrics measures and laboratory measurements) will be compared between the intervention and control groups using one-way ANOVA or Chi 2 tests.We will test the research hypothesis that there is a greater reduction in mean LDL-C in the intervention group than in the control group using a mixed effects regression analysis. In this model, participants and clinics are assumed to be random effects and intervention group, time, and the interaction are assumed to be estimable fixed effects. Although an autoregressive correlation structure is the logical choice for these repeated measures, exchangeable and unstructured correlation structures will be investigated as well. The secondary outcomes include both continuous and categorical variables. The analyses of the continuous variables will use similar models to those for the primary aim. We will conduct logistic regression analyses for categorical outcomes. Since we are measuring subjects at multiple time points, we will use GEE for these analyses.

2.6.3. Cost-effectiveness analysis: An economic evaluation component based on patient-level trial data will be complemented with a model-based component for long-term costs and effects extrapolation.Trial-based primary economic evaluation will use patient-level data collected from the proposed study. We will document all resources involved in conducting this comprehensive intervention program, as well as all patient-level costs, in 2016 Argentinean Pesos adjusted by Argentina consumer price index (CPI) and then converted into International Dollars (Int$). Primary incremental cost effectiveness ratio (ICER) measure will be cost per mmolof change in LDL-C. Secondary measures will be cost per additional case of reduction of LDL-C by 30-50% in moderate-high CVD risk patients, and per QALY using the Argentina Euroqol EQ-5D developed by our group[42] Non-parametric bootstrapping will be used to estimate parameter uncertainty in the trial-based component (ICER 95% CI, cost-effectiveness scatter-plot and cost-effectiveness acceptability curve). A Markov model will be adapted and further developed to extrapolate the long-term effects of the proposed intervention program throughout patient's lifetime (5% annual discount rate for benefits and costs).

2.7. Dissemination plan

Hypercholesterolemia imposes not only clinical but also economic consequences to an already overburdened health care system in Argentina. Our study will provide an exceptional opportunity for health policy makers, heath care providers, and the public at large to focus on the prevention and control of hypertension and related CVD.The dissemination plan is designed to translate, communicate, and implement the research findings to inform health policy, health practice, and public opinion. We will publish the study findings in international and national journals and make presentations at national and international professional meetings. In addition, we will organize national and regional seminars/workshops and use mass media, social networks (facebook, twitter) and policy briefs to promote the intervention program if proven effective in our study. In addition, IECS works with a program designed for dissemination by sending route e-mailinformation about the different activities of our Institution. The data base containsmore than 20,000 professional contacts in Argentina and other countries. This implementation research proposal, that is strongly supported by the

authorities of the Argentine Ministry of Health (please, see the letters of support) is timely becausestatins will be introduced in the national drug formulary of the public primary care system in 2014. If proven effective, we will disseminate the study findings and scale-up the program to the entire national public primary care network in Argentina.

3.Detailed Workplan and Deliverables Schedule

The study will have three phases(table 2). Phase 1 (in blue, 5 months) is the preparatory phasefocused on the development, adaptation and validation of forms and questionnaires that will be used for the evaluation and intervention programs as well as their standard operations procedures and manuals. It also includes the development of the guideline for the management of dyslipidemias, including the applications for smartphones and computers, and the web-based platform to send SMS to participating patients. During this phase, audit and selection of the PCCs and training and certification of their study personnel will take place. Phase 2 (in green, 16 months), the intervention phase, includes patient recruitment (6 months); collection of baseline data; implementation of theeducational intervention and support tools to health personnel; and data collection at 6 and 12monthsof follow-up. Phase 3 (in red, 3 months) includes the analysis of data, presentations of findings and write-up of results for publication (at both scientific and policy levels).

Table 2.Proposal Schedule.

	YEAR 1												YEAR 2											
Activities	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
Development of forms and SOPs	X	X	X	X																				
Development of the Clinical Practice Guideline and web-based platform		X	X	X																				
Development of e-Health tools (mHealth and EMR)		X	X	X																				
Training Workshops and e-learning modules				X	X																			
Pilot study to test tools, assessment & intervention program				X	X																			
Recruitment and randomization of the PCC						X	X	X	X	X	X													
Educational Outreach Visits						X			X			X			X			X						
Follow-up						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Data entry and QC						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Statistical Analysis																						X	X	X
Manuscript writing, Dissemination and Scale-up																						X	X	X