

Russian research program evaluating the extent of underdiagnosed and undertreated of familial hypercholesterolaemia in the population.

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Abstract

The main aim of the present study is to evaluate the extent to which familial hypercholesterolaemia (FH) is underdiagnosed and undertreated in the Russian Federation for reduction of cardiovascular risk related to atherosclerosis in the country. The target population: subjects of both sexes aged 7–75 years of age. As a first step, total cholesterol (TC) level will be determined in a random sample from Moscow population (n=17912). The number of subjects with TC level ≥ 7.5 mmol/L is 1505 (8%). During 2014, approximately 500 patients will pass through non-invasive clinical examination at the Russian Cardiology Research and Production Complex, including patient demographics, past medical history, family history of hypercholesterolemia, physical findings, current lipid-lowering therapies, blood tests, genetic analysis, echocardiography, carotid duplex ultrasound and exercise SPECT imaging in selected cases. On the basis of the Moscow Program four major Federal Medical Centers will be involved, and *Russian FH Community* with FH Registry will be created as a national, multi-center initiative to screen FH patients, control their diagnosis and management, and track clinical-reported outcomes over time. Establishment of national recommendations for the diagnosis and treatment of FH on the basis of these data and implementation those into physicians' practice in different regions of Russia will allow improving patient care. As an expected outcome, this program will raise awareness and increase appropriate assessment and treatment of FH patients in Russia by 25-30% compared to baseline situation, leading to a timely detection of the disease and therapy initiation.

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Main Section of the proposal.

Primary goal. The main aim of the present study is to evaluate the extent to which FH is underdiagnosed and undertreated in the Russian Federation for global reduction of cardiovascular risk in the country.

Key objectives:

- To establish the actual prevalence of FH and to determine the true number of heterozygous and homozygous forms of FH in Russia.
- To compare the clinical and diagnostic significance of Dutch Lipid Clinic Network criteria and Simon Broome Registry criteria for diagnosis of FH in adults in Russia and to adapt or create (if necessary) the optimal algorithm for the introduction in wide routine clinical practice.
- To develop a check-list (paper and electronic formats) with diagnostic algorithm and treatment strategy for primary care physicians.
- To reveal the distribution of lipoprotein(a) [Lp(a)] in individuals diagnosed with definite and probable FH in the Russian Federation population.
- To evaluate the severity of atherosclerosis in Russian patients with FH.
- To perform genetic testing in cases of possible, probable and definite FH for determination its specificity and sensitivity as FH diagnostic tool in RF.
- To implement a Family Health Team model, including cascade testing in patients with genetic mutations in LDLR, APOB, and PCSK9.
- To create all-Russia Registry of individuals with FH and to develop specific all-Russia Electronic Medical Record system for physicians treating FH individuals.
- On the basis of the Program data and International Guidelines for the diagnosis and management of FH to establish national recommendations for screening, diagnosis and treatment of FH patients.
- To increase the number of FH patients treated appropriately according to current lipid-lowering strategies.
- To reduce risk of atherosclerotic cardiovascular disease associated with FH.

Background.

Contribution to the overall death rate from cardiovascular disease (CVD) in the Russian Federation is 57%, and therefore the cardiovascular mortality is the leading cause of death in Russia. In 2011 the mortality rate (number of deaths per 100,000 population) from CVD in Russia reached 753 cases, while in the developed European countries it is 3-4 times lower. The annual economic damage from CVD in Russia is about 1 trillion rubles (32 billion USD) [Russian State Statistics Committee, 2008]. There are seven main risk factors for premature mortality in Russia: hypertension (35.5%), hypercholesterolemia (23%), smoking (17.1%), inadequate intake of fruit and vegetables (12.9%), overweight (12.5%), excessive consumption of alcohol (11.9%) and lack of exercise (9%) [Oganov RG, 2009]. Among the causes of cardiovascular mortality in the first place is coronary heart disease (CHD, 397 cases per 100,000 people, or 53%), the second place holds cerebrovascular disease (233 cases per 100,000 people, or 31%) [Russian Ministry of Health, 2013].

Due to lifelong elevated plasma low-density lipoprotein (LDL) cholesterol levels, familial hypercholesterolemia (FH) is known common cause of premature CHD [Austin MA, 2004]. With

the estimated 1/500–1/200 prevalence, there are between 14 and 34 million individuals with FH worldwide [Nordestgaard BG, 2013].

To date, in Russia FH is vastly underdiagnosed and as a result the true amount of untreated individuals in the Russian population with FH is largely unknown. Currently, the number of people with FH is based on extrapolations from the calculated for other countries estimated prevalence. According to our preliminary data from the large cholesterol screening survey (n=52075), median total cholesterol in all male age groups over 30 years and in all female age groups over 35 years significantly exceeds the upper desirable limit of TC of less than 5.0 mmol/l for the general population [Igonina N.A., 2012]. In a study conducted in the Western Administrative District of Moscow, from 2400 individuals who have applied to primary physicians for whatever reason, the detection rate of TC above 7.5 mmol/L was 12,2% (n = 291), and the level of LDL cholesterol more than 4.9 mmol/l was detected in 10% of respondents. Among the study participants there were people with different cardiovascular risk estimation as defined by the SCORE chart, including group of CHD patients [unpublished data]. Thus, we expect a high prevalence of FH in Russian Federation.

With the increased understanding of the genetic causes of this disease, direct detection of mutations in the LDLR, ApoB, PCSK9, and LDLRAP genes is now available in many countries [Nordestgaard BG, 2013]. The absence of applied genetic screening in Russia sometimes does not allow to diagnose the disease and to perform correct risk estimation in heterozygote forms.

The detection of subclinical atherosclerosis using noninvasive imaging techniques can improve risk stratification and clinical management, especially in cases with no other cardiovascular risk factor or family history of premature CAD [Civeira F, 2004]. The 2004 International Guidelines for the Diagnosis and Management of Heterozygous Familial Hypercholesterolemia recommended the detection of subclinical atherosclerosis in coronary arteries and other vascular territories using tests for myocardial ischemia, coronary CT scans or vascular ultrasounds in all FH males >40 years and in females > 50 years of age, or younger in high-risk subjects [Civeira F, 2004]. B-mode ultrasound is a noninvasive imaging technique, useful in the assessment of intima–media thickness (IMT) and to detect atherosclerotic plaques in carotid and femoral arteries. It has been shown that FH patients have increased IMT in carotid and femoral arteries compared with controls [de Groot E, 2004. Junyent M, 2008], depending, in part, on the severity of the mutation [Junyent M, 2008].

Over the past two decades, a number of population-based screening and research initiatives have made great strides in improving FH awareness and treatment. National or regional registries have been established in the Netherlands, Spain, the UK, Wales, Australia, Ireland, Norway, Brazil, New Zealand and some others. As the result of such work has become the development of Dutch Lipid Clinic Network diagnostics criteria in the Netherlands and Simon Broome Register in the UK [Umans-Eckenhausen MA, 2001. Neil HA, 2000]. It is important to mention, that FH is a curable disorder, and once diagnosed, heterozygotes can be treated with cholesterol-lowering medication to attenuate development of atherosclerosis and to prevent CHD [Versmissen J, 2008], for homozygotes there are recently developed and already under development new LDL and lipoprotein(a) [Lp(a)] targeting drugs. The Dutch FH cohort showed that after 10 years of therapy, those patients who received statins after screening had a 76% overall reduction in their expected CAD risk, equaling a normal healthy population [Versmissen J, 2008].

Material and Methods.

In December, 2013, the Russian National Atherosclerosis Society (RNAS) in collaboration with the “INVITRO” Laboratory have designed the database of subjects from Moscow itself and Moscow region, who had lipid analysis in September, 2013. This database included 17912 individuals with lipid spectrum analysis (TC, LDL-C, HDL-C and triglycerides). TC was ≥ 8.0 mmol/l in 827 (4.6%) patients and was ≥ 7.5 mmol/l in 1505 (8.4%) patients (picture 1). Only 32% of patients had TC < 5.0 mmol/l (figure 1 in Appendix). In this way, we identified 1505 potential participants eligible for the initial part of the Program.

It is a global program to determine a real magnitude of FH dissemination in Russia. Five leading Federal Medical Centers in different regions of Russia are planning to be involved. The focus of the Program is aimed at cardiologists, endocrinologists, primary care providers (internists, general practitioners from polyclinics), public health practitioners, healthcare providers, patients in the Russian Federation.

Inclusion criteria for individuals to participate in the Program:

- Subjects of both sexes aged 7–75 years, citizens of the Russian Federation;
- Total cholesterol ≥ 7.5 mmol/L or LDL-C ≥ 4.9 mmol/L
- Written informed consent to participate in the study

Exclusion criteria:

- Secondary dyslipidemias

Design.

We have chosen a randomly selected cohort of individuals who have been tested in the Moscow office of the “INVITRO” Laboratory on the basis of advertising campaign held in September, 2013, for the purpose of TC level measurement and determination of cardiovascular risk with the use of SCORE chart. The operator from the “INVITRO” Laboratory identified potential FH patients based on TC (≥ 7.5 mmol/L) or LDL-C (≥ 4.9 mmol/L) values.

Following identification, the potentially eligible participants suspected for FH are sent a notification letter describing the patient’s high cholesterol level, at-atherosclerosis risk status and need for additional screening on the basis of the Russian Cardiology Research and Production Complex. Those who give preliminary agreement for participation in the Program are invited to the Institution, where, after signing the ICF, they will undergo clinical (biochemical, echo, duplex scan) and genetic testing. Those individuals refusing to participate in the Program will be taken into account with fixing the reason of unwillingness to participate.

Patients under the age of 18 will be enrolled only with the explicit consent of a parent or legal guardian. All participants will be provided with the information about the Russian FH Community and Russian FH Registry.

All included subjects will be provided with a screening questionnaire querying the patient demographics, past medical history, patient FH history and diagnosis with FH type heterozygous or homozygous, family history of hypercholesterolemia, physical examination findings, current lipid-lowering therapies, and patients’ contact information for further follow-up. After initialization of online data capture form (Electronic Medical System), the information will be also entered in the system. Blood and gene banks will be formed; analysis of

echocardiography data for aortic valve stenosis, carotid duplex ultrasound for atherosclerosis burden, and exercise SPECT imaging in selected cases of suspected CHD will be performed during the baseline visit. Patients diagnosed with FH on the basis of Dutch Lipid Clinic Network, Simon Broome Criteria and genetic testing will be provided information about screening of first-degree relatives, and additional educational materials about FH (under development).

To determine the true number of heterozygous forms among individuals with a probable diagnosis of FH molecular genetic testing is planned. When a causative mutation is found in the index case, a genetic test will be offered to all first-degree relatives.

Enrolled patients will be asked to update information at annually intervals. Since the last date of data entry, occurrence of major adverse cardiovascular events (acute coronary syndromes, stroke, myocardial revascularization, peripheral revascularization, cardiovascular death), changes in medications, hospitalizations to any reasons, genetic testing, laboratory values, and all-cause mortality will be reviewed.

Follow-up data will be collected yearly following initial enrollment. Updated information on quality of life will be collected. Annual reminder emails will be sent to all patients to call the following physician.

We estimate that at one site during one year (2014-2015) we will screen 500 patients eligible for the participation from the potentially eligible 1505 selected from 17912 individuals.

Examination procedures at the scheduled visits:

1. Signing the ICF.
2. The questionnaires to determine the classical cardiovascular risk factors, past medical history and treatment.
3. Applying Dutch Lipid Clinic Network (DLCN) criteria and Simon Broome Register (SBR) criteria and maintaining of an electronic medical system by physicians participating in the Program.
4. Blood sampling for TC, TG, LDL-C, HDL-C, Lp(a), hsCRP measurement.
5. Blood samples collection for PCSK9 measurement and genetic testing (detection of mutations in the LDLR, ApoB, PCSK9).
6. Echocardiography for the assessment of ascending aorta and aortic valve.
7. Duplex scanning of the carotid arteries for the assessment of intima-media thickness and plaques' characteristics.
8. Exercise SPECT imaging in patients suspicious for CHD.
9. Annual evaluation of cardiovascular events (myocardial infarction, stroke, cardiovascular death, non-cardiovascular death, hospitalization connected with cardiovascular disease, percutaneous coronary intervention or coronary artery bypass grafting performed).

During the second Program phase (2015-2016), a number (n=4) of major Russian Federal Medical Centers (with the presence of Lipid Divisions, appropriate staff, technical equipment, and approval from the Local Institutional Ethical Committee (LEC); contacts are given in the Appendix) will be invited to participate in the *Russian FH Community Program*, in particular, in the *Russian FH Register*.

In case of successful implementation of the first phase of the Program within Moscow, a letter of intent about the need to include additional centers and initiation of the Government

Program for screening and care of FH patients will be formed and sent to the Ministry of Health of the Russian Federation.

FH patients at these 1-st line Sites who meet inclusion criteria as described in the Methods section will be eligible to enroll. The same algorithm as described above will be initiated. Specialized staff from the Russian Cardiology Research and Production Complex (as a Core Center) will monitor the effectiveness and credibility of the undertaken work. Filling in the Electronic Medical System (eCRF) will be checked by the staff from the Core Center, and each year teleconferences will be held between the Sites-Participants of the Program.

Perspectives: since 2018 - the next phases of the Program will include recruitment of new set of Clinics, Polyclinics and Institutions across Russia with specialized lipid clinics that could demonstrate acceptable feasibility for patient enrollment and engagement.

With the help of the Health Ministry, efforts will be made to enroll sites representing all regions and types of institutions to ensure real-world reflection of approaches used to FH detection and management, followed by mandatory standardization of these approaches of screening and treatment of patients with FH across Russia.

Quantification of the amount of change expected for the target audience.

Moscow is a city with 12 million population. Of 17912 subjects evaluated on the first stage of our study about 1000 have TC more than 7.5 mmol/L. At least, five to ten percent of them (or 50 to 100 of 18000 – 0.3-0.6%) will have heterozygous forms of FH (definite or probable). Any new mutations of LDL-R, APOB, PCSK9 will be revealed. So, we can speculate that approximately 50,000 – 100,000 Moscow inhabitants have definite or probable FH. Overall, number of FH patients in the Russian Federation may reach 500,000 – 750,000 with mosaic prevalence in different regions. Despite combined efforts of the Government and medicine community during last 5 years (Russian National project «The Health», primary and regional vascular centers opening with new tomography and angiography equipment), CVD mortality remained extremely high. FH high rate and underestimation could impact largely on CVD epidemiology. Estimated and anticipated challenges related to this problem in percentage are provided in Table 1 and 2. In the US less than 10% of FH patients are formally diagnosed and many are not appropriately treated. We state that in the Russian Federation the true number of such patients that are being informed about their disease is unknown, and could be estimated about 1%.

Table 1. Changes in FH challenges expected from the Program implementation.

FH challenges	Estimated at baseline	Anticipating absolute increase from baseline
% of informed about personal cholesterol level	1%	↑ 10-20%
% of them taking statins	20%	↑ 30-40%
% of them with target LDL-C level on statins	5%	↑ 10-20%
% FH treated with lipoprotein apheresis	cases	↑ 20%
% of doctors knowing and implementing FH Guidelines	10%	↑ 30-50%
% of doctors knowing FH Criteria	10%	↑ 30-50%

High-intensity lipid-lowering therapy prescribed to this category of patients on a regular basis will lead to lower rates of cardiovascular deaths and after implementation of this treatment strategy country-wide will be result in a significant budget economy.

Table 2. Anticipated challenges and solutions.

RISKS	Possible Solutions
1. Unwillingness of patients to be informed about their health.	1. Prominent advertisement
2. Low awareness of physicians and managers of health care facilities.	2. Educational lectures under the auspices of the RNAS.
3. Underestimation of the FH problem by the Russian Ministry of Health.	3. providing data on the true prevalence of the disease in Russia.

Methods for engagement of the Program outcomes.

During the first year of the Program, after the preliminary evaluation and applying FH criteria all studied patients (n=500) will be separated into FH and non-FH subjects with an estimated proportion of ~1:4. LDL-C and TC cut-off levels specific for the Russian Federation as well as simple questionnaire will be used for all system stratas. Next we will apply statistical algorithm and mathematical model as well as cascade screening to choose and eliminate probable and definite FH persons from the rest of population. Using database from the “INVITRO” laboratory in Moscow and other participating cities health care providers will find high-risk people with suspicious FH during the second year of the Program.

Based on the first year results there will be an estimation of precise prevalence of FH in RF. The second year of the Program will allow us to enlarge the true FH cohort and to spread and disseminate over the country all educational materials through clinical facilities and health care ministries and organizations (requiring additional money costs) in all large Russian cities using the main Ministry of Health channel.

Below is the list of necessary materials to fulfill all Program requirements and aims:

- Screening questionnaire
- Paper education materials (e.g. *Measure Your Blood Cholesterol Now!*)
- Social Video Advertisement for Federal TV channels
- Advertisement on the RNAS website, where all necessary materials including Portal for self-registering will be placed
- Distribution of posters about importance of cholesterol measurement and referral to a Cardiologist, brochures and booklets about atherosclerosis, FH fact sheet, tear sheets with physical findings, lifestyle management and treatment strategies, in all out-patient clinics over-the-country.

It is planning to have a one year telephone contact in all patients who will agree to provide information about treatment compliance, lab results for LDL-C goal and new cardiovascular events (myocardial infarction, stroke, hospitalization for unstable angina and/or revascularization or aortic valve replacement). The main reason for obtaining of follow-up data is to improve the maximal engagement feasibility and validity of the Program scientific content.

Moreover, there will be on-line registry and questionnaire for family physicians to elucidate applicability of Program materials.

Plan for the broad dissemination of the Program outcomes.

The main purpose for dissemination of the Program outcomes is:

- to accelerate the formation of the legislative acts of the Health Ministry on the significance of FH as a socially and medically important disease with appropriate management;
- to include homozygous and severe heterozygous FH into the list of orphan diseases in the Russian Federation, with the opportunity to be treated by lipoprotein apheresis in cases refractory to medical therapy.
- to focus efforts on creation of lipid clinics with the presence of staff and equipment for LDL apheresis held under medical insurance coverage.

The focus of the program is aimed at cardiologists, endocrinologists, primary care providers (internists, general practitioners), public health practitioners, health service planners and healthcare providers, patients in the Russian Federation.

Development of a Program with an electronic medical system which will allow to set up an evaluation for a population-based screening and intervention monitoring in the clinics and policlinics that have been already supplied with the computers (With the implementation of the State Program of “Russian Health Modernization” the majority of hospitals in Russia were equipped with PCs).

Establishment of the National Recommendations for the diagnosis and treatment of FH on the basis of these data and implementation those into physicians’ practice in different regions of Russia will raise awareness and increase appropriate assessment and management of FH in Russia.

Work-plan and Deliverables Schedule.

Expected outcomes (Deliverables, Table 3).

First of all, these data will be used to identify the extent to which FH is underdiagnosed and undertreated in Moscow on the basis of number estimation of diagnosed patients. According to *RosStat* 2014, the population of Moscow is 12,111,194 people; the population density is 4823.26 per km². Addition of the information from the sites in different geographic regions of Russia will allow performing epidemiological modeling of the situation with FH in Russia.

It is important, to note that the RNAS partners with several large healthcare organizations from the public and private sectors that can facilitate the conduction of standardized Electronic Medical System for identification potential FH patients based on TC / LDL-C lab values and some clinical data. The development of uniform large electronic medical system will be used for identification of patients eligible for clinical trials and other registries, including in future hypertriglyceridemia and other lipid disorders.

The next stage would be distribution the access to this Program via the official society’s website (www.noathero.ru and website of the *Russian FH Community*) among the Russian population for self-assessment of the likelihood of FH probability in the individual case, and navigation in finding specialized cardiologist and lipidologist in the suitable geographical area. The appropriateness of the work with the Registry will be patronized and controlled by the key

team members of the RNAS. These data will enhance patient engagement in their disorder by allowing them to participate in the monitoring of their lipid values, therapies, quality of life and prognosis.

On an annual basis reports with collected data (occurrence of major adverse cardiovascular events and mortality, adherence and medication changes, side effects of treatment, lipid values, quality of life measurements) will be posted on the website, highlights of clinical outcomes and treatment patterns, genetic testing for enrolled patients will be sent to the Health Ministry and Federal Centers involved in the Program.

After accumulating a critical mass of knowledge about the status of the problem in Russia during first two years, the results of the Program will be presented in lectures and reports for physicians and the public, as well as in social advertising.

Before initiating the second phase of the Program, all participating Sites will be required to obtain LEC approval before starting data entry.

The overall data received in this Program can be used to develop Russian-population specific clinical criteria to diagnose FH with the algorithm of examination and treatment strategy.

The organization process and management of the *Russian FH Community Program* will be supervised and directed by an Executive Committee consisting of the representatives from the Russian Cardiology Research and Production Complex (Director, Eugene I. Chazov) and the RNAS (President, Yuri A. Karpov; Director, Igor V. Sergienko), including FH specialists and specialist in genetics.

The authors of this Proposal – VV Kukharchuk, MV Ezhov, IV Sergienko, MS Safarova – are solely responsible for the design and conduct of this Program, all study analyses and content herein. Draft of the Protocol was approved by the administration of the Institute of Clinical Cardiology, the part of the Russian Cardiology Research and Production Complex (Director, Irina E. Chazova).

Methods to control the effectiveness of the Program.

Initially, before the results of the Program will be disseminated, a short survey to assess physician and patient understanding of FH disease characteristics and diagnosis, associated health risks, available treatment options, family member screening will be performed in Moscow, following other regions.

After demonstration the main results and implementation into practice the deliverables, the follow-up survey will be performed in the same clinics and policlinics to estimate the changes in the extent of diagnosed and treated FH patients in the population in comparison with the baseline.

Sites participating in the *Russian FH Community Program* and *Russian FH Registry* will receive annual data feedback reports that will highlight the status for their enrolled patients compared with the national results. These reports will be designed to facilitate quality improvement interventions at participating sites and improve the treatment and outcomes of FH patients.

As we are proposing the only active Russia-based registry for FH, aimed to optimize diagnostic and therapeutic management with subsequent improvement in the clinical outcomes and quality of life of FH patients, we believe that this Program can provide valuable insights and

the evidence base needed to the government to review its healthcare delivery system and policies in the direction of the treatment of patients with atherosclerotic cardiovascular diseases.

We suggest promoting implementation of cascade screening of family members, because of known international data on more timely disease identification and treatment prescription with the use of such approach. Thus, we would be able to assess the natural history of FH in our population and the potential benefit in life-years gained from effective treatment.

At the forefront we place improving FH awareness and its treatment. It should be mentioned, that the baseline knowledge in the disease situation and the prognosis of these patients in Russia is known only from extrapolation from the other populations' registries, clinical trials and small pilot Russian studies.

National or regional registries have been established in the Netherlands, Spain, the UK, Wales, Australia, Ireland, Norway, Brazil, New Zealand, US. However, Russia is not mentioned in this list.

We assume that in our capability is to develop and validate specific for Russia criteria using a well known set of lipid values, genetic testing, physical signs and symptoms, family history to determine FH diagnosis.

Cost-effectiveness analysis would be supportive for understanding the significance of introduction this model in the broad clinical practice.

Knowledge and insights obtained from the data collection and validation processes is going to be essential in establishing rigorous methods for collecting high-quality data over time.

As one of the methods to increase awareness in the population we will also use US experience in form of data entered by self-enrolled patients in the online patient portal (FH Foundation and CASCADE Registry).

Table 3. Expected outcomes and timelines.

DELIVERABLES	SCHEDULE
Information about the prevalence of FH patients with the true number heterozygous and homozygous forms of FH in Moscow and then in whole country.	2016
Development of paper case report form for eligible subjects (for physicians' use, Appendix).	January 2014
Development and management of database of potential FH patients (for physicians' use)	December 2013 December 2016
Determination the distribution of lipoprotein(a) in individuals diagnosed with definite and probable FH in Moscow, followed by knowledge obtained in Russia	December 2016
Assessment of the severity of atherosclerosis in Russian patients with FH (using carotid duplex and SPECT imaging)	December 2016
Determination of specific for the Russian FH population mutations. Forming "GeneBank" for FH disease mutations.	2014 - 2016
Detection of prevalence of aortic valve stenosis in FH patients, taking into account the level of Lp(a)	2014 - 2016

Development and managing of standardized Electronic Medical System for identification potential FH patients (for physicians' use)	March 2014 - 2016
Creation electronic system called <i>Russian FH Community</i> (for physicians' and patients' use, Appendix)	April 2014
Creation and management of all-Russia Registry of individuals with FH (<i>Russian FH Registry</i> , Appendix)	April 2014 - 2016
Comparative analysis of the clinical and diagnostic significance of Dutch Lipid Clinic Network criteria and Simon Broome Registry criteria for diagnosis of FH in adults in Moscow / Russia Potentially, adaptation or creation (if necessary) the new Criteria of FH diagnosis.	December 2015 / 2016
Elaboration of Russian National Recommendations for screening, diagnosis, management and treatment of FH patients	2017 - 2018
Development of educational programs and platforms within the websites noathero.ru and " Russian FH Community ", the RNAS educational programs in Moscow and regions all over the RF, mass media, and Health Ministry, e.g.: - specific reminders and manuals for identifying individuals with FH; - memos and check-lists with diagnostic algorithm and treatment strategy for primary care physicians (cardiologists, internists, endocrinologists), - educational videos about lipid metabolism, FH for physicians and patients - social advertising about high cholesterol levels	Starting from 2015
Constant monitoring program of the implementation process of the proposed Educational Platforms and Recommendations for FH patients and physician's awareness of the possibilities in managing these patients	2014 - 2016
Designing a Family Health Team model	Starting from 2016
Growth of a new generation of dedicated clinicians, well-informed patients, and forward thinking politicians	Starting from 2016
Formation of the legislative acts from the Health Ministry on the significance of FH as a socially and medically important disease with appropriate management	2016 - 2018
Official inclusion of homozygous and severe heterozygous FH patients into the list of orphan diseases in the Russian Federation, with the opportunity to be treated by lipoprotein apheresis in cases refractory to medical therapy.	2016 - 2018
Creation of lipid clinics with the presence of staff and equipment for LDL apheresis in different parts of Russia held under medical insurance coverage.	2016 - 2020

Organizational Detail.

Leadership and Organizational Capability.

The present research program is designed and patronized by the **Russian National Atherosclerosis Society (RNAS)**, a membership-based non-profit voluntary organization. It was established by the initiative group of cardiologists and lipidologists, citizens of the Russian Federation. *The aim and scope of the RNAS* is to bring together specialists involved in the atherosclerosis research and forward them in direction of solving actual problems related to pathogenesis, diagnosis, prevention and treatment of atherosclerosis and its complications. RNAS is aimed to disseminate modern scientific achievements among the medical community and the public, which should lead to reduction in cardiovascular morbidity and mortality in Russia. The official website is www.noathero.ru. RNAS is responsible for the content of the Journal of Atherosclerosis and Dyslipidaemias. RNAS is the part of the International Atherosclerosis Society. The office is based in Moscow, Russia.

The execution of the project will be supported and facilitated by the Federal State Institution "Russian Cardiology Research and Production Complex" of the Health Ministry of the Russian Federation (Moscow) and Independent research laboratory "INVITRO".

Independent research laboratory "INVITRO" was founded in 1998. It provides an opportunity to determine more than 1000 parameters of biochemical, immunological and other analyses. Quality Management System meets the requirements of ISO 15189:2007 regulations for Medical laboratories. In addition, the quality management system to medical services (clinical and diagnostic) of the Laboratory meets the requirements of GOST R ISO 9001-2008 (ISO 9001:2008). It organizes a network of medical offices in various districts of Moscow and other cities of Russia. There are eight technological complexes on the territory of Russia: Moscow, St. Petersburg, Chelyabinsk, Novosibirsk and Samara. There are offices on the territory of Ukraine in Dnepropetrovsk, on the territory of the Republic of Belarus in Minsk, and on the territory of Kazakhstan in Almaty. The official website is www.invitro.ru.

Advantages of INVITRO laboratory:

- Wide dissemination 500 medical offices operating under the trademark of "INVITRO"® throughout Russia, Ukraine, Kazakhstan and Belarus.
- Multi-level quality control system.
- Test systems from leading manufacturers.
- Performed laboratory tests are recognized by all medical institutions in Russia.

"INVITRO" laboratory will provide a database of subjects undergoing blood test analysis for the lipid profile results. The database will contain only the participants' codes with no other personal information. Institute staff will select subjects according to inclusion criteria (age 18-70 years and TC \geq 7.5 mmol/l). Selected subjects will be notified by the "INVITRO" staff about the opportunity of participation in the National Program of FH screening and diagnosis via e-mail or phone. Those who give preliminary consent to participate, will be invited to the *Lipid Center* in the Russian Cardiology Research and Production Complex.

Russian Cardiology Research and Production Complex had been founded in 1967. Nowadays the Institution consists of two Institutes: Institute of Clinical Cardiology named after A.L. Myasnikov and Institute of Experimental Cardiology. *Institute of Clinical Cardiology* conducts medical treatment, training, research and organizational activities as a leading institution of the Russian Federation. Established scientific and research programs involve

application of the latest equipment, powerful computer facilities and are carried out by well-coordinated and highly authoritative teams and staff supervised by active and dynamical Scientific Board. There are 16 departments and 4 independent diagnostic laboratories. The official website is www.cardioweb.ru. The study will be conducted on the basis of the *Atherosclerosis Department, Laboratory of Immunology and Biochemistry, Laboratory of Ultrasound, Department of Radionuclide Diagnostic, and Laboratory of Genetics*.

Three investigators (cardiologists) from the Atherosclerosis Department will consult potential participants. After signing the written informed consent form (is provided in the supplementary material part), included subjects will be examined for demographics, past medical history, FH history and diagnosis with the use of Dutch Lipid Clinic Network criteria and Simon Broome criteria, FH type (heterozygous or homozygous), family FH history, physical findings, current lipid-lowering therapies.

Blood tests will collected for genetic and biomarker analysis, including lipid spectrum, lipoprotein(a), C-reactive protein, PCSK9, on the basis of the Laboratory of Immunology and Biochemistry and the Laboratory of Genetics. Blood samples will be frozen and stored at 70°C.

Transthoracic echocardiography for identification patients with aortic valve stenosis and carotid duplex ultrasound for measurement of carotid atherosclerosis burden (intima-media thickness, presence and number of atherosclerotic plaques, structure of atherosclerotic plaques, degree of lumen narrowing) will be performed by the highly-trained staff and with the use of equipment of the Laboratory of Ultrasound. In patients with suspected CHD exercise SPECT imaging will be done on the basis of the Department of Radionuclide Diagnostic.

Paper and electronic CRF (template is given in the supplementary material form) will be completed by the staff of the Atherosclerosis Department. Based on the findings patients will be advised with the lifestyle modification changes and guideline-driven medical therapy. The patients with lipid-lowering medication recommendations will be advised to check the safety and efficacy profile after 1 month with the possibility of consultation of the blood tests. A group of specialized cardiologists from the Atherosclerosis Department will enter annual follow-up data on demographics, laboratory values, treatment and clinical events.

After completing the initial part of the Project, with the initialization of the proposed algorithms in Moscow during 1.5 years, other large Russian Federal Medical Centers, as:

- Samara State Medical University (Samara),
- Research Institute of Internal Medicine (Novosibirsk),
- Center of atherosclerosis and lipid disorders in Clinical Hospital №122 named after LG Sokolov (Saint Petersburg),
- Chelyabinsk State Medical Academy (Chelyabinsk) will be included in the Program.

Staff Capacity						
Role in the Project	Name	Degree	Position and workplace in the Russian Cardiology Research and Production Complex	Work experience, years	Time to the initiative, %	Responsibility
PI	Valeriy V. Kukharchuk	Professor, DMSc, MD,	Head of the Atherosclerosis department. RNAS Past President	49	30	Overall project management
Project manager	Marat V. Ezhov	DMSc, MD	Senior Researcher of Atherosclerosis department. RNAS Vice-President	20	60	Project and CRF development, organization of teamwork, project management. Heading the Clinical Research analysis. Monitoring the statistical analysis and epidemiological modeling. Development of Educational materials.
Project manager, Study Coordinator	Igor V. Sergienko	DMSc, MD	Senior Researcher of the Atherosclerosis department. RNAS Director	18	60	Project and CRF development, organization of teamwork, project management. Organization of the subdivisions' work. Cooperation with the other Russian Medical Centers. Development of Social Advertisement and Educational materials.
Medical advisor, Study Coordinator	Maya S. Safarova	PhD, MD	Research associate of the Atherosclerosis department	7	70	Project and electronic medical system development. Creation and management of FH register. Monitoring the statistical analysis. Echocardiography data analysis. Development of Educational materials.
Investigator	Anna E.	PhD, MD	Research associate of	11	50	Development of FH register.

	Semenova		the Atherosclerosis department			Entering baseline and annual follow-up data. Physical examination of participants, consultation. Development of Educational materials.
Investigator	Vladimir V. Malakhov	PhD, MD	Research associate of the Atherosclerosis department	11	50	Entering baseline and annual follow-up data. Physical examination of participants, consultation.
Assistant	Diana N. Nozadze	MD	Postgraduate of the Atherosclerosis department	5	40	Blood sampling and labeling, centrifugation and freezing of the samples.
Sub-Investigator	Tatiana V. Balahonova	Professor, DMSc, MD,	Head of the Ultrasound Department	27	20	Monitoring the specific algorithms of carotid artery duplex scanning. Development of Educational materials.
Sub-Investigator	Olga A. Pogorelova	PhD, MD	Research associate of the Ultrasound Department	14	30	Carotid artery duplex scanning
Sub-Investigator	Maria I. Tripoten	PhD, MD	Junior Researcher of the Ultrasound Department	12	30	Carotid artery duplex scanning
Sub-Investigator	Valeriy P. Masenko	Professor, DSc, MD,	Head of the Biochemical and Immunology Laboratory	42	10	Blood test analyzing. Measurement of hsCRP, Lp(a), PCSK9 levels
Sub-Investigator	Anton Yu. Postnov	Professor, DSc, MD	Head of the Genetic Laboratory	32	10	Genetic analysis. FH disease gene mutations. Single-nucleotide polymorphisms in LPA. Development of Educational materials.
Sub-Investigator	Vladimir B. Sergienko	Professor, DSc, MD	Head of the Department of Radionuclide Diagnostic	39	20	Monitoring the specific algorithms of radionuclide myocardial scintigraphy data processing

Sub-Investigator	Ludmila E. Samoylenko	PhD, MD	Senior Researcher of the Department of Radionuclide Diagnostic	35	40	Radionuclide myocardial scintigraphy analysis
Sub-Investigator	Konstantin P. Ivanov	PhD, MD	Research associate of the Department of Radionuclide Diagnostic	16	30	Bicycle ergometry testing
Sub-Investigator	Alexey A. Ansheles	PhD, MD	Research associate of the Department of Radionuclide Diagnostic	11	60	Software developing. Supporting and monitoring the electronic medical system and web site for FH community, including register
Sub-Investigator	Grigory I. Heymets	PhD, MD	Senior Researcher of the New Research Methods Department.	34	30	Epidemiological modeling, statistical analysis
Role in the Project	Name	Degree	Position and workplace in the "INVITRO" Laboratory	Work experience, years	Time to the initiative, %	Responsibility
Sub-Investigator	Elena A. Kondrashova	DSc, MD	Senior Manager	11	10	Project management, development of the "Letter of request" to the potential participants
Sub-Investigator	Tatiana N. Savelieva	PhD, MD	Director of Corporate Sales	8	10	Development of a database of subjects who were screened in "INVITRO"
Sub-Investigator	Catherine V. Skuridina	PhD, MD	Operator	6	40	Telephone and email contacts with the potential participants

Detailed Budget

Completed Budget Template form is attached as Appendix.

Direct Labor Costs.

Project Leader: provides overall management of the project, provides leadership support, controls the process of data collection and processing, produces the necessary correction.

Other staff:

- Gene bank for FH disease mutations
- Social Advertisement (about high cholesterol level, FH)
- Screening questionnaire, clinical exam
- Creation and management electronic system called Russian FH Community (Electronic Medical System for identification potential FH patients)
 - Creation and management of all-Russia Registry of individuals with FH (Russian FH Registry)
 - Lp(a), CRP, PCSK9 measurement
 - Echocardiography for aortic valve stenosis
 - Carotid duplex ultrasound for atherosclerosis burden
 - Exercise SPECT imaging
 - Annual evaluation of enrolled patients
 - Development of monitoring program for FH patients and treating physicians
 - Elaboration of Russian National Recommendations for screening, diagnosis, management and treatment of FH patients
 - Development of paper case report form for eligible subjects
 - Development and management of database of potential FH patients
 - Development of educational programs and platforms. Educational materials about FH (brochures and booklets about atherosclerosis, FH fact sheet, tear sheets with physical findings, lifestyle management and treatment strategies, educational videos about lipid metabolism, FH and atherosclerosis for physicians and patients
 - Statistical analysis. Standard statistical approaches commonly used in observational analyses will be utilized.
 - Forming a working group for preparation of the Russian National Recommendations for the screening, diagnosis and management of patients with familial hypercholesterolemia

Direct Initiative Costs .

RNAS fully covers expenses for this position

Annual assessment variations in lipid management, clinical events, and patient-reported outcomes to evaluate temporal changes in these variables will be performed on the basis of the included Medical Centers. Estimation of patient's drop-out during the first year of the Program from the study cohort (n=1505) is approximately 30%.