CLINICAL RESEARCH PROJECT

Protocol # 15-H-0042
IND/IDE # none
Closed to accrual: July 10, 2019

NHLBI Protocol: Evaluation of the effects of Niacin therapy on lipoprotein composition and function

Short Title: Niacin and lipoprotein composition/function

Keywords Words: HDL, LDL, VLDL, Cholesterol, Lipoproteins, Niacin

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Subjects in study:

Number	Sex	Age Range
200 (goal is 32 completed studies)	M/F	≥18

Product Uses Ionizing Radiation: No
Project Uses IND/IDE: No
Project Uses "Durable Power of Attorney": No
Off Site: No
Multi-Institutional Project: No

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1. Précis

This single center clinical pilot study will investigate the effects of niacin on blood lipids and lipoprotein composition in human subjects who are healthy. Niacin (vitamin B3 or nicotinic acid) is a common nutrient found in many foods and is currently sold over the counter as a nutritional supplement. Extended-release versions of niacin are available over the counter (e.g., Slo-Niacin®) or by prescription (Niaspan®) and help to alleviate symptoms of flushing associated with larger doses of the vitamin. Studies of the effects of niacin therapy on clinical lipid measures consistently indicate a shift toward a healthier lipoprotein profile with increased HDL-C and decreases in both triglyceride and LDL-C. Despite this favorable shift in lipid profile, cardiovascular outcome studies on patients receiving niacin alone or in combination with statin therapy have resulted in mixed results creating uncertainty of the value of niacin therapy. The proposed study will examine in detail the effects of niacin therapy on lipoprotein composition and function, while also tracking measures of vascular health.

2. Introduction

Despite numerous academic and therapeutic advances, CVD remains the leading cause of morbidity and mortality in developed countries[1]. Clinical strategies for assessment of CVD risk involve the measurement of specific lipoprotein associated lipid levels including low density lipoprotein associated cholesterol (LDL-C), and is positively correlated with disease, and high density lipoprotein associated cholesterol (HDL-C), which is thought to be protective. The statin classes of drugs reduces LDL-C and are the current standard of care for reducing CVD risk, but only decrease cardiovascular events by approximately 30-35%[2]. Thus, even after LDL-C lowering is accomplished with statin therapy there remains significant amount of residual cardiovascular risk. One potential avenue for reducing this residual risk may be through treatments that increase HDL-C. HDL has been demonstrated to possess a multitude of beneficial functions, which likely contribute to its cardio-protective nature. The most extensively studied of these functions is HDL's role in the process of reverse cholesterol transport (RCT), whereby excess cholesterol is removed from peripheral tissues and transported to the liver for excretion. In addition to RCT, HDL also has various antioxidant, anti-inflammatory and vasodilator activities, all of which are thought to contribute to the overall cardio-protective role for HDL [3]. These properties make HDL stand out as the obvious next target for prevention of cardiovascular disease.

While the prospect of raising HDL-C to prevent CVD is enticing, recent clinical trials involving the raising of HDL-C have been largely disappointing. Although a few small molecule compounds, which effectively raise HDL-C are still under development, such as the cholesteryl ester transfer protein (CETP) inhibitors, none of these compounds in early stage clinical trials have shown promise.

The only currently FDA approved drug for raising HDL-C is Niaspan ®. Niacin is a water soluble vitamin found in many foods (meat, fish, fruits and vegetables) and has been shown

to have a favorable impact on plasma lipid measures, increasing HDL-C by as much as 15 to 35%, while at the same time decreasing plasma triglycerides (20-50%) and LDL-C (5-25%). Early clinical studies performed by the Coronary Drug Project on the effects of long term niacin treatment showed beneficial effects on overall mortality in the niacin treated group [4]. The HDL-Atherosclerosis Treatment Study (HATS) combined niacin with statin therapy to determine if any further clinical advantage could be gained by adding a HDL-C modifying agent to the standard of care for LDL-C lowering. This study pointed strongly to a beneficial effect of niacin in combination with Simvastatin. Patients in the Simvastatin-niacin group had a 42% reduction in LDL-C and 26% increase in HDL-C. Additionally, while stenosis progressed by 3.9% in the placebo group, atherosclerotic regression occurred in the combination treatment group and clinical endpoints (e.g. myocardial infarction and death) were reduced from 24% to 3% (placebo vs. Simvastain-niacin) [5]. These beneficial effects were suggested to be a result of a shift in HDL subspecies distribution to include an increase in the level of large α-1 HDL particles, which have been shown to be protective against CVD[6]. However, two recent large clinical trials of niacin, namely AIM-High and HSP2-Thrive have failed to show cardiovascular benefit from using niacin on top of a statin [7,8]. Although these trials have been criticized because of their design [9] they have raised questions about the clinical utility of niacin and HDL-C as a therapeutic target.

Plasma lipoproteins, especially HDL, are highly heterogeneous populations of particles. Within the total HDL pool there are subpopulations of particles with varying protein and lipid compositions. These distinct subpopulations have varying functionality, which are dependent upon their composition, with some being more protective and some less protective against CVD. In addition to their lipid and protein cargo, HDL has recently been demonstrated to carry microRNAs in the plasma and deliver them to specific cell types where they can modulate various functions[10]. The detailed characterization of lipoprotein subpopulations and their functional attributes is still a fairly new area of research and the effect of pharmacologic compounds in this area is largely unexplored. To date, most of the drug development efforts based on HDL have used the cholesterol content of HDL (HDL-C) as its target. Although HDL-C is inversely related to cardiovascular disease based on epidemiologic studies, other composition or functional attributes of HDL may be more closely related to its atheroprotective function and hence a better target for drug development. It may also be that although niacin raises HDL-C, it causes other detrimental changes in HDL that ultimately diminish its ability to protect against cardiovascular disease. A more thorough understanding of how niacin is affecting the composition and functionality of HDL and other lipoproteins would allow us to better predict its clinical utility and may lead to new insights in how to develop future HDL modifying agents.

3. Primary Objectives

- Determine the effect of oral niacin on lipoprotein composition, including but not limited to Lipoprotein Profile (NMR), proteome, lipidome and microRNA cargo.

- Determine the effect of oral niacin on lipoprotein functionality, as measured by ability to efflux cholesterol from cultured macrophage cells.

- Determine the effect of oral niacin therapy on inflammatory status and gene expression in white blood cell populations.

- Correlation of above parameters with vascular health, as assessed by CAVI.

4. Study Design and Methods

4.1 Study Population and Recruitment

This novel pilot study will be carried out at the NIH Clinical Center outpatient clinic 7 in healthy volunteers. We will screen up to 200 subjects, males and females, to obtain at least 32 completed studies. Participants will be recruited via flyer, and/or recruitment advertisement placed in the NIH Record, the NHLBI Recruitment website, the Clinical Center News and by email/listserv.

4.2 Study Procedures

Blood Draw: In addition to Section 8 blood tests listed, subjects will have 4 research blood draws of 10 mL each, stored at -80ºC and analyzed when sufficient samples are accumulated.

Diet & Exercise Assessment: Subjects will also be asked not to change their routine diet or exercise habits, during the study period. A short physical activity assessment will be collected with each visit to review any changes in physical activity.

Cardio-Ankle Vascular Index (CAVI): CAVI is a novel indicator of arterial stiffness. This measurement will be obtained to assess initial stiffness of the arteries and changes during the treatment phase. The test is not invasive and consists of measurement of BP in the four extremities while monitoring ECG by single lead and the heart sound.

4.3 Study Visits

There will be up to 5 visits for this study. The return visits can be delayed up to two weeks, if there are scheduling problems. The first study day will be the screening and baseline followed by three additional visits coinciding with study landmarks. The study will be discussed in detail with interested subjects. Any procedures needed to assess eligibility (i.e. blood laboratory tests, pregnancy test) will be performed after obtaining informed consent.

Visit 1: At the first visit (screening and baseline), the subjects will be consented, and have a diet and exercise assessment to determine their nutritional status and a physical examination. The subject will have vital signs and Body Mass Index measured, and will undergo a history and physical examination. During this visit, fasting screening and baseline laboratory tests and a pregnancy test for female subjects of childbearing potential will be obtained. In

addition, 10 mL of blood will be stored for research tests. At the end of the first visit, if the subject is not yet excluded from the study, a Cardio-Ankle Vascular Index (CAVI) test will be performed. Once eligibility is confirmed, subjects will receive a 4 week supply of the dietary supplement of Extended Release Niacin (purchased by the NIH CC pharmacy through its vendors such as Rugby/Watson or Major; 250 mg, 500mg or 1000mg/capsule) and will be instructed to take 500 mg/day for the first seven days and then increase to 1000 mg/day, which may be taken bid and/or with other dosing flexibility) during the following 7 days.

Re-screening Visit as applicable: Repeat laboratory values, including baseline research blood, may be needed to reassess eligibility within 40 days of a screening failure. If a subject is found ineligible, during or after the first visit, the 10 mL of research blood will be discarded.

Visit 2: Two weeks after the first visit (+/- 2 weeks) the subjects participating in the niacin supplementation portion of the study will return for their second visit. The subject will have vital signs and Body Mass Index measured and undergo a brief physical examination. Fasting blood will be collected for laboratory and pregnancy tests (in female subjects of child bearing potential) and 10 mL of blood will be stored for research tests. At the end of the 2nd visit, the subjects will be escalated to 2000 mg/day (which may be taken bid and/or with other dosing flexibility) extended release niacin for an additional 14 weeks.

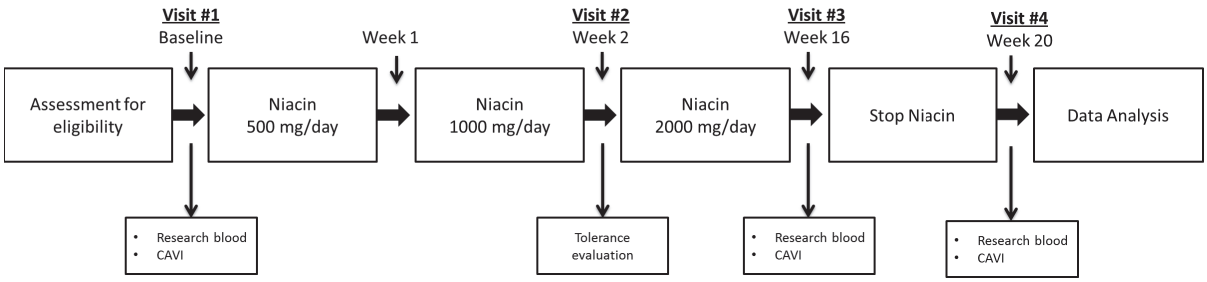
Visit 3: The third visit will occur 16 weeks (+/- 2 weeks) after starting niacin supplementation. At this visit, the subject will be given a diet and exercise assessment, a repeat CAVI test, and a brief physical examination. A nurse will take the subject's vital signs and Body Mass Index and fasting blood will be collected for laboratory testing, and 10 mL of blood will be stored for research. At the end of the 3rd visit, the subjects will be instructed to discontinue niacin supplementation.

Visit 4: The fourth, and final, visit will occur 4-6 weeks after stopping niacin supplementation. A two weeks window extension may be used to accommodate for scheduling problems. At this visit, the subject will be given a final diet and exercise assessment. A nurse will take the subject's vital signs, Body Mass Index measured, and will undergo a brief physical examination and fasting blood will be collected for laboratory testing, and 10 mL of blood will be stored for research. A repeat CAVI test will be performed.

Subjects will be encouraged to complete the seven day food record prior to the first and third study visits, in order to facilitate the nutritional and exercise assessment. However, if the subject does not complete, or only partially completed the seven day food record, the nutritional and exercise assessment will still take place and it will determine any changes in life-style.

Note: The slow increase in niacin dose is standard practice and has been found to minimize the incidence and severity of potential adverse events, which usually only occur in the first few days of niacin administration. Should a subject require additional time to adapt to the dose schedule, they will be allowed to continue to take the current dose for no greater than 2 weeks beyond the scheduled dosing period and their return date for next visits will be adjusted accordingly and will not be considered a protocol deviation or AE.

Fig 1. Study design



5. Subject Eligibility

5.1 Inclusion Criteria

- Males and females who are at least 18 years of age at time of enrollment.
- Subject understands the investigational nature of the study and provides written, informed consent.

5.2 Exclusion Criteria

- Subjects taking any lipid modification therapy, including but not limited to statins, fibrates and bile acid sequestrants.
- Subjects taking fish oil or any other supplements, which in the investigator's opinion may interfere with the study.
- Subjects with acute liver disease or active peptic ulcer disease.
- Subjects with elevated uric acid levels (>10mg/dL) or gout
- Pregnancy or women currently breastfeeding.

- Female subjects taking hormonal contraceptives or hormone replacement therapy may be included in this study only if they have been on a stable dose for at least 3 months.

- BMI less than 18.5

- Subjects with weight that varies greater than 20% over the past 3 months.

- Subjects taking the following medications for at least six weeks, which may interfere with the study, will be excluded: BAS, antibiotics, anticoagulants, anticonvulsants, antiarrhythmic, Cyclosporine, Mycophenolate and Synthroid. Subjects with chronic diarrhea, gastric bypass or lap band procedures, ostomies, bowel motility problems, or other conditions that could affect intestinal fat absorption.

- Subjects initiating new medications or patients on multiple medications may also be excluded.

- Inability to swallow capsules

- Patients with a history of type I or type II diabetes or HbA1c > 6.5%.

- Volunteers may also be excluded, if in the opinion of the study investigators, they have some other condition or disorder that may adversely affect the outcome of the study or the safety of the volunteer.

6. Pharmaceuticals

6.1 Study Agent Information

Product Name: Niacin Extended Release

Supply: Commercially available

Product Description: Extended Release Niacin (purchased by the NIH CC pharmacy through its vendors such as Rugby/Watson or Major.

Storage: Room temperature (20 to 25°C or 68 to 77°F)

Route of Administration: Oral

Toxicities: None known

Stability: Each lot is dated to three years expiration

Preparation: Rugby Extended Release Niacin is an oblong, green-clear-yellow capsule for oral administration and is available in 250 mg capsules. The capsules also contain the inactive ingredients sugar, shellac, gelatin, cornstarch, talc, turmeric, riboflavin and the following coloring agents: FD&C green #3 and FD&C yellow #6. Any other substitute Niacin Extended release will have similar or comparable inactive ingredients.

6.2 Dosing Instructions

The assigned dosing is consistent with earlier clinical trials. To minimize impact of the common side effect of flushing, subjects may be instructed to take niacin with a small snack prior to going to sleep. At each study visit, subjects will be given enough niacin to last them until their next visit plus an additional two weeks to allow for continuation of supplementation in the event of scheduling issues.

6.3 Study Agent Compliance

The subjects will be instructed to return remaining capsules, in original containers, to NIH at each applicable study visit for a pill count. Between visits a member of the clinical trial team may contact subjects to monitor compliance and any side effects, and to provide any additional study information, answer questions, and motivate participants.

Participants may receive a *Don't Forget! Instructions and Study Schedule* information sheet to help keep track of when they should begin taking the study drug, the time and date of schedules appointments, and when to complete the seven day food record, which also has instructions.

6.4 Regulatory Status

Whether an IND is needed for a clinical investigation evaluating a dietary supplement is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required.

7. Research Laboratory Methods

Approximately 40 mL of fasting blood samples will be collected at each visit and used to perform the following routine clinical laboratory tests: Electrolytes, Lipid Panel, Lipoprotein Profile analysis by NMR, liver function tests (AST, ALT, bilirubin), ApoA-I, ApoB, Thyroid Panel, uric acid, creatinine kinase, hs-CRP, HbA1C, and insulin. In addition, we may perform tests for leptin (research), adiponectin (research) and other lipid and lipoprotein metabolism related markers (research). In addition, approximately 10 ml of research blood will be used or stored for future testing related to lipoprotein metabolism. Routine diagnostic tests will be performed in the Department of Laboratory Medicine on the second floor of building 10 in the Clinical Center (CC). The following research tests may be done in the Lipoprotein Metabolism Section's laboratory: lipoprotein distribution will be assessed after

separation by FPLC and HDL and LDL sub-fraction analysis may be done on a BioAgilent Analyzer in the Lipoprotein Metabolism laboratory. FPLC isolated lipoproteins may be analyzed for miRNA content and protein and lipid content by chemical assays and mass spectrometry. *In vitro* cholesterol efflux experiments may also be performed. The following research tests may be performed by the Center for Human Immunology, Autoimmunity and Inflammation on the seventh floor of bldg. 10: RNA expression by microarray, flow-cytometry phenotyping of white blood cells, and measurement of plasma cytokines. For any future research in stored samples not described above we will request NHLBI IRB approval.

8. Listing of tests that may be used on this research

Clinical laboratory tests:

- Liver function test (ALT, AST, bilirubin)
- Uric acid
- Creatinine
- Creatinine kinase (CK)
- Insulin
- Fasting glucose
- Pregnancy testing

Clinical lipid and lipoprotein related tests:

- Lipid Panel (Total cholesterol, LDL-C, HDL-C, Triglyceride)
- Lipoprotein Profile (NMR)
- ApoA-I
- ApoB
- Hs-CRP
- HbA1C
- Alpha-1-antitrypsin

Other research tests:

- Leptin
- Adiponectin
- Other lipid and lipoprotein metabolism related markers
- FPLC lipoprotein lipid profiles
- Proteomics/Lipidomics analyses of lipoprotein subfractions
- In vitro cholesterol efflux assay
- RNA expression by microarray
- Flow cytometry phenotyping of white blood cells
- Measurement of plasma cytokines
- Cardio-Ankle Vascular Index (CAVI)

- Endothelial function assay

*Standard of care laboratory tests and procedures not listed above may be requested and will not be used for this research but will only be used to evaluate or elucidate the patients' health condition as specified on item 5.2.

9. Sample Collection, Storage, and Data Management

INTENDED USE OF THE SAMPLES/SPECIMENS/DATA

Samples and data collected under this protocol may be used to study changes in lipids, and lipoproteins that may help reduce high cholesterol levels in subjects and could be used in conjunction with other therapies available. No DNA genetic testing will be performed.

HOW SAMPLES/SPECIMENS/DATA WILL BE STORED

Samples will be stored at -80C freezers on the 2nd floor of building 10 in the Department of Laboratory Medicine or at -80C freezer (freezer 2) on the 8th floor of building 10 in the Department of Lipoprotein Metabolism Section, following current NIH sample storage guidelines. Access to research samples will be limited, using a locked freezer. Samples and data will be stored, using codes assigned by the investigators or their designee(s). Data will be kept on the NHLBI P: drive, accessible through password-protected computers. Only the members of the research team will have access to the samples and data.

All human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability, eligibility and consent verification will be recorded in and stored in a secured NIH drive. Primary data obtained during the conduct of the protocol will be kept in secure network drives that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual participant.

HOW SAMPLES/SPECIMENS/DATA WILL BE TRACKED

Research samples will be stored using BSI in accordance with NHLBI DIR Biospecimen policy.

WHAT WILL HAPPEN TO THE SAMPLES/SPECIMENS/DATA AT THE COMPLETION OF THE PROTOCOL?

At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol or a repository.

WHAT CIRCUMSTANCES WOULD PROMPT THE PI TO REPORT TO THE IRB LOSS OR DESTRUCTION OF SAMPLES/SPECIMENS/DATA

The NIH Intramural Protocol Violation definition related to loss of or destruction of samples (for example, due to freezer malfunction) will be followed in reporting to the IRB.

Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) will be reported to the IRB.

Transmission of Data to Outside Investigators:
Collaborator, Tomas Vaisar, Ph.D., with the University of Washington Diabetes Institute, will receive aliquots of human serum collected from subjects taking the lipid altering vitamin niacin. High density lipoprotein (HDL) will be isolated from the serum and then used for an in vitro assay to determine HDL's influence on endothelial cell function. The samples will be coded and sent to collaborator following a fully executed MTA.

10. Monitoring of Subjects and Criteria for Withdrawal of Subjects

10.1 Stopping Rules for Subjects (off-study criteria)

- Ineligibility to start the niacin supplementation portion of the study
- Pregnancy
- Development of hyperuricemia (male >8.6 mg/dL, female >5.8 mg/dL) with clinical symptoms or an absolute laboratory value >10 mg/dL
- Development of diabetes (HbA1c > 6.5%)
- Development of hyperuricemia (men > 7 mg/dL; women > 6 mg/dL).
- Severe gastrointestinal discomfort
- Subjects taking less than 2/3 of the niacin pills **or** not taking the pills for 7 consecutive days.
- Any other severe symptoms related to niacin supplementation and as determined by contact with the physician.
- On study onset of any of the exclusion criteria listed above (Section 5.2)

Routine clinical laboratory data will be reviewed after each study visit and the study will be discontinued, if it is observed that niacin is associated with any significant change in liver panel (indicated by > 3-fold increase above baseline in ALT or AST), electrolyte profile (at

discretion of observing physician), or sustained muscle aches (Grade 2, according to CTCAE 4.03 criteria).

11. Analysis of the Study

The primary outcome measurements of this study are changes in protein or lipid composition of any lipoprotein fraction and changes in vascular compliance as measured by CAVI.

11.1 Sample Size Determination

With a sample size of n = 32 completed studies, the study will have 80% power to detect a 15% change in plasma HDL cholesterol levels between the baseline and niacin treatment periods, using a normal approximation to the one-sample (paired), two-sided t-test at alpha = 0.05. A standard deviation of 15 mg/dL was assumed for the paired differences in plasma cholesterol levels between the baseline and final treatment period. Since up to a 30% subject attrition is expected, a minimum of n = 48 subjects will be recruited for the study.

11.2 Statistical Analysis

Descriptive statistics (mean, standard deviation, minimum, maximum, and median) will be calculated for all variables. All response variables will be assessed for conformance to the normal distribution and transformed as needed to meet the assumptions of normal distribution and homogeneity between periods. If necessary, non-parametric analyses will be performed.

The analysis of the data will investigate the effects of niacin in the plasma cholesterol levels of the pooled genders primarily, but the effect in male and females may also be analyzed separately.

Food records will be analyzed, using the Nutrition Data System for Research (NDSR) software developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN[11].

12. Human Subject Protection

12.1 Rationale for Subject Selection

Subjects of both genders will be considered for inclusion in this study. There will be no racial, ethnic, or gender discrimination. Cognitively impaired and institutionalized persons will not participate in this study. Criteria for exclusion or withdrawal from the study are based on the presence of other disease processes that may interfere with the interpretation of our results or situations that may be harmful to the health of subjects.

"Recruitment, enrollment and compensation of NIH employee subjects will be consistent with NIH Manual Chapter 23s00-630-3" Leave Policy for NIH Employees".

12.2 Rationale for the Exclusion of Children

Children under 18 years of age will not be considered for inclusion in this study due to increased potential for liver toxicity.

12.3 Rationale for the Exclusion of Pregnant Women

Subjects must not be pregnant or actively seeking pregnancy in order to participate in this study. Pregnancy may introduce unpredictable effects on lipoprotein metabolism and influence the results of the study. The specific effects of pregnancy in this context may be the subject of a separate study. Some form of contraception must be used by subjects while enrolled. Contraception use will be determined by a questionnaire given to the subjects at time of enrollment.

12.4 Inclusion of NIH Staff

- NIH staff (employees, NIH contractors, special volunteers, guest researchers, and trainees) may voluntarily participate in this protocol.

- Recruitment, enrollment and compensation of NIH employee subjects will be consistent with the Guidelines for the Inclusion of Employees in NIH Intramural Research Studies (December 2015) (SOP 14F, Appendix A) and NIH Policy Manual Chapter 2300-630-3,"Leave Policy for NIH Employees Participating in NIH Medical Research Studies" (SOP 14F, Appendix B)

- If the individual requesting to participate in the protocol is a co-worker, the consent from the NIH staff member (co-worker) will not be obtained by the staff member's direct supervisor but by another research staff member approved for obtaining informed consent and who is also not a co-worker.

- Neither participation nor refusal to participate as a subject in this protocol will have an effect, either beneficial or adverse, on the participant's employment or position at NIH.

- The consenting staff member will make the NIH Information Sheet on Employee Research Participation available to staff members who are considering enrolling in research. (SOP 14F, Appendix C)

- Staff subjects' privacy and confidentiality will be respected by protocol and consenting staff the same as for all subjects participating in research protocols. However, all subjects will be made aware that there are limits to these protections.

12.5 Evaluation of Benefits and Risks/Discomforts

As of July 10, 2019, this study is now closed to new subject accrual and continues in data analysis only and the level of risk is minimal.

Benefits:

There are no direct benefits to the patient, however, increasing HDL-C and decreasing LDL-C and triglyceride levels in the general population is thought to be beneficial [23].

Subjects will be provided information from routine clinical laboratory tests.

Risks/Benefit Analysis:

Risk (45 CFR 46.406): Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the condition or disorder under study.

Study Agent: One drawback of niacin supplementation is the common occurrence of side effects, such as flushing and itching of the skin. These are experienced by most patients to varying degrees may result in poor adherence to niacin regimens but these side effects have not been shown to lead to serious medical problems. To overcome this side effect an extended release form of niacin will be employed and extensive guidance will be given to each subject on the best times and forms to take the supplement to minimize these side effects. Other side effects may include myositis and changes in liver enzymes, which will be monitored at each visit.

Blood Draw: Subjects may feel lightheaded or dizzy after having blood drawn. There may be pain at the blood draw site and a slight risk of bruising. To minimize this risk, the routine blood-drawing protocol will be followed and pressure will be applied to the site.

The protocol will follow the NIH Clinical Center MAS policy M95-9 guidelines for limits of blood drawn for research purpose in the Clinical Center. For adults, no more than 10.5 mL/kg or 550 mL, whichever is smaller, will be drawn for research purposes over any 8-week period.

Cardio-Ankle Vascular Index (CAVI): Inflation of blood pressure cuffs may cause transient discomfort. Subjects with fragile skin may suffer minor trauma (as per ABIs, related to usual BP measurements). This procedure involves the use of a VaSera VS-1500N system; an FDA approved vascular screening system.

12.6 Protocol Consent Processes and Documents

Each subject will receive an oral and written explanation of the goals, procedures, and risks of this study. The Principal Investigator and those Associate Investigators who are listed on the cover page of the protocol with an asterisk next to their name may obtain informed consent from research participants. Consent will be obtained at the NIH Clinical Center.

The original, signed informed consent document will be placed in the medical record, and the subject will receive a signed copy of the informed consent document. A copy will also be placed in the shadow chart. A member of the protocol team will be available to answer questions about the study to be performed.

12.6.1 Consent Processes for NIH Employees

If the individual requesting to participate in the protocol is a co-worker, the consent from the NIH staff member (co-worker) will not be obtained by the research coordinator or the employee's direct supervisor but by another research staff member who is approved for obtaining informed consent, and who is also not a coworker.

12.6.2 Consent Processes for non-English Speaker

If there is an unexpected enrollment of a non-English speaking research participant for which there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document.

We request prospective IRB approval of the use of the short form for up to a maximum of 5 participants in a given language and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form. Should we reach the threshold of 5, we will notify the IRB of the need for an additional use of the Short Form and that we will have that consent document translated into the given inherent language.

13. Conflict of Interest

None of the investigators have any conflict of interest to report.

14. Adverse Event Management

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. Adverse events will be attributed (unrelated, unlikely, possibly, probably or definitively) to study medication and/ or disease and AEs will be graded by severity utilizing CTC version 4.0. A copy of the criteria can be downloaded at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All adverse events occurring during the study, including those observed by or reported to the research team, will be recorded.

14.1 Reports to the IRB

The PI or designee will refer to HRPP Policy 801 "Reporting Research Events" and HRPP 802 "Non-compliance in Human Subject Research" to determine IRB reporting requirements and timelines.

14.2 Reports to the CD

The PI or designee will refer to NHLBI DIR guidelines to determine CD reporting requirements and timelines.

15. Data and Safety Monitoring Plan

Safety Monitoring

Principal Investigator: Accrual and safety data will be monitored by the PI. The protocol will be continuously evaluated for any unusual or unpredicted complications with the aim of detecting and preventing unacceptable increase in morbidity and mortality over and above that anticipated from niacin.

NHLBI IRB

Accrual and safety data will be monitored and reviewed annually by the Institutional Review Board (IRB). Prior to implementation of this study, the protocol and the proposed patient informed consent document will be reviewed and approved by the properly constituted IRB operating according to the 45 CFR 46 Code of Federal regulations. This committee must approve all amendments to the protocol or informed consent document, and conduct continuing annual review so long as the protocol is open to accrual or follow up of subjects.

16. Compensation

Compensation will be provided to the subjects for their time and inconvenience of participating on this protocol based on the values listed below. Compensation of NIH staff participants will be consistent with the NIH Manual Chapter 2300-630-3: Leave Policy for NIH staff.

Procedures	Inconvenience Unit	$	Frequency	Total $$
Outpatient Visit (first hour)	2	$20	Up to 5	$100
Outpatient Visit (additional hours up to 4 hours)	1	$10	Up to 5	$200
Physical Examination	1	$10	5	$50
Screening Blood Draw	1	$10	Up to 2	$20

Research Blood Draw	1	$10	4	$40
Diet & Exercise Assessment	1	$10	3	$30
CAVI	2	$20	3	$60
Total potential compensation:				$500

Subjects will receive partial compensation (one third payment) if they participate up to at least the second outpatient visit but will receive full compensation after only completing the entire study. Subjects that fail to complete the study return for the second outpatient visit for reasons independent of their control (i.e. medical reasons, unplanned pregnancy) will also receive partial compensation. In cases where screening failure is independent of subject will (laboratory values), then compensation will be given to the subject for the tests performed and will be calculated based on the table above.

17. References

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18. APPENDIX A: NIH INFORMATION SHEET ON STAFF RESEARCH PARTICIPATION (April 2016)

As an NIH employee, contractor, Special Volunteer, Guest Researcher, or trainee, you may participate in intramural research studies unless it is prohibited by your Institute or Center (IC), or if you are excluded by the criteria of the protocol in which you want to enroll. The inclusion of NIH staff in a particular protocol must also be approved by the IRB. You may be motivated by altruism, a commitment to research in your own or related fields, or want access to clinical trials of potential direct therapeutic benefit. When deciding, you should make an informed decision about participation. This information sheet offers some points to consider for NIH staff who are considering research participation at NIH.

First, similar to any individual who is considering research participation, you should seek adequate information about the study purpose, what is required of you in terms of procedures, interventions and time, and the potential risks and benefits of participation.

For more information, see the NIH Clinical Center's public website "Are Clinical Studies for You?" at http://www.cc.nih.gov/participate/studies.shtml.

When you are thinking about participation in a research study that is being conducted by your supervisor, or others with whom you work closely in your laboratory, branch, or unit, you should consider some additional factors:

A. Possible bias: Are you confident that you can be unbiased about reporting answers, side effects, or other information that could influence the study outcome or risk to you?

B. Confidentiality: Has the principal investigator (PI) spoken about what information will be collected from you as part of the study? Has the PI discussed what information will be available to those within, and outside, the study team? If applicable, are you comfortable sharing your medical history (including, for example, mental health history or STDs) and your social history (e.g. substance use) with study investigators who may be your coworkers, or with the possibility of them discovering something about your health during the study (e.g. pregnancy status or a new diagnosis)? Although every effort will be made to protect your information and keep it private and confidential, your information may, depending on the nature of the protocol, become available in medical records or to authorized users outside of the study team. Discuss any concerns with the PI.

C. Pressure: Do you perceive any pressure or expectations from your supervisor or colleagues regarding participation? Could that pressure influence your decision or make it difficult for you to choose whether or not to participate? Remember that it is your choice whether or not to participate and that your decision to participate or not should not have an effect, either beneficial or adverse, on your position at NIH.

D. Time and Compensation: Can you take time off from work to complete the study requirements or participate solely during non-duty hours? Can you receive compensation for your participation in this study? Will your supervisor give you permission to participate during work hours? See the NIH Policy Manual 2300-630-3 “Leave Policy for NIH Employees Participating in NIH Medical Research Studies.”

E. Consent Process: Is the person obtaining your consent for the study your supervisor, a subordinate, or co-worker? If so, is there an independent person monitoring the consent process? If the study PI is a supervisor and intends to obtain consent from you, an independent person (e.g., through Bioethics or the NIMH Human Subjects Protections Unit [HSPU], or others as approved by the IRB) must monitor the consent process. If the person obtaining consent from you is a co-worker then an independent person (e.g., through Bioethics or the NIMH HSPU, or others as approved by the IRB) may be required to monitor the consent process, as determined by the IRB for the specific study.

If you are thinking of enrolling as a subject at the NIH Clinical Center and you have any questions or concerns, please contact the Office of Human Subjects Research Protections (OHSRP) at 301-402-3444 and/ or the Patient Representative if you are thinking of enrolling as a subject at the NIH Clinical Center on 301-496-2626. If you are at a NIH site outside the Clinical Center then please contact local site leadership.