Systems Biological Assessment of Statin Effect on Vaccine Responses
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PROTOCOL TITLE: Systems Biological Assessment of Statin Effect on Vaccine Responses

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**Please note that [redacted] will not be engaged in human subjects research.*

VERSION: 2.0

FUNDING SOURCE: Internal fund

REVISION HISTORY

Revision #	Version Date	Summary of Changes
2.0	11Oct2023	- Specified that for the memory aid, participants will have an option between online survey or paper form - Clarified that clinical labs will be collected at baseline for all participants and that these may be repeated at investigator discretion

Table of Contents

1. Study Summary

Project Title	Systems Biological Assessment of Statin Effect on Vaccine Responses.
Project Design	Longitudinal cohort study in which participants will receive either 8 weeks of statin therapy and a seasonal quadrivalent influenza vaccine (QIV) or a seasonal quadrivalent influenza vaccine (QIV) alone. Immune responses in the blood will be assessed.
Primary Objective	Compare the antibody (Ab) response to QIV in statin recipients and non-recipients.
Secondary Objectives	Assess the safety profile of statin therapy + QIV v/s QIV alone.
Exploratory Objectives	• Explore the effect of statin therapy on immune signatures after vaccination. • Evaluate the effect of statin therapy on plasma cytokine responses to vaccination.
Research Intervention(s)/Interactions	Initiation of 8 weeks of statin therapy and immunization with a single dose of seasonal QIV.
Study Population	Healthy adults (age 18 to 50 years) without history of statin use and without current receipt of seasonal influenza vaccine or recent influenza infection.
Sample Size	N=30 in the Statin + QIV arm. N=30 in the QIV alone arm.
Study Duration for individual participants	8 months.
Study Specific Abbreviations/ Definitions	Ab –antibody QIV – seasonal quadrivalent influenza vaccine
Funding Source	Hope Clinic Internal funds

2. Objectives

Primary Objective:
Compare the antibody (Ab) response to QIV in statin recipients and non-recipients.

Secondary Objective:
Assess the safety profile of statin therapy + QIV v/s QIV alone.

Exploratory Objectives:

1. Explore the effect of statin therapy on innate immune signatures to QIV.
2. Evaluate the effect of statin therapy on plasma cytokine response to QIV.

3. Background

Statins are widely used for their lipid-lowering and cardiovascular protective effects[1]. Additional research has shown that statins can be anti-inflammatory, and play a part in modulating the immune system[2-4]. These effects are called into action in events such as pneumonia[5], influenza[6,7], and sepsis[8].
Statins decrease cholesterol synthesis by inhibiting the enzyme HMG-CoA reductase. This results in the activation of the SREBP pathway which promotes cholesterol uptake and synthesis[9]. One study investigated the role of SREBP signaling in B cell responses using a mouse model. It was demonstrated that SREBP inhibition decreased gene activation involved in lipid metabolism and fatty acid synthesis which is essential for antibody production. This resulted in a decrease in B cell differentiation to plasma cells and a deficiency in production of high-affinity antibodies[10].

Studies evaluating the effects of statins on the immune system's response to the influenza vaccine have provided mixed results. Many studies have shown that chronic statin therapy negatively influences the influenza vaccine's efficacy, with titer levels markedly lower than in statin nonusers[11]. Other researchers showed that statin therapy may only partly alter the immune response to the influenza vaccine against some strains, while the protection against other strains remained intact[12]. Another study involving a large population of statin users and statin nonusers, found that statin users had lower influenza vaccine effectiveness against acute respiratory illness than nonusers[13]. However, other retrospective cohort studies found that the difference in vaccine effectiveness between statin users and nonusers was not significant and did not translate into a difference in the clinical course of the disease[14,15].

One study compared the gut microbiota in statin users and statin non users. The results proved that statin therapy significantly lowered the prevalence of gut microbiota dysbiosis. The reshaping of the microbiota to limit potentially harmful bacteria and increase beneficial bacteria, as well as the increase in gut microbiota diversity may contribute to a better vaccine response[16]. In fact, Oh et al. conducted a study on influenza vaccine which showcased the role of the microbiota in boosting vaccine immunity. The findings prove that the microbiome is one of the factors contributing to the effectiveness of vaccines[17].

Systems vaccinology involves applying systems biology principles to the field of vaccinology with a view to predict vaccine efficacy. Our objective is to identify molecular signatures or patterns of gene expression that are altered after the use of chronic statin therapy and analyze the innate and adaptive immune mechanisms responsible for this effect[18].

4. Study Endpoints

Primary Endpoint:
Magnitude of antibody responses to QIV at 29 days after vaccination in each study group.

Secondary Endpoint:
Frequency and severity of adverse events until Day 29 and serious adverse events until D181 after vaccination in each study group.

Exploratory Endpoints:

1. Identification of innate immune signatures until 7 days after vaccination that predict the magnitude and durability of Ab response Days 29, 91 and 181after vaccination in each study group.
2. Plasma cytokine response until 7 days after vaccination in each study group.

5. Study Intervention/Investigational Agent

5.1 Description

Atorvastatin therapy
Atorvastatin is a lipid-lowering agent of the statin family that functions by blocking a rate-limiting enzyme, HMG-CoA reductase, in the lipid metabolism. This agent is commonly used for primary and secondary prevention of dyslipidemia. Participants will be asked to take Atorvastatin 80 mg daily at night, for 4 weeks prior to the vaccination and continue the statin therapy for 4 weeks after vaccination.

The 80mg dose of atorvastatin allows for evaluation of the immunologic effects of statin medication with a short duration of therapy prior to vaccination. Studies have shown that 80mg of atorvastatin for 1 month affects inflammatory responses while lower doses of statin for longer periods may not. The 80mg dose reduced inflammation related to including NF-kB while other studies looking at lower doses of statin for 3 months did not find a difference in NF-kB[19]. Observational studies have investigated the dose-response question for statin therapy and vaccine effect but they either had insufficient sample size for that question[20] or there was a trend toward lower vaccine efficacy with higher dose statin, though this was not statistically significant[21].

Quadrivalent seasonal influenza vaccine
The FDA-approved quadrivalent seasonal influenza vaccine contains four distinct strains: two influenza A viruses and two influenza B viruses. The approved seasonal QIV will be purchased from the manufacturer to be given for each season of influenza.

5.2 Drug Handling

Atorvastatin and QIV will be stored at the Emory Investigational Drug Service (IDS) per the manufacturer's instructions. It will be prepared by an IDS pharmacist on site at the Hope Clinic satellite IDS. Logs of receipt, temperature, maintenance, and disposal will be maintained in the study file.

The Atorvastatin therapy will be dispensed by a study coordinator, nurse or provider at the Hope Clinic with clear instructions on how and when to take the pills. Participants will be instructed to contact the clinic staff immediately if they develop concerning symptoms following the administration of the drug.

QIV will be administered by a study nurse or provider at the Hope Clinic as a single 0.5mL intramuscular injection in the deltoid muscle.

5.3 Accountability Procedures for Study Products

The IDS pharmacist will maintain accurate drug accountability logs which will be kept at the IDS pharmacy until the completion of the study. Upon completion of the study, a final drug accountability will be done. Following the completion of the drug accountability, the original copies of the logs will be maintained. When the vaccine is administered to a participant, the date, time and location of the injection will be recorded in the participant's study source documentation records.

6. Procedures Involved

For a schedule of procedures, see Appendix A.

6.1 Screening and Consenting (D-60 to D-32)

6.1.1 Potential participants interested in the study study will respond to study ads. Recruiters from the Hope Clinic will then contact them for a telephone screening, during which the research study will be explained in lay terms and eligibility criteria will be reviewed. If all eligibility criteria are met and the participant remains interested, an in-person screening appointment will be scheduled. Prior participants in other studies conducted at the Hope Clinic, and who had indicated their willingness to participate in other studies may also be contacted for a telephone screening visit.

6.1.2 At the in-person screening appointment , study staff will review the informed consent form with the participant and will answer all questions related to the study. Once the participant signs the informed consent, they will be assigned a unique study participation number. The following procedures will be performed:

- Recording of demographic information and review of medical history including recent influenza infection, including current medication use (medications that may interact with Atorvastatin) and vaccination history (previous receipt of influenza vaccines).
- Vital signs and targeted physical exam as indicated based on review of participant health status.
- A urine pregnancy test will be performed if the participant is a woman of child-bearing potential.
- Blood sample collection for baseline immunological assays and baseline clinical labs. Clinical labs may be repeated at investigator discretion.

6.1.3 Participants who remain eligible for the study will be randomized to either Statin therapy + QIV arm or QIV alone arm. Participants randomized to the Statin therapy+ QIV arm will receive the Atorvastatin pills with clear instructions on how to use them in a separate visit.

6.1.4 Clinical staff wil provide participants with a stool collection kit along with an information sheet explaining how the stool collection is done. The steps will be explained to the participant who will be asked to provide a stool sample on D-31, D1, and D29.

6.2 Initiation of Statin therapy (D-31 to D-29)

Participants randomized to the Statin + QIV arm will be asked to come back to the Hope Clinic for an extra visit one month prior to date of vaccination. The following procedures will be performed:

- Review of interim medical history for any updates or changes.
- Review of concomitant medications for any updates or changes.
- Recording of vital signs and targeted physical exam if indicated.
- Blood sample collection.
- Stool sample collection.
- Re-verification of eligibility criteria.
- Completion of prescription form by licenced provider and dispension of Atorvastatin 80mg by the pharmacy at the clinic.
- Distribution of the drug to participant by study coordinator or nurse or provider with clear instructions on modalities of administration of the drug and common side-effects.

6.3 Phone call (15 days after initiation of Statin therapy)

Fifteen days after initiation of Atorvastatin therapy, the study staff will call participant to assess participant compliance and any complications due to the drug. If needed, the participant will be asked to come to clinic for further assessment. The call will last approximately 15 minutes.

6.4 Vaccination Visit (D1)

The following actions will be performed on the day of vaccination:

- Review of inclusion and exclusion criteria to confirm eligibility.
- Review of medical history, concomitant medications and vaccinations.
- Collection of vital signs.
- Completion of a targeted physical exam if needed.
- For participants of child-bearing potential, a negative urine pregnancy test is required.
- For the statin therapy group, participant compliance to the drug will be assessed.
- Blood samples for immunologic assays will be collected prior to vaccination
- Stool sample collection
- Participants will receive the CDC influenza vaccine information sheet and review it prior to vaccination.
- Participants will then receive QIV via the intramuscular route, administered by a clinical research nurse or provider.
- Participants will be observed for a minimum of 15 minutes for any immediate hypersensitivity reactions.
- Participants will be asked to fill a memory aid for 7 days after vaccination. Participants will have the option of an online survey or paper memory aid.

The visit will last approximately 60 minutes.

6.5 Follow-up Visits (D2, D4, D8, D15, D29, D91, D181)

All participants will return for follow-up visits following vaccination. During these visits, study personnel will:

- Review the participant's current health status.
- Note any changes in health history since the screening visit, including current medication use and vaccination history.
- Collect blood samples for immunological assays.
- Review memory aid until Day 8.
- Record adverse events until Day 29.
- Record serious adverse events until D181.

The visit will last approximately 30 minutes.
Participants will be asked to provide a stool sample on D29 in addition to the above described procedures.

7. Statistical Analysis Plan

This is an exploratory, non-placebo controlled analysis of immune responses obtained from blood samples. This will provide us with descriptive data to analyze immune responses.

Analysis of Primary Endpoint: Magnitude of antibody responses to QIV at 29 days after vaccination in each study group.

Analysis of Secondary Endpoint: Frequency and severity of adverse events until Day 29 and serious adverse events until D181 after vaccination in each study group.
Descriptive analysis, e.g. tables and histograms, will be conducted to present severity of all AEs. The frequency will be tabulated. Ad hoc analyses of correlations of reactogenicity events with innate and adaptive immune responses may be conducted.

The study staff will aim to enroll 30 participants in each of the statin therapy+QIV and QIV alone arms.

8. Data and/or Specimen Banking

Particiants will be asked for permission for the principal investigator to keep any remaining (residual) specimens derived from venous blood collection for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria. Future use samples/specimens will not be sold or used directly for production of any commercial product. These samples/specimens are protocol-required; thus, participants must agree to future use of these samples/specimens as a condition of their study participation.

These samples/specimens will be stored at the Hope Clinic and shipped regulary to [redacted] lab at Stanford and other collaborating labs. The de-identified (all personal identifying information of the participant will be removed) samples/specimens will be labeled and stored in freezers at -80°C or in liquid nitrogen tanks.

In keeping with NIH policy on scientific data sharing, gene expression (RNA sequencing) data and immunological assay results will be made publicly available through public database deposition and peer-reviewed publication. Participants will be fully de-identified (i.e., disseminated data will not contain direct identifiable information). Demographic data (e.g., age, race and/or ethnicity, sex/gender) associated with participants will be kept strictly separate from all experimental results, including gene expression data. This practice has become standard to protect participant privacy.

9. Sharing of Results with Participants

Laboratory results

Immunologic assay or omicsresults will not be reported to participants as these are intended for research purposes only and therefore cannot be reported to patients per Clinical Laboratory Improvement Amendment (CLIA) regulations.

The results from safety laboratory tests conducted prior to statin therapy can be shared with participants.

Incidental findings
Incidental findings that appear in the results of the safety labs drawn will be disclosed and explained to the participant by the study investigator, who will provide a referral to the appropriate clinical specialist and information on how to obtain health insurance to secure treatment if needed. The study investigator will also send a message to the participant's primary care provider requesting follow-up with the participant if the participant authorizes this and provides relevant contact information.

10. Study Timelines

Individuals will participate in this study for a total of 8 months. Recruitment of all participants will require 24 months. The study and data analysis should be concluded within 48 months of start date.

11. Inclusion and Exclusion Criteria

Inclusion Criteria
1. Able to understand and give informed consent.
2. Age 18-50 years.
3. Women of child bearing potential must agree to use effective birth control for the first 3 months of the study. A negative urine pregnancy test must be documented prior to vaccination.

Exclusion Criteria for All Participants
1. History of allergy or serious adverse reaction, including Guillain-Barré syndrome, to a vaccine or vaccine products.
2. History of a medical condition resulting in impaired immunity such as active solid tumors, leukemia, lymphoma, use of immunosuppressive drugs, chemotherapy or radiation therapy. Persons with previous skin cancers or cured non-lymphatic tumors are not excluded from the study.
3. History of HIV, Hepatitis B or Hepatitis C infection.
4. Chronic clinically significant medical problems that could be considered active or unstable (i.e diagnosed within the past 3 months or requiring a change in medication within the past 3 months). This is including (but not limited to):
    a. Insulin dependent diabetes

   b. Severe heart disease (including arrhythmias)
   c. Severe lung disease
   d. Severe liver disease
   e. Severe kidney disease
   f. Severe hypertension: defined as life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit).
5. BMI > 30
6. Current or previous use of statins or any other lipid-lowering drug.
7. Pregnancy or breast feeding, or plans to become pregnant in the first 3 months of study participation.
8. History of influenza infection within the same influenza season.
9. Receipt of blood products or immune globulin product within the prior 3 months.
10. History of excessive alcohol consumption, drug use, psychiatric conditions, social conditions or occupational conditions that in the opinion of the investigator would preclude compliance with the trial.
11. Receipt of any live vaccines 30 days before, or plans to receive any live vaccines 30 days after vaccination.
12. Receipt of any inactivated vaccines 14 days before, or plans to receive any inactivated vaccines 14 days after vaccination.

For participants randomized to the statin therapy+QIV group:

1. Participant is currently taking any medication that has known interactions with statin therapy.
2. History of renal or hepatic impairment.
3. Safety lab results showing:
   a. CPK ≥ 1.5 ULN
   b. AST ≥ 1.5 ULN
   c. ALT ≥ 1.5 ULN
   d. LDL ≥ 160 mg/dL

12. Population

HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol. This may cause fetal harm when administered to pregnant female. Pregnant women are also excluded from the study as their immune responses after vaccination will differ from the general population.

13. Vulnerable Populations

No vulnerable populations will be enrolled. Specifically, pregnant persons, children, prisoners, and cognitively impaired persons will not be enrolled. Non-English speakers will not be excluded.

14. Local Number of Participants

We anticipate needing to enroll and screen 150 participants locally to identify 30 participants in the statin therapy QIV arm and 30 participants in the QIV alone arm.

15. Recruitment Methods

15.1 Patients will be recruited following IRB approval.
15.2 Participants will be recruited from the general population of metro Atlanta with the methods detailed below.
15.3 Participants may be identified and recruited from past subjects who agreed to be contacted for future studies or by self-referral from IRB approved advertisements from

- postings of IRB-approved flyers in and around the Emory University campuses as well as on electronic notification boards ; posting approved flyers on Emory and partner institution shuttles (e.g., Georgia Tech);
- use of various social media platforms such as Facebook, Twitter, Instagram, and other mobile apps in compliance with Emory policy; Study staff will use the official Emory University Facebook account and Instagram Emory Get Involved account, where IRB approved social media ads will be posted. The potential volunteers fill in their contact information in the “lead document form” provided by Facebook by default. The form collects the potential participant’s basic contact information such as name, best contact phone number and email address etc. Facebook collects the leads and provides it to the recruitment staff, who save the data in a password protected database on the Emory Hope Clinic’s shared drive.
- listservs (such as CDC, Emory University, Emory Vaccine Center, and Vaccine Dinner Club), and clinical trial recruitment websites such as Research Match.org;
  listing of clinical trials on the Emory clinical trials database (clinicaltrials.emory.edu);
  contacting past participants from the HIPAA-compliant clinical trials database at the Hope Clinic who have agreed to be contacted for future studies; presentations by Hope Clinic faculty at various University and community venues; and volunteer word-of-mouth (direct referrals).

Study recruiters/coordinators will contact potential volunteers once identified and tell them about the study and see if he/she is interested. If the potential subject is interested, the recruiter will obtain an oral consent and prescreen them for the study using an IRB-approved screening checklist. Qualified subjects will be scheduled to come into the clinic and be fully consented and proceed with screening/enrollment.

16. Withdrawal of Participants

Participants may voluntarily withdraw their consent from all future study activities including follow up at any time without penalty or loss of benefits to which they are otherwise entitled.

Participants may be terminated from the study prior to study completion for reasons that might include, but are not limited to, those listed below. The investigator will inform the participantthat all data acquired prior to termination will be included in the study analysis unless participant withdraws
consent.

16.1 Participant no longer meets eligibility criteria.
16.2 The participant is considered by the PI to be "lost to follow-up" (i.e., no further followup is possible because attempts to reestablish contact with the subject have failed).
16.3 The participant dies.
16.4 As deemed necessary by the PI or designee for noncompliance of any nature.
16.5 The participant becomes pregnant.
16.6 If the study is prematurely terminated by the sponsor or the investigator for any reason, the investigator will promptly inform the study participantsand assure appropriate follow-up, as necessary. The investigator will provide a detailed written explanation of the termination to the IRB.

Participants with early termination status (before Day 8) are replaced as needed to preserve adequate sample size for the primary endpoint analysis.

17. Continuation of treatment

- Following initiation of statin therapy, participants randomized to the statin therapy+QIV group will: Continue receiving the study drug as planned if they experience grade 1 diarrhea or grade 1 elevation in CPK(>ULN - 2.5 x ULN) or LFTs (>ULN - 3.0 x ULN).
- Temporarily halt receipt of statin therapy for three to 7 days days and receive a new set of safety labs (CPK; LFTs) if they experience a grade 2 elevation in CPK (>2.5 x ULN - 5 x ULN) or LFTs (>3.0 - 5.0 x ULN) and without alternative etiology. If afterwards the labs are graded 1 or within normal limits, the participant may restart the statin therapy. If the labs do not trend to grade 1 , the drug will be halted and the participant will be followed for safety and not vaccination if prior to D1.
- Permanently halt receipt of statin therapy if they experience a grade 3 elevation in CPK (>5 x ULN - 10 x ULN) or LFTs (>5.0 - 20.0 x ULN) after starting ST.
- The same rules apply to diarrhea and myalgias and other symptoms related to statin.

18. Risk to Participants

18.1 Risks of Investigational Products/Interventions

Atorvastatin therapy
Atorvastatin is an FDA-approved lipid lowering drug that is widely used. In some cases, this statin may be associated with the following risks:

- Diarrhea, nasopharyngitis, arthralgia in 4-14%

- Insomnia in 3%
- Nausea and dyspepsia in 4-6%
- Increased transaminases in 2-3%
- Muscle spasms, myalgia, musculoskeletal pain in 3 to 8%

Treatment with Atorvastatin may also be rarely linked to more serious risks such as:

- Hypersensitivity or severe allergic reaction including anaphylaxis, angioneurotic edema, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis
- Acute liver failure or decompensated cirrhosis
- Nonserious and reversible cognitive side effects
- Fatal and nonfatal hepatic failure
- Increases in HbA1c and fasting serum glucose levels
- Myopathy and rhabdomyolysis: risk increased with renal impairment, age>65 and hypothyroidism
- Increases in serum transaminases. These changes occurred following the start of statin therapy, were not accompanied by other symptoms, and reversible after drug discontinuation
- Persistent increases to more than three times the ULN in serum transaminases have occurred in approximately 0.7% of patients
- Immune-mediated necrotizing myopathy: characterized by muscle biopsy showing necrotizing myopathy without significant inflammation, improvement with immunosuppressive agents, proximal muscle weakness, and elevated serum creatine kinase, which persist despite discontinuation of statin treatment

A scientific statement from the American Heart Association[22] supports the safety of statin therapy including in people at low risk for cardiovascular disease, noting the risk of statin-induced serious muscle injury is <0.1% and risk of serious hepatotoxicity is <0.01%. Current product labels do not include the need for routine monitoring of liver enzymes if these are normal prior to initiating statin therapy. For safety, liver enzymes and creatine phosphokinase (CPK) will be monitored on a regular basis during the study.

Seasonal influenza vaccine

The potential harms of receiving the influenza vaccine include, but are not limited to: pain and redness at the injection site, muscle aches, fatigue, and headache. These reactions occur in 10-25% of adults who receive influenza vaccine. Serious adverse reactions including anaphylaxis and Guillain-Barré syndrome are possible, but rare. Potential participants with a history of severe allergic reaction to any component of the vaccine or Guillain-Barré syndrome after previous influenza vaccination will not be enrolled. For further details, see the attached package insert.

18.2 Risks of study procedures

Blood draws
The risks of blood sample collection include a transient feeling of discomfort and may result in a vasvogal reaction. This risk is controlled by having the participantlie down prior to collection, if needed. A bruise might form at the site of the blood draw, and this can be avoided by maintaining pressure to this site following the blood draw. The sites of blood draw are potential sites of infection, but this risk is made very unlikely by the use of sterile technique.

18.3 Risk of Concomitant Medications, Prophylactic Medications and Rescue Medications

While we do not expect to use any additional medication, in case of anaphylactic or hypersensitivity reactions, we have readily available epinephrine (1:1000) and diphenhydramine injections. The use of epinephrine injection may cause side effects such as high blood pressure, arrhythmia, lightheadedness, nervousness, restlessness, tremor, shortness of breath, and diaphoresis; however, the frequency of these side effects is not determined. Diphenhydramine injection may also be necessary to treat potential allergic reactions, and its use may cause low blood pressure, arrhythmia, confusion, dizziness, sedation, restlessness, diarrhea, nausea, and urinary retention, but the frequency of these side effects is also unknown.

When facing a medical emergency, the clinic staff will follow the institutional SOP by calling 911 first (Hope Clinic). If needed, the participantwill be transferred to the Emory University Hospital or Emory Decatur Hospital Emergency Department for further care.

Participants are allowed to use acetaminophen or other symptomatic treatment if they experience a moderate to severe local or systemic side effect after vaccine administration.

19. Potential Benefits to Participants

The participants will be administered the influenza vaccine that has been approved by the FDA, which may potentially provide them with protection against influenza viruses. The United States Advisory Committee on Immunization Practices (ACIP) recommends the influenza vaccine for individuals aged 6 months and above, as it is known to be effective in preventing influenza virus infection.

20. Compensation to Participants

As compensation for expenses/travel and time, participants will receive $75 for each visit that involves a blood draw, $100 for the statin initiation visit, and $125 for the vaccination visit. Any unscheduled visit will be compensated at $50. Phone visits are compensated $20 per call. Compensation is provided in the form of a gift debit/credit card (ClinCard). If a participant completes all visits, total compensation will range from $725-$845 depending on the arm they are randomized to. In the event gift debit/credit cards (ClinCard) are unavailable, gift card reimbursement may be used instead.

21. Data Management and Confidentiality

21.1 Steps taken to secure data

All faculty and staff at the Hope Clinic receive HIPAA, human participants, and EHSO training as part of their onboarding and continuing training. Each participant will be assigned a unique study participant identification number (PTID) and these numbers rather than names will be used to collect and store participant information, including omics data.

Investigators and study personnel will keep accurate records to ensure that the conduct of the study is fully documented. Clinical data from this study, including participant birthdate and demographics, will be associated with the PTID, maintained on a HIPAA compliant clinical management database and a HIPAA compliant RedCap database and/ or password protected Excel file, respectively at Hope Clinic accessible to investigators and study personnel only. Hard copy clinical data forms, for example source or protocol-specific CRFs, associated with the PTID will be stored at Hope Clinic in a locked filed cabinet and accessible to investigators and clinical staff only. A file linking the participant PII (i.e., their name and contact information) to their PTID will be maintained at the Hope Clinic in a separate locked file cabinet and HIPAA compliant clinical management database accessible to investigators and clinical staff only. Study personnel will only send documents containing personal PII via fax or encrypted email in accordance with HIPAA regulations (e.g., to send/receive safety lab data and medical records request to/from primary care provider).

21.2 Quality Control

The Principal Investigator (or designee) will keep accurate records to ensure that the conduct of the study is fully documented. The investigator will ensure that all CRFs and participant study files are legible and complete for every participant. The Principal Investigator (or designee), through the use of an internal Quality Management Plan, appropriate site quality control, and quality assurance monitoring staff, will be responsible for the regular review of the conduct of the study for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data and accuracy of source documentation verification. All charts will be 100% Quality Controlled. The first five volunteers enrolled will receive a 100% Quality Assurance review. The reports of the internal site monitor will be submitted to the Principal Investigator (or designee). The RedCap data entry system will include checks for data that are outside feasible limits (e.g., dates that are in the future) or skipped answers.

21.3 Data and specimen handling

All de-identified samples will be stored at the Hope Clinic by laboratory staff using only the study number, PTID, date of visit, and visit number. Data regarding safety and adverse events will be maintained at the Hope Clinic of Emory University. Data from immunological assays and gene expression analysis (RNA sequencing) will be linked to PTID, maintained by [redacted] laboratory at Stanford University, and accessible to investigators and laboratory staff. Laboratory

data and demographic data may be linked by PTID for statistical analysis by investigators or collaborators (e.g., to control for age); however, PTID will not be published nor will the gene expression (RNA sequencing) data be linked to demographic data in order to protect participant privacy and prevent the discovery of participant identity.

Specimens and demographic data linked by PTID will be stored indefinitely, but all personal identifiable information (PII) and PII/PTID links will be destroyed once the laboratory analysis associated with this protocol is complete and the last manuscript associated with this protocol has been published.

Study investigators and personnel will maintain the highest degree of confidentiality for the clinical and research information obtained from the participants. Medical and research records will be maintained in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of a clinical study, investigators will permit authorized representatives of regulatory authorities to examine (and when required by applicable law, to copy) clinical records for the purpose of quality assurance reviews and evaluations of study safety and progress. Unless required by laws that permit copying of records, only the PTID associated with documents or with other participant data may be copied (and all personally identifying information will be removed). Authorized representatives described above are bound to maintain the strict confidentiality of medical and research information that is linked to identify individuals.

Blood tubes will be labeled at the Hope Clinic with a unique identifier and will be transported to the lab at the Hope Clinic in EHSO-approved transport containers.

22. Plans to Monitor the Data to Ensure Safety of Participants and Data Integrity

☒ **More than minimal risk** – Continue below.

Review our Data and Safety Monitoring Questionnaire and insert the relevant monitoring table at the end of this section. Also upload the completed questionnaire in the "Basic Study Information" smartform section in eIRB, question #8, as a separate document.

Mark the risk categorization, as determined by the Data and Safety Monitoring Questionnaire, that applies to your study below:

Select one of the following (do not delete this table; review the guidance document for definitions):	
☒ Medium Complexity	
☐ High Complexity Category A	
☐ High Complexity Category B	

If choosing this category for a study under an IND or IDE because you believe the study intervention does not significantly impact morbidity or mortality, please provide your rationale:

DSMP Requirement	**How this Requirement is Met**	**Frequency**	**Responsible Party(ies)**
Real-time review of participant data during initial data collection.	100% QC review by CRC/CRN and peer review within 3 business days. QM will review first 5 participants in real time.	*Expectation is that this happens every time you obtain information.*	CRC/CRNs QM Manager/Team
Site Monitoring at pre-determined intervals: The Principal Investigator has a responsibility to ensure that the study is following all aspects of the protocol.	*There should be a standard operating procedure to review data (whether a sample or 100%) at pre-determined intervals to ensure that there is adequate documentation of critical elements such as eligibility criteria. Monitoring is required at the following timepoints (but may be done more frequently):* • *study initiation* • *at least every six months while participants are receiving intervention and* • *annually while participants are in follow-up*	*At a minimum, a review is required annually when no one has been enrolled or the study is in long term follow up. Additional risk-based interim monitoring may be required at least once every 12-24 weeks based on the site activity, to include the possibility of remote monitoring. A longer frequency could be acceptable with justification about risk to participants.*	*Delegate a responsible party for each requirement below.* Self-assessment is acceptable*. *Self-assessment*: a process for self-assessment of protocol compliance and data integrity which can be part of an overall DSMP. See CTAC's self-assessment tool on their webpage.
100% review of regulatory files	Site QM will conduct 100% review of reg files at the beginning and at close-out visit at a minimum.	*Reviewed at a minimum of first and close-out visits*	QM Manager/Team Regulatory Team

100% review of consent forms	CRC/CRNs will perform peer review in real time for 100% of ICFs. QM will conduct 100% review of ICFs.		CRC/CRNs QM Manager/Team
Review of credentials, training records, the delegation of responsibility logs (if applicable)	QM and Regulatory Team will conduct 100% review of credentials/training records/DoA files quarterly at a minimum.		QM Manager/Team Regulatory Team
Comparison of case report forms (CRF) to source documentation for accuracy and completion	QM will conduct 100% review for first 5 participants in real time and on a monthly basis throughout the study.		QM Manager/Team
Review of documentation of all adverse events	SAEs will be reviewed by PI and designee and peer reviewed by CRC/CRNs and verified by QM team and evaluated by the ISM and Emory IRB.		CRC/CRNs QM Manager/Team
Monitoring of critical data points (eligibility, study endpoints, etc.)	QM will conduct 100% review for first 5 participants in real time and on a monthly basis throughout the study.		QM Manager/Team
Laboratory review of processing and storage of specimens	Peer review of sample log in done in real time and answering queries regularly	*Reviewed at first and close-out visits and at least biannually*	Lab Manager or designee
Assessment of laboratory specimens stored locally	Peer review of sample log in done in real time and answering queries regularly-shipment done within 2 weeks		Lab Manager or designee
Test article accountability review	Day to day and monthly per IDS pharmacist	*Reviewed at first and close-out visits and at least biannually*	Research Pharmacist
Accountability logs, dispensing records, and other participant records	Monthly per IDS pharmacist	*At least biannually*	Research Pharmacist

For FDA regulated studies, the following requirements apply:		Timing, frequency, and intensity of monitoring	
Monitoring methods (may include centralized, on-site, and self-assessment)	Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, electronic case report forms (eCRFs), ICFs, medical and laboratory reports, site study intervention storage records, training records, and protocol and GCP compliance. Site monitors will have access to each participating site, study staff and all study documentation according to the Hope Clinic CQMP. Study monitors will meet with all participating site PIs to discuss any problems and outstanding issues and will document site visit findings and discussion.	Monitoring visits are expected to occur monthly or bimonthly. Details of clinical site monitoring are documented in a clinical monitoring plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.	Monitoring for this study will be performed by the QM team.
*For international studies, you are required to engage a CRO that is working in the site country and/or to consult with Emory's legal counsel regarding compliance with the country's clinical research regulations.			

22.1 Study Oversight

The Principal Investigator and the research team (co-Investigators, research nurses, study coordinators, and data managers) are responsible for identifying adverse events. Adverse events will be reviewed regularly by the research team.

22.2 Adverse Events

This section defines the types of adverse events that may occur, and outlines the procedures for appropriate adverse event collecting, grading, recording, and reporting.

Information in this section complies with 21CFR 312; ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and Good Clinical Practice; and applies the standards set forth in the National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events Version 5.0 [Published: November 27, 2017; http://evs.nci.nih.gov/ftp1/CTCAE/About.html]. These criteria have been reviewed by the study investigators and have been determined to be appropriate for this study population.

22.2.1 Safety Reporting

22.2.2 Adverse Events

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the procedure, without any judgment about causality.
After vaccination, the following adverse events in the indicated intervals may be reported to Vaccine Adverse Event Reporting System (VAERS).

- Anaphylaxis or anaphylactic shock (7 days)
- Shoulder Injury Related to Vaccine Administration (7 days)
- Vasovagal syncope (7 days)
- Any acute complication or sequelae (including death) of above events (interval - not applicable)
- Events described in manufacturer's package insert as contraindications to additional doses of vaccine: hypersensitivity, including severe allergic reactions after previous dose of influenza vaccine

22.2.3 Suspected Adverse Reaction (SAR)

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug or procedure caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

SARs after vaccine administration may include:

- Local reactions: injection site redness, injection site swelling, pain at the site of injection, itching of the skin at the injection site.
- Systemic reactions: headache, fever, nausea, dizziness.

SARs after phlebotomy may include:

- Local reactions: pain at the site of venipuncture, bruising at the site of venipuncture, infection at the site of venipuncture
- Systemic reactions: lightheadedness or fainting

22.2.4 Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

An adverse event or suspected adverse reaction is considered ''serious'' if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Serious adverse events will be reported and recorded for the entire duration of the study.

An adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of the investigator, its occurrence places the patient or participant at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Any serious adverse event (for duration of study) will be recorded and reported within 24 hours to ISM.

22.2.5 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction
An adverse event or suspected adverse reaction is considered ‘‘unexpected’’ if it is not listed in the Summary of Product Characteristics or is not listed at the specificity or severity that has been observed; or, if the Summary of Product Characteristics is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

22.2.6 Independent Safety Monitoring
The ISM, is a physician with relevant expertise in clinical studies whose primary responsibility will be to provide independent safety monitoring in a timely fashion and to provide recommendations regarding the safe continuation of this study.

The ISM will evaluate safety data generated from study participants against the known safety profile of the study product or study procedure to assess for possible changes to the overall risk of the study.

The ISM will communicate with the Principal Investigator as needed. The study has provisions for a back-up ISM to ensure that independent safety monitoring happens at all times during the study.

22.2.7 Collecting and Recording Adverse Events and Pregnancy
Adverse events may be identified during this study through any of these methods:

- Examination of the participant during study visits.
- Questioning the participant during study visits.
- Receiving a safety contact from the participant at any time during the study

Note: participants will be asked to call the site if they develop any of the following:

- Any adverse event that limits self-care activities of daily living (e.g. bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bed ridden) even if he/she decides not to seek medical care

Reactogenicity of any grade is collected for 7 days after vaccination.

Serious adverse events will be recorded if they occur at any time during the study.
A complete recording of safety events in the CRF will include event term; date(s) of onset and resolution/stabilization; assessment of severity; relationship to procedures/intervention(s); expectedness; determination of whether the AE qualifies as serious or non-serious; treatment required; action taken with study anticipation; and outcome. AEs qualifying as serious also require a narrative of the event. Updates in safety events will be recorded as additional information becomes available.

Information on pregnancies will be collected from the time a participant signs the consent until the participant completes study participation. If a participant becomes pregnant after study entry, the investigator will discuss with the participant and/or the treating provider the known possible risks to the fetus. Participants becoming pregnant after study entry will be withdrawn from the study and followed until the end of the pregnancy for safety. A pregnancy resulting in congenital anomaly/birth defect will be considered a SAE. Any premature termination of the pregnancy will also be reported and assessed as an SAE as needed.

22.3 Grading and Attribution of Adverse Events

22.3.1 Grading Criteria

Adverse events will be graded according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 5.0 [November 27, 2017; http://evs.nci.nih.gov/ftp1/CTCAE/About.html] This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events. All adverse events whether or not listed in the NCI-CTCAE will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual (A semicolon indicates 'or' within the description of the grade):

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care Activities of Daily Living (ADL) refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Not all Grades are appropriate for all AEs; therefore, some AEs are listed with fewer than five options for Grade selection.

Anaphylaxis is a disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death. Severity grading of anaphylaxis as per the NCI-CTCAE manual is as follows:

- Grade 1= not applicable
- Grade 2= not applicable
- Grade 3= Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
- Grade 4= Life-threatening consequences; urgent intervention indicated
- Grade 5= Death

Severity grading of AEs of laboratory abnormalities will be assessed as per the NCI-CTCAE manual.

22.3.2 Definition of Attribution

The site investigator will initially determine the relationship of an adverse event. The relationship of an AE to study participation will be determined is RELATED or UNRELATED.

22.3.3 Reporting Timelines

Reporting Serious Adverse Events to the Independent Safety Monitor

The Principal Investigator will notify the ISM by email of any SAE within 24 hours of becoming aware of the event. The ISM may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the adverse event.

Notifying Institutional Review Board

The Principal Investigator will ensure the timely dissemination of SAE information, including SAEs requiring expedited review by the ISM and to the IRB in accordance with IRB regulations and guidelines. Serious adverse events that are unanticipated, related to study participation, and involving risk to participant or others will be reported to the IRB within 10 business days of event occurrence or of the PI becoming aware of the event per IRB guidelines.

22.4 Stopping Rules

Study Stopping Rules:
Study procedures will be suspended pending expedited review of all pertinent data by the institutional review board and the ISM if Atorvastatin or QIV were recalled by the manufacturer.

Also, procedures will be suspended pending review of all pertinent data by the ISM after the occurrence of any of the following:

- 1 case of statin-induced necrotizing autoimmune myopathy
- 1 case of acute liver injury
- 2 cases of severe myalgia

Individual participant **Stopping Rules:**
Early study termination will occur in participants due to any of the following circumstances detailed in Section 16.

Conditions for continuation of treatment or early termination of treatment/Follow-up:
Please refer to Section 17.

Follow-up After Early Study Termination:
Participants who are prematurely terminated from the study due to an AE will be followed until resolution of the AE or until 28 days after a participant terminates from the study. Resolution of an AE is defined as the return to baseline status or as stabilization of the condition with the expectation that it will remain chronic.

After assessing terminated participants for safety under the provisions stated above, the subject will be seen in clinic, if necessary.

Participant Replacement
In the case of premature termination (Day 8 or earlier), extra participants may be recruited, at the discretion of the Principal Investigator, to maintain the target sample size.

22.5 Protocol Deviations

Deviations occur when the investigators, study staff, or participants fail to adhere to protocol requirements or when there is non-adherence to GCP guidelines.

Upon determination that a protocol deviation has occurred, the study staff will notify the Principal Investigator promptly. Substantive protocol deviations from the protocol that affect rights, safety or welfare of participants , their willingness to continue in the study or impact the integrity of the research data will be reported promptly to the IRB per IRB regulations.

23. Provisions to Protect the Privacy Interest of Participants

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a unique patient identification number (PTID) and these numbers rather than names will be used to collect and store participant information and samples. A file linking the participant identity, i.e., name, to their unique study participant ID (PTID) is maintained at the Hope Clinic in a separate locked file cabinet and on a HIPAA compliant clinical management database. Screening, consenting, and study visits will take place in private clinic rooms.

Any publications from this study will not use information that will identify participants by name or PTID. A description of this trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This web site will not include information that can identify participants . At most, this web site will include a summary of the results. Site personnel will only transmit documents containing personal identifiable information (PII) using encrypted email or fax in accordance with HIPAA regulations (e.g., to send/receive safety lab data and medical records to/from primary care provider).

24. Economic Burden to Participants

There is no cost to participants for the research tests, procedures, or study product while taking part in this study. Procedures and treatment for clinical care may be billed to the participant , participant's insurance or third party. Participants may be compensated for their participation in this study. Compensation will be in accordance with the local IRB policies and procedures, and participant to IRB approval.

If it is determined by the principal investigator that an injury occurred to a participant as a direct result of the tests, procedures or treatments that are done for this study, then referrals to appropriate health care facilities will be provided to the participant. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the participating site. No financial compensation will be provided to the participant for any injury suffered due to participation in this study.

25. Informed Consent

25.1 Statement of Compliance

This study was designed to ensure the protection of participants according to the ethical principles of the Declaration of Helsinki and amendments concerning medical research in human participants. This clinical study will be conducted using current good clinical practice and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by the IRB, as well as any other appropriate health authorities. Any amendments to the protocol or to the consent materials will also be approved by the appropriate bodies listed above prior to implementation.

25.2 Informed Consent Process

The informed consent form will provide information about the study to a prospective participant to allow for an informed decision about participation in the study. Prospective participants must be given ample opportunity to review the informed consent and inquire about the results of the study. The consent form will be provided electronically to the prospective participant during the first screening phone call. A copy of the informed consent form will again be provided to a participant for review prior to any study procedure during the in person screening visit. The Principal Investigator or an approved designee will discuss the consent with the prospective participant and answer questions. Study staff will read through the consent form with potential participants and answer any questions. Participants will be allowed sufficient time to consider participation in the study, after having the nature and risks of the trial explained to them and have the opportunity to discuss the trial with their family, friends. The prospective participant will be told that being in the study is voluntary and that he or she may withdraw from the study at any time, for any reason. The consenting process will take place in private exam rooms at the Hope Clinic. We anticipate that the consent process will take about 30-60 minutes.

All participants must read, sign, and date a consent form before undergoing any study procedures. Consent materials will be provided in the English language, however, shortforms and a qualified interpreter are available and IRB approval will be requested for use in consenting non-English speaking participants. A copy of the signed consent form will be given to the participant. The informed consent form will be revised and receive IRB approval whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the study.

Participants will be compensated for their time and travel. The informed consent form will specify the amount of compensation for each participant.

26. Setting

Potential participants will be recruited and screened from the general population of metro Atlanta. Participants will be enrolled at the Hope Clinic, Decatur, Georgia.

27. Resources Available

The Hope Clinic has a database of more than 5000 previous volunteers who can be considered for screening for the study. The Hope Clinic also has a website and the ability to reach out to potential participants through advertising around the Emory University campus.

27.1 Facilities

The Hope Clinic is a community-based vaccine research clinic and is the clinical arm of the Emory Vaccine Center. The Winship Cancer Institute is the only National Cancer Institute–Designated Comprehensive Cancer Center in Georgia and one of only 50 in the country.

27.2 Participant Support

Referrals to appropriate medical or psychological health care facilities will be provided by the investigators to the participant as needed due to the anticipated consequences of human research. Study personnel will try to reduce, control, and treat any complications from this study. Immediate medical treatment may be provided by the relevant site (Hope Clinic or Winship).

27.3 Study Personnel Training

All faculty and staff at the Hope Clinic receive HIPAA, human participants , and EHSO (e.g., bloodborne pathogens) training as part of their onboarding and continuing training. In addition, all study personnel will complete ongoing approved protocol review and provide documentation of this training to study quality management personnel.

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Appendix A. Schedule of Procedures

	-60 to -32	-31 to -29	1	2	4	8± 1	15 ±2	29± 3	91± 7	181 ±15	Phone call^
	V 1	V2	V3	V4	V5	V6	V7	V8	V9	V10	
Informed consent	x										
Demographics, medical history	x										
Interim medical history		x	x	x	x	x	x	x	x	x	x
Medications	x	x	x	x	x	x	x	x	x	x	x
Targeted physical exam	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
Vital signs	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
Blood draw for screening	x										
Stool Sample collection		x	x					x			
Pregnancy test (if applicable)	x		x	(x)	(x)	(x)	(x)	(x)	(x)	(x)	
Vaccination			x								
Statin therapy*		x	x	x	x	x	x	x			
Memory Aid			x	x	x						
Blood draw for immunological assays	x	x	x	x	x	x	x	x	x	x	
Clinical labs for statin therapy	x		x					x			
Adverse events		x	x	x	x	x	x	x			x
Serious adverse events		x	x	x	x	x	x	x	x	x	

Conducting a visit outside window is allowed at investigator discretion
Parentheses indicate a given procedure will be conducted if relevant for the visit: vital signs and pregnancy testing if applicable will be on the day of screening, prior to statin therapy initiation and prior to vaccination.
*Each participant receiving statin therapy will have clinical labs drawn. The tests conducted will be: Lipid profile, Creatinine Phosphokinase, Liver function tests, CRP. These tests will be valid for 30 days.

^phone call is completed 15 days after initiation of statin therapy.