Participant Name: _____ Date: _____

Title of Study: Effect of Simvastatin on Hepatic Decompensation and Death in Subjects Presenting with High-Risk Compensated Cirrhosis

Site Principal Investigator: David E. Kaplan **VA Facility:** Corporal Michael Crescenz VA Medical Center

Principal Investigator for Multisite Study: Dr. David E. Kaplan and Dr. Tamar H. Taddei

KEY SUMMARY INFORMATION ABOUT THIS STUDY

You are being invited to take part in a research study that is being paid for by the VA Clinical Science and Development (CSRD) office. Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive. Taking part in this study is completely voluntary.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

In this study we are collecting information on the safety and effectiveness of Simvastatin in patients with cirrhosis. This medication is approved by the Food and Drug Administration (FDA) to lower cholesterol, but it has not been approved for treatment of cirrhosis or any liver disease.

We hope to learn whether Veterans with compensated cirrhosis (when the liver is scarred and damaged but without any symptoms) who have a high risk for hepatic decompensation (developing symptoms of cirrhosis), can lower the risk of developing symptoms of cirrhosis (such as bleeding events, liver cancer and ascites) by taking simvastatin, a medication usually used to lower cholesterol in the blood to prevent heart problems and strokes. We also want to see how the use of statins affects the quality of life of Veterans with compensated cirrhosis and explore how changes or differences in two genes (SLCO1B1 and KIF6) and other related genetic differences affects the safety and effectiveness of simvastatin.

Your participation in this research will last about two years.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You may or may not benefit from your participation in this study. If simvastatin works like we think it will, future patients may benefit from avoiding complications of cirrhosis. For a complete description of benefits, refer to the Detailed Information section of this consent.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

The FDA currently recommends that simvastatin not be used in patients with active liver disease. However, there are other organizations that disagree. The American Association for the Study of Liver Diseases feels that serious liver injury from statins is quite rare and that several studies have established the safety of statins in patients with liver disease. The National Institute of Health has studied the effect of simvastatin on liver injury and believes that the side effect is exceedingly rare – if 50,000 patients took simvastatin for 2 years as in this study, approximately 1 would be expected to have a liver injury. A complete description of risks are listed further down in the Detailed Information section of this consent.

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DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The local person in charge of the study is Dr. David E. Kaplan . If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his contact information is: 215-823-5800 ext. 207236.

DETAILED INFORMATION ABOUT THE STUDY

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this research is to gather information on the safety and effectiveness of simvastatin in patients with cirrhosis. The brand name of simvastatin is Zocor®. This medication was approved by the Food and Drug Administration (FDA) in 1991 to lower cholesterol, but it has not been approved for treatment of cirrhosis or any liver disease.

In order to test the safety and effectiveness of simvastatin in patients with cirrhosis, we are conducting a randomized, double-blind, placebo-controlled, multi-center study. There will be two groups of Veterans. One group will receive simvastatin. The other group will receive a placebo. A placebo looks like the real drug (simvastatin) but does not contain any medication. The placebo group is used for comparison to the group that does receive the drug. Randomized means that you will be assigned to one of the groups by chance – it is like flipping a coin. You will have a 1 in 2 chance of receiving the placebo instead of simvastatin. Double-blind means that neither you nor your doctor or any one on the research team will know if you are receiving simvastatin or the placebo. Double-blind procedures are used so that the research team doesn't accidentally treat patients receiving the active drug different from those receiving the placebo.

HOW LONG WILL I BE IN THE STUDY?

There are ten VA Medical Centers participating in this study. We expect to enroll about 50 Veterans here in Philadelphia and 500 overall. This research study is expected to take approximately 4 years. Your individual participation in the study will take 2 years.

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WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

If you decide to participate in this research study, you will undergo a screening visit to make sure that you are eligible for the study. If you are eligible, you will be scheduled for study visits every 3 months for two years. Each study visit should take about one hour. You will meet with a study provider and the study coordinator throughout the study. The study also involves answering questionnaires during some of the study visits. You are free to skip any question you do not wish to answer. All the study visits will take place in the regular GI/Liver clinic. In this study, the study doctor may be the same doctor that will see or sees you for your liver care.

Screening Visit

At the screening visit, a member of the research team will meet with you and discuss the study. Your medical history and current health issues will be reviewed in detail to confirm that you are eligible for the study. We will also conduct alcohol use screening and counseling, if necessary, review all your current medications to determine if some of them will interact with the study medication, and ask about the different procedures and tests you have had. For example, as part of standard of care liver cancer surveillance you would normally receive an ultrasound of your liver and AFP (alpha fetoprotein) blood testing about every 6 months. AFP is a protein made by the liver that may signify the presence of liver cancer. You may also normally have had an upper endoscopy within the past three years as part of your routine medical care to determine if you have varices of the esophagus. Varices are enlarged veins in the esophagus or stomach at risk of bleeding that may need to be managed. If you have not had these standard tests we may schedule them for you as your standard of care procedures so this would not be considered part of the research and you would be responsible for any co-pay you normally pay.

We will also draw blood to check some basic indicators of your health status such as your body's fluid level, how well your kidneys and liver are working, and your platelet count. The total amount of blood drawn will be about 14ml or 1 tablespoon. Other study procedures that will take place at this visit or the next visit (Visit 1) are:

- Collect saliva for genetic testing
- Complete Montreal Cognitive Assessment (MoCA) test to assess your memory

If you are female and of childbearing capability, we will ask that you take a urine pregnancy test.

Whether or not you are qualified for the study you will receive $45 for your time and effort during the screening visit. If you do not qualify, your participation in the study will end here. If you qualify and agree to participate, you will be scheduled for a lead-in visit (Visit 1). This visit can be done on the same day as this screening visit.

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At Visit 1 the following procedures will take place:

- Physical exam (a full exam is not needed if your screening visit is less than 30 days old)
- Take vital signs including blood pressure, and weight (if your screening visit is more than 30 days old)
- Measure your height (if not done at the screening visit)
- Draw blood to check some basic indicators of your health status such as your body's fluid level, how well your kidneys and liver are working, and your platelet count. The total amount of blood drawn will be about 44ml or 3 tablespoons (if your screening visit is more than 30 days old)
- Complete the AUDIT-C alcohol use screening test (if not done at the screening visit)
- Collect saliva for genetic testing (if not done at the screening visit)
- If you are female and of child-bearing capability we will ask that you take a urine pregnancy test (if your screening visit is more than 30 days old)
- Complete Montreal Cognitive Assessment (MoCA) test to assess your memory (if not done at the screening visit)
- Provide you with simvastatin 20mg daily to take for 14 days. This is "Open Label." Everyone will receive real simvastatin (not a placebo) at a dose that is half of what you might take later in the study if you are randomly chosen to get the study drug. This 2-week trial will help the study investigator decide that it is safe to keep you in the study for up to 2 years.
- Schedule subsequent study visit

At Visit 2 (Day 0) the following procedures will take place:

- Interview to see how you are feeling and doing on the open-label simvastatin. If you are having problems with side effects, the study investigator may decide it is not safe for you to continue in the study and your study participation may end.
- Physical exam (a full exam is not needed if your screening visit is less than 30 days old) and update contact and medical history (including medicines that you are taking)
- Take vital signs including blood pressure
- You will turn in your pill bottle from the prior visit
- Draw blood to check some basic indicators of your health status such as your body's fluid level, how well your kidneys and liver are working, and your platelet count. Some of the blood is collected to check how the medicine is affecting you. The total amount of blood drawn will be about 14ml or 1 tablespoon
- Complete the PROMIS-29 Quality of Life Questionnaire that asks how you feel physically and emotionally
- If the investigator at your site feels that it is safe for you to continue on the study, you will be randomized to one group or the other as described earlier in this consent form.

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- If you continue on the study, you will receive enough simvastatin or placebo for 90 days and schedule your subsequent study visit

At Visit 3 (Day 90 ± 14), Visit 5 (Day 270 ± 14), Visit 7 (Day 450 ± 21), and Visit 9 (Day 630 ± 21) the following procedures will take place (Part of Visits 3, 5, 7, and 9 can be done virtually):

- Physical exam (for in person visits only) and update contact and medical history (including medicines that you are taking)
- Take vital signs including blood pressure (for in person visits only)
- Assessment of how you are feeling and doing on the study medication
- You will turn in your pill bottle from the prior visit (you can do this in person or by mail)
- If you are female and of child-bearing capability we will ask that you take a urine pregnancy test.
- Draw blood to check some basic indicators of your health status such as your body's fluid level, how well your kidneys and liver are working, and your platelet count. Some of the blood is collected to check how the medicine is affecting you. The total amount of blood drawn will be about 14ml or 1 tablespoon. If you have a virtual visit, you will still need to get your blood drawn in person.
- You will receive enough simvastatin or placebo for 90 days
- Schedule subsequent study visit

At Visit 4 (Day 180 ± 14), Visit 6 (Day 360 ± 21), and Visit 8 (Day 540 ± 21) the following procedures will take place (Part of Visits 4 and 8 can be done virtually; Visit 6 must be done in-person):

- Physical exam (for in person visits only) and update contact and medical history (including medicines that you are taking)
- Take vital signs including blood pressure (for in person visits only)
- Assessment of how you are feeling and doing on the study medication
- Complete the AUDIT-C (only on Visit 6)
- Complete the PROMIS-29 Quality of Life Questionnaire that asks how you feel physically and emotionally
- You will turn in your pill bottle from the prior visit (you can do this in person or by mail)
- If you are female and of child-bearing capability we will ask that you take a urine pregnancy test. If the urine pregnancy test is positive, you will stop the study drug.
- Draw blood to check some basic indicators of your health status such as your body's fluid level, how well your kidneys and liver are working, and your platelet count. Some of the blood is collected to check how the medicine is affecting you. The total amount of blood drawn will be about 14ml or 1 tablespoon

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- We will make sure that standard of care liver cancer surveillance tests (ultrasound/CT/MRI + AFP) are ordered
- You will receive enough simvastatin or placebo for 90 days
- Schedule subsequent study visit

At the End of Study Visit (Visit 10) the following procedures will take place:

- Physical exam and update contact and medical history (including medicines that you are taking)
- Take vital signs including blood pressure and weight
- Assessment of how you are feeling and doing on the study medication
- Complete the AUDIT-C
- Complete the PROMIS-29 Quality of Life Questionnaire that asks how you feel physically and emotionally
- You will turn in your pill bottle from the prior visit
- If you are female and of child-bearing capability we will ask that you take a urine pregnancy test. If the urine pregnancy test is positive, you will stop the study drug.
- Draw blood to check some basic indicators of your health status such as your body's fluid level, how well your kidneys and liver are working, and your platelet count. Some of the blood is collected to check how the medicine is affecting you. The total amount of blood drawn will be about 14ml or 1 tablespoon
- We will make sure that standard of care liver cancer surveillance tests (ultrasound/CT/MRI + AFP) and standard screening for esophageal varices are ordered. These are standard treatments for patient with cirrhosis (and should be done whether or not you are in the study) but the results may be used for research purposes.
- A member of the research team will let you know when they think the study will end at all the sites, tell you about the plan to let you know if you had been taking simvastatin or the placebo, and discuss how final study results will be available.
- A study team member will calculate your 10-year cardiovascular risk and offer you treatment with a statin if it might benefit you after the study

We will pay you $45 for each of the study visits. There is always the possibility that you may need to come in for an unscheduled visit. This may be because we need to confirm a test result or because you have experienced an adverse event and we need to check you out. We are not able to pay you for any unscheduled visits.

We will try to schedule all study visits during your routine clinic visits. There may be times though when we cannot do this and if this happens you will need to make an extra trip to the Liver Clinic. If

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the doctor discontinues the medication due to adverse effects, we will continue the study visits as scheduled.

WHAT IS EXPECTED OF ME IF I TAKE PART IN THIS STUDY?

- Take the study drug as instructed.
- Keep your study appointments. If you miss an appointment, please contact the investigator or research staff to reschedule as soon as you know you will miss the appointment.
- Tell the investigator or research staff if you believe you might be pregnant
- Keep the study drug in a safe place for your use only and away from children
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing or potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?
Any study has possible risks and discomforts. The procedures in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

Study Medication: The most common side effects of simvastatin in patients without cirrhosis (more than or equal to 5%) are upper respiratory infection, headache, pain in the abdomen, constipation, muscle pain and nausea. Other side effects reported are increased risk of diabetes and kidney injury.

Up to 10% of patients who receive simvastatin may have mild muscle pain and weakness. This side effect goes away after stopping simvastatin and has no long-term consequences. The study team will be monitoring you for this side effect frequently.

A much rarer side effect (<1 in 1000 users) is a more serious muscle injury call rhabdomyolysis, muscle cell breakdown. This results in weakness, cramps, stiffness, and spasms. Untreated rhabdomyolysis can lead to kidney failure and death. It is associated with a higher dose of simvastatin than we are using (80mg rather than 40mg), and is more frequent in patients who are female, have uncontrolled hypothyroidism, are over 65 years of age, take certain other medications, have some kidney disease, or decompensated liver cirrhosis (patients whose livers are this sick are not candidates for this study).

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The best information that we have now about side effects in people with cirrhosis is from a study of 149 patients who had decompensated cirrhosis. We list these side effects below, how often they occurred to people taking simvastatin and how often they occurred to those taking placebo.

Treatment-related Adverse Events	Placebo (N=79)	Simvastatin (N=70)
Overall	14 (17.7%)	16 (22.8%)
Abdominal Pain	3 (3.8%)	0 (0.0%)
Ascites (fluid buildup in abdomen)	2 (2.5%)	2 (2.8%)
Asthenia (feeling poorly)	3 (3.8%)	2 (2.8%)
Gastrointestinal Bleeding	2 (2.5%)	1 (1.4%)
Gynecomastia (breast enlargement)	0 (0.0%)	2 (2.8%)
Hepatic encephalopathy (confusion related to liver)	1 (1.2%)	3 (4.2%)
Iron-deficiency anemia	0 (0.0%)	2 (2.8%)
Severe muscle injury	0 (0.0%)	2 (2.8%)*

* Both patients had total bilirubin > 5 mg/dl and were Child-Turcotte-Pugh Class C

There are also some very rare side effects that have been reported with simvastatin use: drug-induced liver injury (1 in 100,000 people), pancreatitis (< 1 in 1,000), lung disease (< 1 in 1,000), and exacerbation of myasthenia gravis or ocular myasthenia (<1 in 100,000 people).

Risks for adverse side effects are increased when taking certain medications with simvastatin. It is very important that you tell the study doctor about all the medications and herbal preparations and supplements you are taking.

Grapefruit juice may also increase the risks of adverse side effects. You should not drink grapefruit juice while you are in this study.

Because this is a relatively new use of simvastatin we may not know all of its possible side effects.

Randomization to placebo arm: To be enrolled in the study, you cannot have received a prescription for a statin medication in the last year. If you decide to participate in the study, you have a 50:50 chance of receiving the placebo. It is possible that you might get a benefit from taking a statin to reduce your risk of heart disease over the next 10 years. If you are randomly assigned to the placebo group, you would not get the benefit of a statin over the next 2 years. Studies suggest that the harm of not taking a statin for 2 years is very small (<1%). If at any time your primary care provider or other medical provider recommends that you take a statin, and you choose to take one, we would take you out of the Study and you would continue your regular VA care.

Surveys: Surveys may cause some people to feel emotional distress. You do not have to answer any question that you choose not to answer for any reason.

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Blood Draws: Common risks include temporary pain from the needle stick and the possibility of bruising at the site of the blood draw. Occasionally lightheadedness may be experienced. Fainting or infection occurs rarely.

Genetic tests: The study team will be performing some very specific genetic tests using saliva to determine if specific genes predict side effects from the medication or the effectiveness of the study drug. The study team may ultimately study additional genetic mutations to find genes that could be associated with medication safety. You will not be told the results of these tests. It is not expected that the findings of the gene test would affect your health or your family's health. The study team (called the Penn Genomic Analytic Core or PGAC) doing the genetic test and analyzing the results will be given a very limited amount of information about you (your age, whether or not you had muscle aches related to simvastatin) but will not be given any personal identifiers (like your name, date of birth or social security number).

Microbiome testing: Some of your saliva will be shipped to Dr. Jasmohan Bajaj, a VA physician and scientist, to study whether the bacteria present in your mouth before you take the study drug can predict if you get sick from liver disease. You will not be told the results of these tests. It is not expected that the findings of this test would affect your health or your family's health. After all study participants have completed the study, Dr. Bajaj will be given a very limited amount of information about you (your age, what events happened during the study if any, and if you got active drug or placebo) but will not be given any personal identifiers (like your name, date of birth or social security number).

For Women of Childbearing Capability and Nursing Mothers: The safe use of simvastatin in pregnant women and nursing mothers has not been established. Consequently, there may be risks to you (or to your embryo or fetus) if you are or may become pregnant that are unknown. Women of childbearing potential enrolling in this study must (i) have been using a birth control measure (an intrauterine device (IUD), birth control pills, a condom, diaphragm, or abstinence) for the previous three months, (ii) must have a negative pregnancy test, and (iii) must agree to continue to use a birth control measure for the duration of the study. If, while participating in the study, you suspect you have become pregnant, please contact the study physician immediately. Women are considered to be of childbearing potential unless they have been surgically sterilized (for example tubal ligation or hysterectomy) or are post-menopausal, that is, no menstrual period for more than 6 months. Nursing mothers may not participate in this study. There is no known risk to sperm, sperm counts or male fertility. Women who become pregnant will immediately cease taking the study medication, but will be monitored for study outcomes as if they were still taking medication.

Confidentiality of Information: Participation in research may involve a loss of privacy. Your research records will be kept as confidential as possible. We will assign a unique code number to

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identify you in our research records. The code number will not be based on any information that could be used to identify you (for example, social security number, initials, birth date, etc.) The master list linking names to code numbers will be kept separately from the research data. We will need your social security number to obtain your laboratory results from the VA corporate data warehouse.

All research information will be secured in locked files and protected VA electronic databases. Your identity will not be revealed in any reports or publications resulting from this study. Only authorized persons will have access to the information gathered in this study. Authorized persons include regulatory agencies such as the FDA, the Government Accountability Office (GAO), the Office for Human Research Protections (OHRP), Office of Research Oversight (ORO), Corporal Michael Crescenz VA Medical Center Research Office, the sponsor which is the VA Clinical Science and Development (CSRD) office, and the Data Monitoring Committee created for this study to oversee and monitor it.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

There may be no direct/personal benefits to you from your taking part in this research study. However, if you are randomized to simvastatin and if the drug works as we hope it will, you may benefit from avoiding complications of your cirrhosis. The information we get from this study might help other Veterans with cirrhosis.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

You do not have to participate in this study to receive treatment for your cirrhosis. If you decide not to participate in this study, you will continue to receive the customary standard of care medication and procedures.

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HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

In order to protect your confidentiality, we will assign a unique code number to identify you in our research records. The code number will not be based on any information that could be used to identify you (for example, social security number, initials, birth date, etc.) The master list linking names to code numbers will be kept separately from the research data.

All research information will be secured in locked files and protected VA electronic databases. Your identity will not be revealed in any reports or publications resulting from this study. Only authorized persons will have access to the information gathered in this study. Authorized persons include regulatory agencies such as the FDA, the Government Accountability Office (GAO), the Office for Human Research Protections (OHRP), Office of Research Oversight (ORO), Corporal Michael Crescenz VA Medical Center Research Office, the sponsor which is the VA Clinical Science and Development (CSRD) office, and the Data Monitoring Committee created for this study to oversee and monitor it.

Information collected as part of this research, even if identifiers are removed, will not be used or distributed for future research studies.

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We will include information about your study participation in your medical record.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Health Information Portability and Accountability Act (HIPAA)

There are rules to protect your private information. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form, you provide your permission, called your 'authorization,' for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. The study team may also collect other information including your name, address, date of birth, social security number, and information from your medical records such as HIV status, drug, alcohol or STD treatment, genetic test results or mental health treatment.

The research team may also need to disclose the information to others as part of the study progress. Others may include the following: *CSP Clinical Research Pharmacy Coordinating Center*

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(CSPCRPCC); Independent Study Monitor; CSR&D Data Monitoring Committee; Food and Drug Administration (FDA), Office of Human Research Protections (OHRP), the VA Office of Research Oversight (ORO), the Government Accountability Office (GAO; the Penn Genomic Analysis Core (PGAC) at the University of Pennsylvania (coded samples and data only), the VA Institutional Review Board, and the local VA medical facility Human Research Protections Program. The PGAC will assist the study investigators to understand if certain genes are associated with side effects of simvastatin. This lab will receive your saliva and a limited amount of information about you (like your age, if you had side effects from simvastatin or not). Your sample and information will be coded like "Study Patient #123." No personal identifiers (like your name, social security number or date of birth) will be given to the PGAC. Once the principal investigator at the VA gets the results back from the PGAC, he/she will make sure that the PGAC destroys any leftover material and information.

Your health information disclosed pursuant to this authorization may no longer be protected by Federal laws or regulations and may be subject to re-disclosure by the recipient.

While this study is being conducted you will not have access to your research related health records. This will not affect your VA healthcare, including your doctor's ability to see your records as part of your normal care and will not affect your right to have access to the research records after the study is completed.

You can revoke this authorization, in writing, at any time. To revoke your authorization, you must write to the Release of Information Office at this facility or you can ask a member of the research team to give you a form to revoke the authorization. Your request will be valid when the Release of Information Office receives it. If you revoke this authorization, you will not be able to continue to participate in the study. This will not affect your rights as a VHA patient to treatment or benefit outside of the study.

If you revoke this authorization, Dr. David E Kaplan and his or her research team can continue to use information about you that was collected before receipt of the revocation. The research team will not collect information about you after you revoke the authorization.

Treatment, payment or enrollment/eligibility for benefits cannot be conditioned on you signing this authorization. This authorization will expire at the end of the research study unless revoked prior to that time.

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WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

Participant payment:

You will receive $45 for each of the study visits. At your site, you will receive either a check, or an electronic fund transfer (EFT), or a debit card, or a voucher that you will take to the agent cashier. Your social security may need to be collected to be able to pay you for your participation. Depending local policies, payments to you may result in reporting income to tax authorities and you may receive a 1099 tax form.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury is due to non-compliance by a study participant with study procedures or if the research is conducted for VA under contract with an individual or non-VA institution.

There are no plans to provide compensation for disability or other losses occurring over the long term or if an injury becomes apparent after your participation in the study has ended. However, by agreeing to participate in this research study, you are not waiving or giving up any legal rights to seek compensation.

If you should have a medical concern or get hurt or sick as a result of taking part in this study, call: Dr. David E. Kaplan at 215-823-5800 ext. 207236

DURING THE DAY: 215-823-5800 ext. 207236

AFTER HOURS: 610-316-8039.

DO I HAVE TO TAKE PART IN THE STUDY?

Your participation in this study is voluntary. Your refusal to take part in this study will involve no penalty or loss of benefits to which you are otherwise entitled. You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled.

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You may decide to discontinue taking part in the study at any time by contacting David E. Kaplan at the number listed above and on the last page of this Consent Form. We will ask you to come in for a final study visit so that we can check to see if you are okay. You may also ask that your saliva sample be stripped of all identifiers that could link the sample to your identity, or that the sample be destroyed. However, we will still use the information that we gathered previously about you in order to preserve the integrity of the study results. We will also ask for permission to access your medical records to collect data related to the trial until the end of the study.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

Your participation in this study may be terminated without your consent if:

- It is deemed not in your best interest to remain in the study or if it is unsafe for you to continue
- You do not comply with the requirements of this study
- If the sponsor withdraws support
- If you need to start taking simvastatin outside of this study

If the doctor discontinues the medication due to adverse effects we will continue the study visits as scheduled.

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

If you have any questions, complaints, and concerns about the research or related manners please contact Dr. David E. Kaplan at 215-823-5800 ext. 207236. You may also contact the Patient Advocate at 215-823-5800 x 205803.

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the VA Central Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VA Central IRB toll free at 1-877-254-3130 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

Sometimes during the course of a research study, new information becomes available about the drug that is being studied that might change a person's decision to stay in the study. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will arrange

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for your medical care to continue. If you decide to continue in the study, you might be asked to sign an updated informed consent form. Your research doctor could also decide it to be in your best interests to withdraw you from the study. If so, he or she will explain the reasons and arrange for your usual medical care to continue.

DOES THIS STUDY INVOLVE GENETIC RESEARCH AND HOW WILL MY GENETIC INFORMATION BE PROTECTED?

We will be testing your saliva for specific genetic tests that might be associated with the safety or effectiveness of statins. This research will *not* include whole genome sequencing.

- The genetic testing of your saliva is for research purposes only. No results of genetic testing from this study will appear in your medical record.
- Genetic test results will not be made available to you, your family, your doctors, your other clinicians or any other clinical staff.
- To protect the confidentiality of computer records related to you or your family members, information that could be used to identify you individually will be stored only on a protected VA server.
- A laboratory at the University of Pennsylvania will do the genetic testing for the study. This laboratory will not receive any personal information about you, but instead will be provided your sample using a code number. Any extra material will be destroyed after testing. The "key" which links your unique study number and this code will be kept in a protected VA server using procedures described above to protect your confidentiality. There will be no document (paper or electronic) where the genetic information will be stored with information that can identify you.

Federal laws and policies provide you with protection from discrimination by health insurance companies, group health plans, and most employers based on your genetic information. A federal law called the Genetic Information Nondiscrimination Act (GINA) generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information obtained from this study.
- Health insurance companies and group health plans may not use your genetic information obtained from this study when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information obtained from this study when making a decision to hire, promote, or fire you or when setting the terms of your employment.

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Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. It also does not prohibit discrimination on the basis of already known genetic disease.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr./Mr./Ms_____ _____has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study and authorize the use and disclosure of your health information in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it. A copy of this signed consent will also be put in your medical record.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date

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