HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

CONSENT TO PARTICIPATE IN A RESEARCH STUDY AND RESEARCH SUBJECT HIPAA AUTHORIZATION

Protocol Title:	**A5333s FINAL Version 3.0, dated 1/28/16; Letter of Amendment 1, 8/17/16** Effects of Pitavastatin on Coronary Artery Disease and Inflammatory Biomarkers: Mechanistic Substudy of REPRIEVE
Principal Investigator:	Pablo Tebas, MD 502 Johnson Pavilion, Philadelphia PA 19104 **(215) 349-8092**
Project Manager:	Eileen Donaghy, MSN, CRNP
24 hr. Emergency Contact:	Immunodeficiency Program Doctor on call (215) 662-6059

Introduction:

You are being asked to take part in this research substudy because you will be taking pitavastatin or the placebo for pitavastatin for REPRIEVE (A5332). This study is sponsored by the National Institutes of Health (NIH). The doctors in charge of this substudy at this site are: Dr. Pablo Tebas. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

Why Is This Study Being Done?

The purpose of this substudy is to learn about the effects of pitavastatin on the vessels that supply your heart with blood "coronary arteries" and the atherosclerotic plaque within the wall of these vessels (known as "hardening of the arteries"), as well as inflammatory biomarkers (blood tests that indicate the body's immune system is active) among people infected with HIV.

How Many People Will Take Part in This Study?

About 800 people will take part in this study. About 75 participants are expected to enroll at the University of Pennsylvania.

How Long Will I Be In This Study?

You will be in this substudy for about 2 years

What Do I Have To Do If I Am In This Study?

If you agree to be in this substudy and sign this consent form, you will be asked to come in for 3 visits. Each visit will last about 2-3 hours and will occur at the same time as your main study visits whenever possible. The visits are at entry (when you join the substudy), month 4, and month 24.

Before all visits for the substudy you should not eat or drink anything, including food, beverages, candy, or gum for 8 hours before your visit. You are encouraged to drink water before your visits. If you are not fasting we will ask you to return to have your blood drawn within 21 days of the study visit.

The procedures described below will be done *in addition* to your participation in the REPRIEVE (A5332) study.

Explanation of study procedures

You will be asked to fill out a questionnaire about your quality of life at entry and month 24.

Study staff will ask you questions about your diet and physical activity at month 24.

For women capable of having children, a pregnancy test will be done immediately before the CT of your heart. This test is required as part of your participation in this study. You will be told the results of the pregnancy test. You must notify the research staff if you are pregnant, think you may be pregnant, or if you are trying to become pregnant. If do become pregnant while on the substudy, you will be taken off the substudy and will not have any more substudy tests.

At entry and month 24 we will check your kidney function, complete blood count (CBC), CD4 T-cell count (how many infection fighting cells are in your blood), and HIV viral load (how much HIV is in your blood). The test to check your kidney function is required as part of your participation in this research study. Approximately 3 teaspoons of blood will be collected at each the entry and month 24 visits for these tests.

You will be told the results of these tests.

Storage of Samples for Future Tests

You will have about 1-4 tablespoons of blood drawn in addition to the blood drawn for REPRIEVE (A5332) at the entry, month 4 and month 24 visits. This blood will be collected and stored for tests that will be done later on in the study or after the study is over. These tests will measure various substances in your blood related to cholesterol (fat in your blood), blood sugar, metabolic tests (how your body processes food), inflammation, and immune function (how your body reacts to infection). You do not need to agree to store this blood to join the study and you may change your mind about storing your blood at any time. You will not be told of the results of the research done on your blood.

Genetic Testing

Approximately 1 teaspoon of blood collected will be used to look at genes that may affect your risk for cardiovascular disease. Genetic testing is a laboratory test that looks at differences in people's genes. Your body, like all living things, is made up of cells, and cells contain deoxyribonucleic acid, also known as "DNA." DNA is like a string of information put together in a certain order. Parts of the string make up "genes." For the substudy we will do a test to look at your RNA. RNA is made from DNA and is short for ribonucleic acid. RNA is a genetic material that has a major role in making proteins. Proteins are the building blocks of your body, cells, and organs. Genes contain instructions on how to make your body work and fight disease. The testing in this study will focus on certain RNA's that are known to be related to cardiovascular disease and effects of statins. New RNA's of interest may be identified in the

future and may also be looked at. You do not need to agree to store this blood to join the study and you may change your mind about storing your blood at any time. You will not be told of the results of the research done on your blood.

Your body's genetic makeup is unique to you, so there is a risk with genetic research that even with all the security measures in place, someone using your samples or genetic information may still find out which information is yours. However, this risk today is very small, but it may increase with time since science and technology are developing rapidly.

In the event that your genetic information becomes linked to your name, the US federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. This law prohibits health insurance companies, group health plans, and most employers from denying services based on your genetic information. However, GINA does not protect against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

If at a later date you change your mind and want your samples destroyed, contact the research staff. There are two ways to withdraw your permission. You could allow researchers to remove all your personal identifiers from your samples, so that they are not linked to you anymore. These samples will then become anonymous. Or, you can ask researchers to destroy your samples, so that they cannot be used for future research. However, in either case, researchers will not be able to destroy samples or information from research that is already underway.

<u>CT Scan</u>
You will have a computed tomography (CT) scan ("Cat" scan) of your heart at entry and month 24.

A computed tomography (CT) scan is an imaging method that uses x-rays to create cross-sectional pictures of the body. You will be asked to lie on a narrow table that slides into the center of the CT scanner. Depending on the study being done, you may need to lie on your stomach, back, or side. Once you are inside the scanner, the machine's x-ray beam rotates around you. It is important to remain still during the exam, because movement causes blurred images. You may be told to hold your breath for short periods of time. The scans take about 15 minutes or less to complete

A small amount of dye (intravenous contrast) will be injected into your arm during the CT scan to better see the vessels that supply your heart with blood. If your heart rate is more than 65 beats per minute, we may inject a drug called a beta-blocker into your arm via the intravenous line. A beta-blocker is used to slow down your heart rate. A low heart rate is needed in order to make the best pictures of your heart and coronary arteries. In addition, a drug called nitroglycerin will be given to you by mouth in order to obtain better images of the blood vessels of the heart. We will also check your heart rhythm with an electrocardiogram (ECG). To do this, wires with sticky pads attached will be placed on your chest before the scan.

For women, a pregnancy test will be performed prior to CT scanning. Pregnant women will not be allowed to undergo CT scanning. For all patients, a blood test for kidney function will be performed before the CT scan and patients with abnormal kidney function will not undergo CT scanning.

Because the test results are being used for research only, the results created by this study will not become part of your hospital record unless we discover an unexpected medical problem that must be communicated to the study doctors or your primary care physician. If you are found to have a critical blockage of the vessels supplying your heart with blood or another important non-cardiac abnormality

that may affect your health, we will provide the results of the CT to your study doctor. The cost of any additional testing will not be covered by the study.

Other Information
You may withdraw from this substudy at any time and still remain on the main study. If you decide to withdraw from the substudy early (before month 24) or stop taking the study treatment in the main study or if you decide to withdraw from the main study you will be asked to return to the clinic to have the procedures listed in the table below

Procedure	Stopping the study or the study treatment early
Fasting Blood	X
Blood Collected	X
Pregnancy Testing	X
Computed Tomography of your Heart	X
Quality-of-Life Assessment	X

Why Would The Doctor Take Me Off This Study Early?
The study doctor may need to take you off the study early without your permission if:

- the doctor thinks it is in your best interest
- the study is cancelled
- you are not able to attend the study visits as required by the study
- you are unable to complete the computed tomography of your heart at the entry visit
- you become pregnant
- you have to stop participating in the main study
- your kidney function becomes abnormal during your study participation
- you develop asthma during your study participation
- you develop an allergy to the contrast dye during your study participation
- your body mass index (a measure of body fat based on your height and weight) is greater or equal to 40

What Are The Risks Of The SubStudy?
The scanning on CT machines will not cause any physical discomfort other than from having to lie still on the table for the duration of the test.

Risks of Radiation Dose from CT
This research study involves exposure to radiation from the CT scans, one at entry and one at month 24. Therefore you will receive a radiation dose. This radiation dose is not necessary for your medical care and will occur only as a result of your participation in the study. At doses much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. At the doses you will receive, it is very likely that you will see no effects at all.

CT Imaging and Incidental Findings
It is possible that during the course of the research study, the research staff (and/or radiologist that

reviews your CT scan) may notice an unexpected finding (s). Should this occur, the finding (s) will be considered by the appropriate medical personnel and the study principal investigator will inform you if necessary. These finding(s) may or may not be significant, and may lead to further testing (such as additional imaging studies, or biopsy). This may result in anxiety or harm to you caused by the additional testing. The costs of such additional testing will not be covered as part of this research study.

Risk of IV contrast agents used in CT imaging:
Most CT contrast reactions (approximately 95%) are mild to moderate in degree and most resolve themselves without treatment. However, life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. People with heart disease, kidney disease or allergies are more likely to have a more severe reaction to contrast agents. If you have a history of heart disease, kidney disease, or allergies please inform the study staff.

Common effects of iodinated IV contrast agents are feelings of overall warmth, especially in the bladder area after injection. A metallic taste during the injection, warmth, burning sensation or momentary pain during the contrast injection at the injection site can occur. Less common are nausea, vomiting, headache, hives and itching. Rare, but serious reactions are rapid heartbeat, changes in blood pressure, heart attack, kidney failure, pulmonary edema, serious life threatening allergic reaction.

It is important to tell your study staff if you have had an allergic reaction to iodinated contrast.

Contrast-Induced nephropathy (CIN)
CIN is a kidney injury caused by contrast and is usually reversible. CIN almost always occurs in people who already have abnormal kidney function. To be enrolled in this study you must have normal kidney function, and for this reason CIN is very unlikely (less than 5 out of 1,000).

Risk of pregnancy and ionizing radiation
Pregnant women will be excluded from having a CT scan due to the possibility of unforeseen side effects to the fetus. All female subjects that are capable of becoming pregnant must take a pregnancy test within 24 hours prior to the CT exam to rule out pregnancy. CT scans produce x-rays, if there is a chance of pregnancy you should inform the study staff, the CT exam should be postponed.

Risks of IV Needle Placement
- Hemorrhage (bruise at the injection site)
- Infection (catheter related infection) at the injection site (very rare)
- Leaking of contrast agent outside of the vein at the place where the IV is inserted.
- Minor discomfort
- Bleeding
- Infection
- Bruising

Risks of Beta-blockers and Nitroglycerin
Beta-blockers and nitroglycerin are used by millions of Americans and are generally considered safe. These drugs are routinely administered prior to cardiac CT to improve the quality and interpretability of the study.

The risk of beta-blockers includes slow heart rate (bradycardia), low blood pressure (hypotension), and wheezing (bronchospasm). Allergic reactions to beta-blockers are rate. Persons with asthma treated

with inhalers should not receive beta-blockers. Study staff will assess this and other reasons for you not to have beta-blockers with you prior to the CT.

The side-effects and risks of nitroglycerin are generally mild and of short duration and include low blood pressure (hypotension), high heart rate and abnormal rhythm (tachyarrhythmia), headache, lightheadedness, and visual disturbance. Persons who take erectile dysfunction medications such as Viagra, Cialis, or Levitra (sildenafil, tadalafil, or vardenafil) will need to stop these drugs at least 5 days prior to receiving nitroglycerin on the day of the cardiac CT scan. Nitroglycerin should not be given to persons with a low blood pressure. Study staff will assess this and other reasons for you not to have nitroglycerin with you prior to the CT.

Other Risks/ Additional Risks of CT Scans
• Discomfort
• Claustrophobia

Risks of Drawing Blood
Having your blood drawn may cause discomfort, bleeding, and bruising where the blood is drawn. Occasionally, there is swelling in the area where the needle enters the body and there is a small risk of infection. There is also a risk of lightheadedness, fainting, and blood clots.

Risks of Fasting
Some people find fasting to be bothersome. It may make some individuals feel anxious, irritable, or hungry. Patients who are required to take their morning medications with food should wait until after the visit has been completed to take their medications.

Genetic Testing
The results of your genetic tests are for research purposes only and no individual results will be given back to you. The results of the genetics studies will never become a part of your medical record. We will protect your confidentiality to the fullest extent. Blood samples for genetic studies will be identified in a way in order to maintain your confidentiality.

Research study results will not be given to your family members, insurance companies, employers, or third parties without your written permission and approval of the Institutional Review Board at the University of Pennsylvania.

Additional Risks
The CT scan of your heart is being done to answer research questions, not to examine you medically. This scan is not a substitute for one your doctor would order. If the radiologist thinks that there may be an abnormality in your scan, we will contact you and will help you get medical follow-up for the problem. If you have a primary care doctor, we can contact your doctor, with your permission, and help him or her get the right follow-up for you. It is possible that you could be unnecessarily worried if a problem were suspected, but not actually found.

Are There Benefits to Taking Part in This Study?

If you take part in this substudy, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

What Other Choices Do I Have Besides This Study?

Instead of being in this study you have the choice of:

- participating in REPRIEVE (A5332) only
- not participating

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

What About Confidentiality?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

People who may review your records include the ACTG, Office for Human Research Protections (OHRP), other government agencies as part of their duties, University of Pennsylvania institutional review board (IRB), National Institutes of Health (NIH), Food and Drug Administration, study staff, study monitors, the drug company supporting this study and its designees. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on www.ClinicalTrials.gov. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

HIPAA AUTHORIZATION

The authorization part of the consent gives more detailed information about how your personal health information may be used and disclosed by the University of Pennsylvania Health System (UPHS), the School of Medicine and the individual Principal Investigator, subject to University of Pennsylvania procedures.

What information about me may be collected, used or shared with others?

- Name, address, telephone number, email address, dates directly related to you such as date of birth and clinic visits.
- Personal and family medical history
- Current and past medications or therapies
- Results of tests and procedures you will undergo during this research
- Social Security Number, Medical record number

Why is my information being used?

Your information is important for the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right

- to evaluate and manage research functions

Who may use and share information about me?
The following individuals may use or share your information for this research study:

- The Principal Investigator and the Investigator's study team
- Other authorized personnel at Penn, including offices that support research operations.

Who, outside the School of Medicine, might receive my information?
As part of the study, the Principal Investigator, the study team and others listed above, may disclose your personal health information, including the results of the research study tests and procedures. This information may be disclosed to those listed below:

Individuals or organizations responsible for administering the study:

- ACTG Data Coordinating Center, Frontier Science Technology Research Foundation (FSTRF): Data for this study will be recorded on case report forms, keyed into a central database and electronically submitted to the Data Coordinating Center. The data will be cleaned and stored at this facility until it is ready to be analyzed.
- Statistical Data Analysis Center (SDAC): Approved data will be downloaded from FSTRF to the statistical data center for the AACTG at the Harvard School of Public Health. Specific study reports will be periodically provided to the study team and data safety review board to monitor if the trial is safe.
- Contract Research Organization (PPD, Inc): Monitors from PPD will visit the AACTG on a quarterly basis to review data and correct mistakes before the data are sent to SDAC for analysis.
- Regulatory and safety oversight organizations: Data from this study will be made available to the The Office of Human Research Protections, Food and Drug Administration and to the National Institutes of Health/Division of AIDS (DAIDS)/National Institute for Allergy and Infectious Disease (NIAID), for them to evaluate the safety and efficacy of the treatments being used in this study.

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations. Data are reported to the sponsor on Case Report Forms that identify you by your unique study number and not your name, date of birth or medical record number. Information regarding your health, such as side effects of the study drug you experience will be reported only by code number. All samples collected for analysis will be labeled with your study number, visit number and date of your visit.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You must do so in writing to the Principal Investigator at Infectious Disease Division, 502 Johnson Pavilion Philadelphia PA 19104. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study. You will also be given the UPHS and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your personal health information.

What is an Electronic Medical Record?
An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

What If We Can No Longer Reach You During Your Study Participation?
In the event you cannot be reached after multiple attempts to contact you, study staff may try to contact you through alternate phone numbers of family, friends, case manager, or acquaintances obtained at screening and updated at each visit. If you are unable to be reached through the alternate contacts we will attempt to obtain information about you from other sources such as family members, other designated contacts, or clinic records. The purpose of obtaining this information is to determine if you have died and the cause of death since last contact.

What Are the Costs To Me?
There will be no cost to you for the study drugs, the study visits, physical examinations, laboratory tests or other tests required by the study. You or your insurance company, or your health care system will be responsible for the costs of your regular medical care as well as for the costs of drugs not given by the study.

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

Will I Receive Any Payment?
You will be compensated $50 for the entry and month 24 visits and $25 for the month 4 for participation in the substudy. This will be given on a Clincard (a debit card). The maximum amount of compensation

for the study is $125. There is no other form of compensation available such as reimbursements for parking, tokens or child care. In order to be compensated for your participation in this study, you must provide your Social Security Number. Additionally, please note that the University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

What Happens If I Am Injured?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania or the National Institutes of Health to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

What Are My Rights As a Research Subject?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your healthcare provider will treat you the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

What Do I Do If I Have Questions Or Problems?

If you have questions about this study or a research-related injury, please contact the research team listed on page 1 of this consent form.

For questions about your rights as a research subject, contact:

- Director of Regulatory Affairs at the University of Pennsylvania by phoning (215) 898-2614

CONSENT

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you. You will also be given the University of Pennsylvania Health System and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your health information. This consent is:

	the initial consent for this participant. The study staff will provide an overview of the study, required visits, treatment regimen, risk and all elements of consent. The physician investigator(s) or licensed Nurse Practitioner will conduct a focused discussion about risks, benefits and alternatives.
	a subsequent consent for this participant that does not alter the risks for investigational product or products, alternatives or benefits. Research staff will conduct the consent discussion.

Your permissions and signature/initials

Tests on Stored Samples

On page 2 of this form, we told you about storing samples for tests This blood will be collected and stored for tests that will be done later on in the study or after the study is over. These tests will measure various substances in your blood related to cholesterol (fat in your blood), blood sugar, metabolic tests (how your body processes food), inflammation, and immune function (how your body reacts to infection). . **Please write your initials in the boxes next to the option you choose.**

☐ I agree to have my stored samples tested for cholesterol, sugar, metabolic tests, inflammation and immune function.

☐ I do not agree to have my stored samples tested for cholesterol, sugar, metabolic tests, inflammation and immune function..

Genetic Testing

On page 2 of this form we told you about using some of the blood collected to look at your genes (RNA). **Please write your initials in the box next to the option you choose.**

☐ I allow my samples to be stored and used for genotyping

OR

☐ I do not allow my samples to be stored and used for genotyping.

If you agree to join this study, you will need to sign below. Before you sign this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.
- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

RESEARCH STAFF CONSENT

Name of Subject (Please Print)	Signature of Subject	Date/Time
Participant's Legally Authorized Representative (print) (As appropriate)	Legally Authorized Representative's Signature	Date/Time
Name of Person Obtaining Consent (print)	Signature	Date/Time

INVESTIGATOR CONSENT

The risks, alternatives, and benefits have been reviewed with me by the Investigator, and I understand what we have discussed.

Name of Subject (Please Print)	Signature of Subject	Date/Time

I verify I have reviewed risks, alternatives, benefits with this subject, who demonstrates good understanding.

Investigator Name (PRINTED)	Signature	Date/Time