**Protocol Title:** Statins TO Prevent the Cardiotoxicity from Anthracyclines (STOP-CA)

**DF/HCC Principal Research Doctor / Institution:** Tomas G. Neilan, M.D, MGH

**DF/HCC Site-Responsible Research Doctor(s) / Institution(s):** Eric Jacobsen, DFCI, Michael Jerosch-Herold, BWH, Marielle Scherrer-Crosbie, UPENN, Jeremy Abramson, MGH, Aarti Asnani, MD, BIDMC

## A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have lymphoma that is being treated with a chemotherapy medication called doxorubicin. One of the side effects of doxorubicin is the development of heart failure and a reduction in the pumping function of the heart, commonly called the ejection fraction (EF). This research study is a way of testing whether atorvastatin, a drug commonly prescribed for reducing cholesterol levels, can protect the heart during chemotherapy with doxorubicin. Atorvastatin is from a family of medications that are commonly called “statins”.

The names of the study *[drug]* involved in this study is

- Atorvastatin

For purposes of this research, you will be referred to as a “participant”.

The effect of atorvastatin will be compared to the effect of “placebo”. A placebo is a pill that doesn't contain any active medicine. Half of the participants will be given atorvastatin and half will be given placebo.

It is expected that about 300 people will take part in this research study at MGH, BWH, DFCI, and BIDMC.

The National Institutes of Health (NIH) is supporting this research study by providing funding for the research study.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to

participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor. We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

## B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the effectiveness of a drug and determine whether the investigational drug works in treating a specific disease. “Investigational” means that the drug is being studied.

The chemotherapy drug that you have been scheduled to be treated with, doxorubicin, has been associated with the development of heart failure in some patients.

This research study is testing whether atorvastatin can protect the hearts of patients being treated with doxorubicin and can reduce cardiac injury and the risk of heart failure. Atorvastatin is not approved by the FDA (the U.S. Food and Drug Administration) for use to reduce the cardiac injury after doxorubicin. Atorvastatin is approved by the FDA for lowering cholesterol and for reducing the risk of heart attack and stroke. The heart is a muscle that pumps blood and atorvastatin may protect the heart by preserving cardiac muscle function.

We will test whether atorvastatin protects the heart using a combination of imaging tests on your heart, blood tests, and stress testing. The imaging tests will involve an echocardiogram (an echo) and cardiac magnetic resonance (CMR), a type of magnetic resonance imaging (MRI) scan.

## C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include standard cardiac monitoring after chemotherapy:

- Standard monitoring of your heart as decided by you and your physician.
- Participation in another research study.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

## D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

**Before the research starts (screening):**

After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **Medical history** which includes questions about your health, prior or current use of medications such as atorvastatin or other statins, current other medications, and any allergies
- A standard **CMR screening form. In this form we will ask you questions to determine whether it is safe for you to have a CMR. These questions will include asking whether you have metallic implants (pacemakers, defibrillators, or aneurysm clips) or metallic fragments in your eye.**
- **Determination of your kidney function and liver function** by review of the medical records or by a blood test.
- **A urine pregnancy test** will be done if you are a female able to become pregnant. If you are pregnant, you cannot take part in the study.

We will also ask you to sign a CMR safety screening form that makes sure it is safe for you to have the CMR scan. If you have metallic implants (pacemakers, defibrillators, or aneurysm clips) or metallic fragments in your eye, you should not have a CMR.

If these tests show that you are eligible to participate in the research study, you will begin the study. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

**After the screening procedures confirm that you are eligible to participate in the research study:**
The study consists of up to four visits. Participants who agree to be part of the study will be given either atorvastatin or a placebo. A placebo is a pill that doesn't contain any active medicine. The investigators will not be aware of which group you will be assigned to. This process is called blinding and is perfumed to ensure that there is no bias. There is an equal chance (50/50) that you will be assigned to atorvastatin or placebo.

**Visit 1:**
Visit 1 will take place prior to starting doxorubicin chemotherapy. The visit will take about 2.5 hours. Study visit 1 will involve:

- A heart CMR scan
- An echocardiogram
- Some blood work for measuring your kidney function and liver function.

**CMR Scan:** For the CMR scan, you will be asked to lie still on the scanner table that slides into a tunnel-shaped machine. Four electrocardiogram (EKG) patches with wires attached will be placed on your chest or your back to check your heart rate. We will place an intravenous (IV) catheter in one of your arms. An IV catheter is a thin plastic tube that is put into a vein with a needle. The IV catheter will be used to give you a CMR contrast dye (gadolinium). The dye will help us to identify subtle changes within the heart muscle. This dye, gadolinium, is used routinely in CMR studies. We will also draw a sample of blood from the IV catheter to measure your red blood cell count. The CMR study will take between 50-70 minutes

**Echocardiogram:** An echocardiogram is a test used by doctors to monitor heart function. An echocardiogram is a safe test that uses ultrasound to image the heart. After completion of the CMR test, you will have an echocardiogram. This test will take place in the same area as the CMR test. The echocardiogram test will take 40-50 minutes.

**Blood testing:** Before your CMR scan we will take some blood via the IV cannula. We will take 2 ½ tablespoons of blood. From this blood we will test for blood markers of liver function, kidney function and measures of cardiac injury and compare these results to your other tests.

**Visit 2 (optional):**
Visit 2 will take place about 3 months after you start the study.

Study Visit 2 will involve:
- An echocardiogram similar to Visit 1
- Blood work (2 ½ tablespoons of blood) similar to Visit 1.

**Visit 3 (optional):**
Visit three will take place 6 months after you start your doxorubicin chemotherapy. In this optional study visit we will test using CMR whether scar develops in the hearts of patients after doxorubicin chemotherapy. Please see Section O for more information.

Study Visit 3 will involve:
- A heart CMR similar to Visit 1
- Blood Work (2 ½ tablespoons of blood) similar to Visit 1.

**Visit 4:**
Visit 4 will take place 12 months after you start your doxorubicin chemotherapy.

Study Visit 4 will involve:
- A heart CMR scan similar to visit 1
- An echocardiogram similar to visit 1.
- Blood work (2 ½ tablespoons of blood) similar to visit 1.

**Telephone Call Follow-up:**
The study team will call you 1 year after your final study visit and ask questions to determine whether you have developed heart failure. The phone call will last about 10 minutes.

## E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this research study for up to 24 months.

The research doctor may decide to take you off the research study for many reasons including if:
- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- You are a female and become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to close the study

- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

## F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

**Risk Associated with Atorvastatin:** The following are the risks associated with taking atorvastatin:

- Muscle toxicity: Muscle pain has been reported by 3% of patients taking atorvastatin. This is typically described as pain all over the body. It typically resolves on decreasing the dose of the study medication and if it does not resolve with decreasing the dose then the study drug is stopped. In rare cases (less than 0.1%) serious kidney injury and kidney failure has occurred as a result of atorvastatin. This has rarely resulted in the need for dialysis.

- Liver toxicity: Elevation in liver blood tests has been reported in 3% of patients taking atorvastatin and is not usually a serious side effect and responds to stopping the medication. The elevation is liver tests occurs without symptoms and is detected by measuring blood tests of liver function. In rare cases (less than 0.1%) liver failure has been reported.

**Risks Associated with Gadolinium**: "Contrast-enhanced CMR" is a procedure in which a dye (gadolinium) is injected into your vein to make the CMR pictures clearer. Giving a contrast dye through the vein has risks. The same gadolinium dye is used routinely in CMR studies and can produce allergic reactions. In research studies, less than 2%of subjects have had reactions possibly related to the dye, including:

- nausea
- dizziness
- headache
- itchy watery eyes
- tingling sensation in the throat
- feeling a sensation of redness and warmth on your face
- itching
- rash
- hives (raised bumpy rash, usually itchy)

The risk of an allergic reaction is low and is treatable by the study doctor. In people with kidney disease, the dye can cause a life-threatening condition. The condition is associated with swelling and tightening of the skin, red or dark skin patches and difficulty flexing or extending the joints. This condition only develops in people with serious kidney problems..

The dye used during the CMR scan may involve risks to an embryo or fetus (a developing baby still in the womb) that are currently unknown.

**Risks Associated with CMR Scan:** When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Participants with pacemakers, or certain metal implants from surgery should not have a CMR exam. CMR is generally considered a safe procedure and is approved by the Food and Drug Administration (FDA).

For the heart CMR scan, no radiation (X-ray exposure) will be used. The CMR scans may possibly raise a person's body temperature slightly.

If we do see something that looks like a medical problem, we will ask a radiologist or cardiologist (a doctor who specializes in heart scans/test results of this sort) to review the results. If the radiologist thinks there might be a problem, we will tell you and help you get follow-up care. If the radiologist thinks that you might have a medical problem, but it turns out that you don't, we may have caused you to worry needlessly about your health.

**Reproductive Risks:**
The drugs used in this research study may affect a fetus. While participating in this research study you should not become pregnant or father a baby, and should not nurse a baby. We can provide counseling about preventing pregnancy for either male or female study participants. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

**Non-Physical Risks:**
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

## G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

Taking part in this study may or may not help you. This study may help researchers learn information that may help people in the future.

## H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to

stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the study drug. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

## I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will be compensated for each of the individual study visit separately. Compensation will be scheduled as follows:

- Study visit 1: $200
- Study Visit 2 (optional): $100
- Study Visit 3 (optional study): $100
- Study Visit 4: $200

Study staff will review the compensation plan and any requirements for reimbursement with you. The study sponsor may reimburse you for qualifying study-related travel costs and/or expenses. You will additionally be reimbursed for parking.

## J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You will not be charged for atorvastatin or placebo. You or your insurance company will be charged for portions of your care during this research study that is considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Brigham and Women's Hospital: (617) 732-5524 or (617) 732-7485
- Dana-Farber Cancer Institute: (617) 632-3455
- Massachusetts General Hospital: (617) 726-2191

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

## K. WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

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

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to your insurance company. You will be responsible for deductibles and co-payments. There are no plans to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We will not use this information for any other purpose.

## L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file.

The results of this research study may be published. You will not be identified in publications without your permission.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. 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.

## M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

**Massachusetts General Hospital**

- Tomas G. Neilan, M.D.: 617-724-5351
- Jeremy Abramson, M.D.: 617-724-4000
- Michael Jerosch-Herold, PhD.: 617-525-8959

**24-hour contact:** Page at (617) 632-0000 beeper 33288.

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

## N. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. **What protected health information about me will be used or shared with others during this research?**

   - Existing medical records, including mental health records.
   - New health information created from study-related tests, procedures, visits, and/or questionnaires

2. **Why will protected information about me be used or shared with others?**

   The main reasons include the following:
   - To conduct and oversee the research described earlier in this form;
   - To ensure the research meets legal, institutional, and accreditation requirements;
   - To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
   - To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug for the purpose of this or other research relating the study drug and its use in cancer; and,
   - Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. **Who will use or share protected health information about me?**

   - DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. **With whom outside of DF/HCC may my protected health information be shared?**

   While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

   - Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as

analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, and its agent(s): the National Institutes of Health.
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

**5. For how long will protected health information about me be used or shared with others?**

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

**6. Statement of privacy rights:**

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this

information only after the study is completed. To request this information, please contact the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"

## O. OPTIONAL RESEARCH STUDIES:

You are being asked to participate in an optional study. If you decide not to participate in the optional study, you can still participate in the main research study. Please take your time to make your decision and discuss it with others and your primary care physician.

Your participation in this optional research study is voluntary, and you will not be penalized or lose any benefits if you refuse to participate or decide to stop.

Optional Study: CMR Sub-Study

In a sub-study of 80 participants, you would undergo the one additional CMR study. It is the same CMR study described in Visit 1. This optional extra CMR study is called optional visit 3 and would take place 6 months after you start your doxorubicin chemotherapy. Myocardial fibrosis is where scar tissue develops in the heart and we have shown that scar tissue builds up in the heart after certain types of chemotherapy. We are testing whether atorvastatin reduces the development of scar tissue. This optional study would be compensated as described in Section I.

Please indicate whether or not you want to take part in this optional research study.

☐ Not applicable

☐ Yes _____ Initials _____ Date

☐ No _____ Initials _____ Date

## P. DOCUMENTATION OF CONSENT

My signature below indicates:

- ☐ I have had enough time to read the consent and think about participating in this study;
- ☐ I have had all of my questions answered to my satisfaction;
- ☐ I am willing to participate in this study;
- ☐ I have been told that my participation is voluntary and I can withdraw at any time

_____ _____

Signature of Participant or Legally Authorized Representative — Date

_____

Relationship of Legally Authorized Representative to Participant

**To be completed by person obtaining consent:**

## Adult Participant

The consent discussion was initiated on_____(date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

*As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.*

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is illiterate

*The consent form was read to the participant who was given the opportunity to ask questions.*

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate