IRB NUMBER: 09-99-30.
IRB APPROVAL DATE: 7/9/2019
IRB EFFECTIVE DATE: 7/9/2019
IRB EXPIRATION DATE: 7/8/2020

UNIVERSITY HOSPITALS CLEVELAND MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v.09.2016) Form#4 Clinical Evaluation

Project Title: Pulmonary immune responses to *Mycobacterium tuberculosis*

Principal Investigator: Richard F. Silver, M.D.

Introduction/Purpose

This study is designed to increase medical knowledge about the ability of white blood cells to migrate into the lungs of individuals who have been exposed to the *Mycobacterium tuberculosis (M. tuberculosis*), the bacteria that causes tuberculosis. For comparison studies involving lung cells, white blood cells are being obtained from the peripheral blood of several select groups You have been asked to participate in this study because either:

_____ A. You are a healthy, 18-50 year old non-smoker with latent tuberculosis infection (LTBI) as indicated by a positive tuberculosis skin test (PPD test or tuberculin test), or a positive tuberculosis blood test (Interferon-gamma (IFN-γ) release assay (IGRA) test).

_____ B. You are a healthy, 18-50 year old non-smoker and have **not** previously had a positive skin or blood test for tuberculosis.

_____ C. You are a healthy, 18-50 year old non-smoker and you have previously been vaccinated with the tuberculosis vaccine BCG but do not have evidence of latent tuberculosis infection.

Please initial on the line below to indicate that you agree that the above checked statement best describes your volunteer status. _____

Print Name of Participant _____

To stimulate local immune responses, a small amount of the skin test material PPD will be placed into a localized portion of one of your lungs. PPD stands for "purified protein derivative" and is a sterile commercial preparation composed of proteins that have been purified from cultures of *Mycobacterium tuberculosis*. PPD is not infectious and does not contain living bacteria. The PPD used in this study is approved for other uses but is not approved for use in bronchoalveolar challenge. PPD is considered experimental in this study and is therefore, regulated by the U.S. Food and Drug Administration (FDA). The cells will be used in laboratory studies of tuberculosis. The bacteria that cause tuberculosis will be used only in the laboratory studies and you will not be exposed to it through your participation. The sponsor of the study is the National Institute of Health and the US Department of Veterans' Affairs Office of Research and Development. Approximately 500 volunteers will be enrolled from Case Western Reserve University (CWRU) and other Cleveland area medical and educational institutions, for participation in this study. There is a possibility that the investigators may become aware of new findings that may affect your willingness to continue participation. You will be informed of these new findings so that you may chose to continue or discontinue your voluntary participation.

UNIVERSITY HOSPITALS
CLEVELAND MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v.09.2016) Form#4 Clinical Evaluation

Project Title: Pulmonary immune responses to *Mycobacterium tuberculosis*

Principal Investigator: Richard F. Silver, M.D.

Study Procedures

You have been invited to participate in this research study because you are a healthy, 18-50 year old non-smoker fitting our research criteria as indicated by the checked statement above and you have indicated that you are willing to undergo a series of two bronchoscopy procedures for research purposes only. The details of the bronchoscopy procedures are described in a separate consent form.

Because this research project is the first to make use of PPD in bronchoscopic challenge procedures, the extra precaution of having pre-procedure medical evaluation of all volunteers is being preformed. We therefore have asked you to undergo a series of laboratory tests, and in some cases, x-rays, in order to confirm that you are an appropriate subject for the bronchoscopy procedures.

However, if you are already certain that you do not wish to undergo any research bronchoscopy procedures, you should not undergo this medical evaluation. Those volunteers who qualify to enter the bronchoscopic challenge protocol will have further testing performed after the challenge procedures to monitor the clinical effects of bronchoscopic administration of PPD. Bronchoscopies and screening procedures will be performed in the Dahms Clinical Research Unit (DCRU) and the Outpatient Radiology Department of University Hospitals Cleveland Medical Center (UHCMC).

A. Your participation in the initial screening program involve having the following tests performed:

All subjects will undergo the following blood tests:

Complete Blood count (CBC): to check for anemia, immune cell problems, or impaired blood clotting

Blood chemistry panel: to check for abnormalities of kidney function, disturbances in sodium or potassium levels, or undiagnosed problems with blood sugar

Liver enzyme panel (ALT and AST): to evaluate liver function

Some subjects will be required to perform additional testing, the investigators will indicate with a check mark any of the studies that you specifically will need to complete in addition to that required of all subjects:

____ **Urine pregnancy test** (for female subjects only): To insure that research bronchoscopy studies will not be performed on any woman who may be pregnant. This testing must be done within 48 hours of the time at which you are scheduled to receive the bronchoscopic PPD challenge.

____ **Chest x-ray** (for LTBI subjects who do not have documentation of having a chest x-ray performed in the past 6 months): To evaluate for any abnormalities that could suggest active tuberculosis.

You will be informed of the results of all of the tests performed in this screening. If any of the screening

tests are not normal, you will be advised as to what further medical follow-up is appropriate.

B. If you are found to qualify for participation in the study, some of these procedures will be repeated following your bronchoscopic PPD challenge procedure. Specifically, the following will be performed:

48 hours after the bronchoscopic administration of PPD:

Repeat blood tests (complete blood count, blood chemistry panel, and liver enzyme panel)
Chest x-ray

3 weeks after the bronchoscopic administration of PPD, only if your chest x-ray performed at 48 hours after PPD administration shows findings that could be related to the procedure:

- Repeat chest x-ray

C. All subjects who receive bronchoscopic challenge with PPD will be asked to record a diary of symptoms they have experienced each day. Diary entries will begin the night of the challenge procedure and will be entered nightly for a total of 7 days. Diary cards may be returned to Dr. Silver's office as soon as they are completed, or, if required, at the time that you come for your appointment to receive your repeat chest x-ray 3 weeks after bronchoscopic challenge with PPD.

THE PROCEDURE OF BLOOD DRAWING:

Blood drawing procedures will be performed in Dr. Silver's laboratory at the CWRU School of Medicine, or in the Dahms Clinical Research Unit (DCRU) of University Hospitals Cleveland Medical Center (UHCMC). Your blood will be obtained by insertion of a small needle into a vein in your arm. You will be told prior to the procedure exactly how much blood will be taken, but it will not exceed 8 ounces (240cc, or half of the amount of blood taken in a standard blood donation).

You will be seated during the procedure; an area of skin on your arm will be washed with a small amount of alcohol. A tourniquet will be tied around your arm to make the veins in your arm easier to see and use in collecting the blood sample. A needle will be inserted into the vein and blood will be removed into one or more heparinized syringe(s) or directly into a vacuum-style blood collection tube. The tourniquet will then be removed and a bandage will be placed over the area where the needle was inserted.

It is essential that you inform the investigators if you are known to be anemic or have a low blood count, if you have recently had any episodes of bleeding or given blood for any reason in the past 6 weeks, or if you have been sick in any way in the past 2 weeks. If you have had any of these conditions, you will not be able to participate in the study at this time.

THE PROCEDURE OF URINE PREGNANCY TESTING:

If you are a female, you will be given a small specimen up to take into a private restroom in order to give a urine sample. You will be asked to urinate into the cup and to bring the specimen back to a nurse or physician prior to participating in the bronchoscopy procedure.

THE PROCEDURE OF UNDERGOING CHEST X-RAYS:

In the radiology department you will be asked to remove your shirt and any metal articles from your upper body and you will be given a hospital gown to wear during he procedure. You will be asked to stand in front of a metal plate while two images of your chest are obtained. For the first image, you will stand directly in front of the plate. For the second image you will be asked to stand with your side next to the plate with your arms above your head. This procedure will take less than 10 minutes. All LTBI subjects will have a chest x-ray performed as part of their screening evaluation for entry into the study. All subjects will have a chest x-ray performed 48 hours after receiving bronchoscopic challenge with PPD. If this x-ray reveals any abnormalities that could be related to the challenge procedure, a repeat chest x-ray will be performed again 3 weeks after the challenge.

THE PROCEDURE OF MAINTAINING A SYMPTOM DIARY:

Volunteers who do enter the study and receive bronchoscopic challenge with PPD will be asked to fill out a questionnaire, called a symptom diary, regarding various symptoms that could occur over the next seven days. On the night of the procedure and on each night for the next week, you will be asked to take your temperature and to indicate whether or not you have experienced any of a list of symptoms. You will be asked to return the completed symptom diary to the investigators.

Risks

RISKS OF BLOOD DRAW:

The insertion of the needle to draw blood is painful; however, this discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.
If any of your blood test results are found to be abnormal, further evaluation may be needed. The investigators will notify you regarding any abnormal results, and will advise you regarding what follow-up actions should be pursued.

RISKS OF URINE PREGNANCY TESTING:

There are no physical risks involved in the procedure of giving a urine sample for pregnancy testing; however there are potential risks involved in the results of either a positive or negative urine pregnancy test. A positive urine pregnancy test could be inaccurate. If you are found to have a positive test, you be will be advised as to appropriate follow-up studies that would be required to confirm that you are

pregnant. You will also be excluded from further participation in this study unless further studies (usually a blood test for levels or pregnancy-related hormones) indicate the urine pregnancy test was inaccurate and that you are not actually pregnant. The unexpected findings of a positive pregnancy test could be emotionally stressful for you, as could waiting for the results of the confirmatory follow-up testing. Being a part of this study while pregnant may expose the unborn child to significant risks. If you are a woman of childbearing potential, a pregnancy test will be done, and it must be negative before you can enter this study.

RISKS OF UNDERGOING A CHEST X-RAY:

The radiation dose you will receive during the performance of a set of standard 2-view chest x-rays is approximately 20 millirad, and is far lower than that shown to cause harmful effects in adults. The scattered radiation dose from a chest x-ray is also considered acceptable for clinically indicated diagnostic x-rays even during pregnancy. Because a developing embryo or fetus is much more sensitive to the harmful effects of ionizing radiation than adults, any unnecessary radiation to a developing fetus should be avoided. Therefore, YOU SHOULD NOT UNDERGO THIS STUDY IF YOU ARE OR MAY BE PREGNANT.

All precautions will be taken to minimize the risk of your participation, in the event that you are concerned about any symptoms that develop following the bronchoscopy or any part of the clinical evaluation, you may reach Dr. Silver through the UHCMC operator at (216) 844-1000.

Benefits

There will be no direct benefit to you by your participation in this research study. Your participation in this study may aid in our understanding of lung immunity, specifically that related to *Mycobacterium tuberculosis.*

Alternatives to Study Participation

Because of the nature of this research the only alternative is to not participate in this study.

Financial Information

There is no cost to you or your insurance for participation in this protocol. You will be paid for your time and effort for being in this research project. In addition to the financial compensation for participating in the research bronchoscopies, you will receive the following compensation for undergoing the clinical evaluation described in this form:

Screening evaluation: $20 for blood work, 10$ for pregnancy testing if applicable, $20 for chest x-ray if applicable

Follow-up clinical blood work: $20 (done 48 hours after PPD challenge)

Follow-up chest x-ray: $20 each (done 48 hours, and if necessary, 3 weeks after PPD challenge)

Completion of symptom diary for 1 week: $20

You are free to change your mind for any reason and decide not to undergo the second bronchoscopy. If you do this, you will still receive compensation for the procedures that you have completed. If you withdraw, or are withdrawn from the study, you will be paid for the portions that you completed.

To receive payment you must agree to complete a W-9 form, which requires you to provide an address and social security number to the accounting department. The IRS may consider this payment to you taxable income. You will be issued a 1099-Misc form only if payment exceeds $600 from all studies in which you are participating, in a fiscal year.

Research-Related Injury

In the event that a research activity results in injury, you/your medical insurance may be charged for the cost of diagnosing and treating your condition. You may be responsible for co-pays or deductibles. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". To help avoid injury, it is very important to follow all study directions.

Confidentiality

Samples collected for this study will be identified by a study code number only, and not by your name or identifying information. The key to these codes will be maintained in Dr. Silver's locked office. Presentations or manuscripts reporting results of this project will not include any information that would allow you to be identified as a study participant.

Student/Employee Rights

Choosing not to participate or withdrawing from this study will not affect your employment or class standing, nor the will results be shared with your supervisor.

Termination of Participation

The sponsor or the investigator of this study, without your consent, may discontinue your participation in this study. You will however, be compensated for the portions of the study that had been completed prior to the termination of your participation.

Privacy of Protected Health Information

The Health Insurance Portability & Accountability Act (HIPAA) is a Federal law that helps to protect the privacy of your health information and to whom this information may be shared within and outside of University Hospitals. This Authorization form is specifically for a research study entitled "Pulmonary immune responses to *Mycobacterium tuberculosis*" and will tell you what health information (called Protected Health Information or PHI) will be collected for this research study, who will see your PHI and in what ways they can

use the information. In order for the Principal Investigator, Dr. Richard Silver, and the research study staff to collect and use your PHI, you must sign this authorization form. You will receive a copy of this signed Authorization for your records. If you do not sign this form, you may not join this study. Your decision to allow the use and disclosure of your PHI is voluntary and will have no impact on your treatment at University Hospitals. By signing this form, you are allowing the researchers for this study to use and disclose your PHI in the manner described below.

Generally the Principal Investigator and study staff at University Hospitals and Case Western Reserve University who are working on this research project will know that you are in a research study and will see and use your PHI. The researchers working on this study will collect the following PHI about you:

- Your age, gender, address, phone number, and ethnicity
- Results of tuberculosis skin testing (also known as tuberculin or PPD testing) and Quantiferon blood test
- The possible reasons for you having a positive tuberculosis skin test if known (such as occupational exposure to tuberculosis patients, having received a tuberculosis vaccine, etc)
- Limited medical information obtained specifically to confirm that you are an appropriate subject for inclusion in this study (including any history of prior smoking, of asthma or other lung disease, of adverse reactions to topical anesthetics, and of treatment with immunosuppressive medications)

This PHI will be used to confirm that you are an appropriate subject for participation in this study, and to allow the investigators to accurately determine how to classify you within the various categories of volunteers who are being studied in this project. Your access to your PHI may be limited during the study to protect the study results.

Your PHI may also be shared with the following groups/persons associated with this research study or involved in the review of research: the Principal Investigator and other staff from the Principal Investigator's medical practice group and research staff; Members of the Data Safety Monitoring Board for this research study; University Hospitals, including the Center for Clinical Research and the Law Department; Case Western Reserve University, including the Research Staff of the Department of Medicine; the Institutional Review Board of the University Hospitals Cleveland Medical as well as any Institutional Review Board accrediting body; Government representatives or Federal agencies, when required by law, specifically the Food and Drug Administration, the Department of Health and Human Services, Office of Human Research Protections, the National Committee for Quality Assurance, and the Joint Commission for Accreditation of Healthcare Organizations.

5

Your permission to use and disclose your PHI does not expire. However, you have the right to change your mind at any time and revoke your authorization. If you revoke your authorization, the researchers will continue to use the information that they previously collected, but they will not collect any additional information. Also, if you revoke your authorization you may no longer be able to participate in the research study.

To revoke your permission, you must do so in writing by sending a letter to:

Richard F. Silver, M.D.

Division of Pulmonary, Critical Care, and Sleep Medicine
Biomedical Research Building, Room 327
Case Western Reserve University School of Medicine
10900 Euclid Avenue
Cleveland, OH 44106-4941

If you have a complaint or concerns about the privacy of your health information, you may also write to the UH Privacy Officer, Management Service Center, 3605 Warrensville Center, MSC 9105, Shaker Heights, OH 44122 or to the Federal Department of Health and Human Services (DHHS) at DHHS Regional Manager, Office of Civil Rights, US Department of Health and Human Services Government Center, JF Kennedy Federal Building, Room 1875, Boston, MA 02203. Complaints should be sent within 180 days of finding out about the problem.

The researchers and staff agree to protect your health information by using and disclosing it only as permitted by you in this Authorization and as directed by state and Federal law. University Hospitals is committed to protecting your confidentiality. Please understand that once your PHI has been disclosed to anyone outside of University Hospitals, there is a risk that your PHI may no longer be protected; however other Federal and State laws may provide continued protection of your information.

Summary of your rights as a participant in a research study

Your participation in this research study is voluntary. Refusing to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If you withdraw or are withdrawn by the Principal Investigator or study sponsors (with or without your consent), any completed portions of the study will be compensated as noted under the Financial Information section of this consent. If information generated from this study is published or presented, your identity will not be revealed. In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating. If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals Cleveland Medical Center (UHCMC) or elsewhere; however, UHCMC has no plans to provide free care or compensation for lost wages. Because of the nature of this research the only alternative is to not participate in this study.

Disclosure of your study records

Efforts will be made to keep the personal information in your research record private and confidential, but absolute confidentiality cannot be guaranteed. The University Hospitals Cleveland Medical Center Institutional Review Board may review your study records. If this study is regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA might inspect your records. In addition, for treatment studies, the study sponsor and possibly foreign regulatory agencies may also review your records. If your records are reviewed your identity could become known.

Contact information

_____ has described to you what is going to be done, the risks, hazards, and benefits involved. The Principal Investigator Dr. Richard Silver can also be contacted at (216) 3861151 or through the University Hospitals Operator at (216) 844-1000. If you have any questions, concerns or complaints about the study in the future, you may also contact them later.

If the researchers cannot be reached, or if you would to talk to someone other than the researcher(s) about; concerns regarding the study; research participant's rights; research-related injury; or other human subject issues, please call the University Hospitals Cleveland Medical Center's Research Subject Rights phone line at (216) 983-4979 or write to: The Chief Medical Officer, The Center for Clinical Research, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Lakeside 1400, Cleveland, Ohio, 44106-7061.

UNIVERSITY HOSPITALS
CLEVELAND MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v.09.2016) Form#4 Clinical Evaluation

Project Title: Pulmonary immune responses to *Mycobacterium tuberculosis*

Principal Investigator: Richard F. Silver, M.D.

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

X	
Signature of Participant	Date
X	
Printed Name of Participant	

Study personnel (only individuals designated on the checklist may obtain consent)

X	
Signature of person obtaining informed consent	Date
X	
Printed name of person obtaining informed consent	