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UNIVERSITY HOSPITALS CLEVELAND MEDICAL CENTER
CONSENT FOR INVESTIGATIONAL STUDIES
(v.09.2016) Form#1 LTBI testing

Project Title: Pulmonary immune responses to *Mycobacterium tuberculosis*

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

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. To determine your status as a volunteer for this study, a test is needed to establish whether or not you have been infected with *M. tuberculosis.* People who have been infected but do not have active tuberculosis are said to have latent tuberculosis infection (LTBI). The two commonly used ways to test for LTBI involve either a skin test or a blood test. You will be asked to perform one or both of the following to verify your volunteer status as indicated by the check mark below.

_____ **PPD (tuberculin) skin test:** The study will make use of a preparation known as purified protein derivative of *M. tuberculosis* (PPD) which is used in standard skin testing for tuberculosis (known as tuberculin or PPD testing). For the purposes of this research study, testing will involve injection into the skin of two different doses of PPD, as well as a control injection of sterile salt water only. Results are determined by examination of the skin sites 48-72 hours after placement of the injections.

_____ **Interferon-gamma (IFN-γ) release assay (IGRA) test**: These tests are based on assessing immune responses of your blood to specific proteins of the *M. tuberculosis* bacteria. It involves drawing 3-6 mL of blood, which is then stimulated in the hospital laboratory with the *M. tuberculosis* proteins and with positive and negative control stimuli. The results are determined by assessing the production of IFNγ by your blood cells in response to *M. tuberculosis*-specific proteins as compared to the controls.

Print Name of Participant _____

PPD skin testing and IGRA blood testing are both currently used for diagnosis of LTBI. However, it is known that positive PPD skin tests can also result from infection with other closely-related bacteria, and from prior tuberculosis vaccination. The tuberculosis vaccine, called BCG, is not given in the United States, but is commonly used in much of the world. The IGRA blood test should not be positive as a result of BCG vaccination alone, or from infection with most other bacteria that are closely related to *M. tuberculosis*. A positive IGRA test is therefore more specific for tuberculosis infection than a positive PPD test.

The bacteria that causes 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.

Study Procedures

THE PROCEDURE OF BLOOD DRAWING FOR IGRA TESTING:

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 PPD SKIN TESTING:

PPD Skin-testing procedures will be performed by the nursing staff of the DCRU. PPD is given as a small volume injection placed between layers of the skin of your forearms. You will receive up to three (3) injections, each of which will contain 0.1 mL (or about 1/50th of a teaspoon) of fluid. These will include injections of 1) the standard skin-test dose 5.0 tuberculin units (TU) of PPD, 2) a reduced dose of 0.5 TU of PPD, diluted in sterile salt water, and 3) sterile salt water alone. Prior to the injections, the skin of one side of each of your forearms will be wiped with an alcohol solution and then dried with sterile gauze. Each injection will produce a small blister of less than 5 mm (about ¼ inch) in diameter. You will be asked to stay in the testing area for 30 minutes following the administration of the test. You must also return to the research area to have your arm examined 48 to 72 hours after you receive the PPD skin test(s). Skin-test results will be interpreted by the DCRU nurses and/or Dr. Silver

Risks

RISKS OF BLOOD DRAWING FOR IGRA TESTING:

Your participation in this study may involve the following risks, the insertion of the needle to draw blood is painful; however, this discomfort is brief. For most people, needle punctures to get blood samples to not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

RISKS OF PPD SKIN TESTING:

You may feel some stinging and burning during the skin testing procedure at the site of the injections. It is possible, but extremely unlikely, that you may develop an immediate allergic reaction to the skin test material. If this were to occur, the investigators would see a large red area when they examine your arm 30 minutes after

the injection.

You would then be instructed to take an oral antihistamine medication (which would be provided by the investigators), and would be asked to remain in the testing area for an additional 30 minutes for further observation and evaluation. If you were found to be short of breath, or to have wheezing or low blood pressure, you would be escorted to the Emergency Department at UHCMC to receive further care. If none of these additional problems developed during the additional observation period, you would be sent home and provided additional antihistamines to take for another 48 hours.

For subjects who have previously had positive skin-test response to PPD, it is expected that at least some of these sites will develop areas of inflammation of the skin within the 24-48 hour period following the skin testing. These areas will be hard in the center and surrounded by a circle of redness and warmth. All subjects will have to return to the research area 48-72 hours after testing to allow the research staff to examine the injection site.

It is possible that you may have an unusually strong skin-test response to PPD that would result in the development of a very large area of hardness at the site of your skin test. It is possible that the site of a very large response would develop blistering of the skin or break open. If this occurs, you could develop a small scar at the site of the skin test. If a very large response was painful or blistered, the investigators may recommend that you be treated with corticosteroids (such as cortisone or prednisone) that are known to inhibit the local inflammation caused by PPD, and will provide you with this medication.

If any of the skin-test injection sites develop areas of hardness greater than 25 mm or 1 inch in diameter (approximately the size of a quarter), or if your skin breaks open at an injection site, you should contact Dr. Richard Silver. You may also contact Dr. Silver at any time through the UH operator at (216) 8441000 should you have any concerns following this procedure.

It is possible that both positive and negative tests for LTBI can be incorrect, using either PPD skin testing or IGRA blood testing. If results of your testing are unexpected, further evaluation by your own doctor may be helpful in determining if any further testing should be considered.

Testing for LTBI is being performed as part of a research study and is not intended to be of direct benefit to you. However, if you are found to have a positive test, medical treatment could be helpful in reducing your risk of developing active tuberculosis. Whether or not this would be appropriate for you should be determined based on further evaluation with your doctor, or with specific tuberculosis specialists whom the investigators can recommend. Your participation in this study may contribute to improved understanding of immunity to tuberculosis.

Reproductive Health/Sexual Activity

Undergoing blood testing or skin testing for LTBI does not provide any risk to a pregnant woman or unborn fetus. However, undergoing research bronchoscopy procedures does provide risk to both a pregnant woman and her developing fetus. Therefore, women who are willing to participate in research bronchoscopy procedures must undergo urine pregnancy testing within 24 hours of the procedure before being allowed to

undergo research bronchoscopy. A woman who has any suspicion that she may be pregnant should not participate in research bronchoscopy procedures even if her urine pregnancy test is negative.

Alternatives to Study Participation

Because this study offers no direct benefits to participants, your only alternative is to not participate. If you are concerned about the possibility that you may have been infected with the bacteria that causes tuberculosis, you could have PPD skin-testing or IGRA blood tests performed by your own doctor or by the Cuyahoga County Tuberculosis Clinic.

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.

Financial Information

Your participation in this research study will be done at no cost to you. You will be paid for your time and effort for being in this research project. You will be paid $5.00 for each ounce (30 mL) of blood drawn. Since only 6 mL of blood are needed for the IGRA blood test, you will be paid $5.00 compensation for completing the blood draw.

You will be paid $20.00 for your time and effort in this research project for completing a skin test.

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".

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 on the UH secure S drive. 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, email, address, phone number, and ethnicity
- Results of tuberculosis skin testing (also known as tuberculin or PPD testing) and **IGRA** 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.

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.

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) 386-1151 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.

Signature:

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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	