Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____

Medical Record # _____

What is the purpose of this form?

This form provides you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a copy of this form.

Who is funding this study?

This study is being funded by University of Virginia.

Key Information About This Research Study

Principal Investigator:	Eric Houpt, MD University of Virginia Division of Infectious Disease Box 801340 345 Crispell Drive, MR-6, Room 1716 Charlottesville, Virginia 22908 Telephone: (434) 982-1700
Funding Source:	University of Virginia
Funding Source:	Merck & Company

You are being asked to take part in a research study. You do not have to take part in this study. You should only agree to take part in this study after reading this consent form and discussing it with the study team. You may also discuss this with your family, friends, health care providers or others before you make a decision.

What is the purpose of this study?

The purpose of this study is to find out if vaccination with *Mycobacterium bovis Bacillus Calmette Guerin* vaccine can be used to treat *Mycobacterium avium complex* (MAC) lung disease. BCG vaccines have been used to protect people from tuberculosis (TB) in other parts of the world. TB is caused by a bacterium called *Mycobacterium tuberculosis*. The mycobacterium that is the cause of your MAC lung disease is similar to the bacteria that causes TB. Since the BCG vaccine is able to be used against TB, researchers think that it may also work against MAC lung disease.

So far, BCG vaccines have been given to millions of people worldwide. Over 80% of the world's newborns are given BCG vaccine after birth to lower the risk of getting childhood tuberculosis (TB). One trial looked at BCG on protection against COVID-19 in 5393 adults that were up to 83 years old worldwide. In that study local injection site reactions occurred but most were mild and all resolved within 10 days. Additionally, in a randomized trial in Greece involved giving BCG or placebo to 200 hospitalized elderly adults with an average age of 79.9 years carrying a variety of different illnesses. These authors found BCG to be safe and to reduce the number of subsequent respiratory illnesses.

The BCG vaccine in this study is being produced by Merck. It is produced as "TICE® BCG Live for Intravesical Use." For the remainder of this document, we will refer to it as "TICE® BCG." It will be administered by intradermal injection. TICE® BCG is the same formulation that is used to vaccinate against TB. Researchers want to see if the TICE® BCG can help the body's immune system to help fight against MAC lung disease.

MAC lung disease is becoming more common in the United States, and it is very hard to treat effectively. Common symptoms of MAC lung disease are breathlessness, tiredness, fever, unintentional weight loss, chronic cough, and mucous or sputum production. Usual treatment involves multiple antibiotics for at least 12 months. This treatment method frequently fails, so new methods to treat MAC lung disease are needed

You are being asked to take part in this study because:

- You have been diagnosed with Non-Tuberculous Mycobacteria (NTM) lung disease, caused by MAC bacteria (MAC lung disease).
- You are not currently on antibiotic treatment.
- You are a male or female 18 years of age or older.
- You are not severely immunocompromised or immunosuppressed

Why would you want to take part in this study?

You might like to be in this study because:

- You may be helping future patients with MAC lung disease.

Why would you NOT want to take part in this study?

You might not want to take part in this study because:

- Treatment with the study agent (vaccine or placebo) may cause you discomfort or make you feel unwell.
- You will have your blood drawn on 3 separate days, which may cause some discomfort and/or bruising.
- TICE® BCG is a live injectable vaccine, which can cause pain at injection site, fever, muscle soreness, and headaches.

- As with all research, there is a small risk to your privacy from the use of your medical information.

If you get the TICE® BCG instead of placebo, you may test positive on the tuberculin skin test (TST) even if you do not have a TB infection. The TST is a common test used to screen for TB. If you need to be screened for TB in the future, another method called the Interferon Gamma Release Assay (IGRA) is recommended. The results of the IGRA will not be impacted by the TICE® BCG.

What will I have to do if I take part in this study?

Full details of all the procedures listed below are found later in this form. If you agree to take part in this study, you will:

- Receive the TICE® BCG vaccine or placebo injection at UVA **as part of this research study**.
- Come to UVA for in-person visits 3 times (Day 0, Day 60, & End of Study) **as part of this research study**
- Have 32 remote visits over the computer or telephone **as part of this research study**
- Answer surveys and questionnaires about how you are doing **as part of this research study**.
- Have your blood drawn 3 times **as part of this research study**.
- Give the study team personal and demographic information **as part of this research study**.
- If you have any new symptoms, discuss them with the study team **as part of this research study.**
- Provide monthly sputum (a thick mucus made in your lungs) samples. These would be submitted for your usual care and testing will be billed to your insurance, but the results will be recorded as part of this research study.

What is the difference between being in this study and getting usual care?

If you take part in this study, the following things will be done differently than if you do not take part in this study. The things that are done only for this study are clearly marked above “as part of this research study.”

This is a research study about TICE® BCG ®, an investigational drug that has not been proven to be safe or helpful against MAC Lung Disease. This product has been approved by the U.S. Food and Drug Administration (FDA) for intravesical use, but not for intradermal administration or for treating MAC Lung Disease. The FDA has allowed TICE® BCG to be used in this research study by intradermal use for MAC Lung Disease.

What other treatments may I receive if I decide to not take part in this study?

If you decide not to be in this study, you may receive antibiotic treatment as recommended by your doctor. You may also choose to not be treated for your MAC Lung Disease.

How many people will take part in this study?

Up to 48 people will enroll and take part in this study.

How long will this study take?

Your participation in this study will last up to 2 years. There will be 3 in-person visits at UVA. There will be 32 remote visits. The in-person visits will last between one and four hours. The remote visits will be by phone or on the computer. They will last about 20 minutes.

What will happen if you are in the study?

Before you can join this study, we must complete the informed consent process to review and sign this form.

We will first call you to ask you to review this consent together. If you have a computer, we can email you this consent so you can follow along while we talk about the study. If you do not have a computer or email, we can mail you the consent to review together or you can visit in person. You can ask any questions you may have before you decide to join the study.

If you decide to join the study, we will call you to review your medical history. This may be the same phone call as the consenting phone call, but it does not have to be.

At the baseline visit you will have additional tests and a physical examination to make sure that you healthy enough to be in the study. If you qualify you will be in the study.

If you are in this study, you will get either the TICE® BCG or the placebo. This type of study is called a double-blind study. This means that neither you, the study doctor, nor the study staff will know which you got. You will find out if you got the TICE® BCG or the placebo when the study is over. However, if there is an emergency, the study doctor will be able to find out which study treatment you got if he/she thinks that it is needed for your care during the emergency.

The study will last around two years. There will be 3 planned in-person visits and 32 remote visits. The in-person visits will be on Day 0, Day 60, and at the end of the study. End of study is expected to be 2 years after you enrolled, but if you stop the study early we may ask you to complete the end of study visit with blood draw.

SCREENING (visit will last about 1 hours may be completed remotely)

Visit 1 Remote (Day -90 to Day 0):

If you agree to participate in the study, you will sign this consent form before any study-related procedures take place. The study team will schedule your Day 0 (Visit 2), and they will review your medical records.

BASELINE/RANDOMIZATION VISIT (Day 0) visit at UVA will last about 4 hours

At this visit, you will have the following tests to confirm your eligibility:

- Urine pregnancy test, if applicable
- Physical exam by study doctor
- HIV test (by fingerstick)

Women of childbearing potential must agree to practice a highly effective method of birth control from Day 0 to at least 90 days after study intervention. Some examples of acceptable birth controls are:

- true abstinence (refraining from heterosexual intercourse during the entire study),
- copper intrauterine device (IUD),
- hormonal methods (levonorgestrel-releasing intrauterine system, progestogen implant, combined oral contraceptive pill)
- combined with barrier method (using a physical barrier, like a condom or diaphragm, along with a chemical barrier, such as a spermicide, to prevent pregnancy)
- exclusive homosexual relationship
- sole male partner who has undergone surgical sterilization

If these test results do not exclude you, you will be randomly assigned (like the flip of a coin) to 1 of 2 study treatment groups. You have an equal chance of being assigned to any one of the groups. Neither you nor your doctor can choose which treatment you are assigned. Neither you nor your doctor will know which study treatment you will get until the study is done. But if your doctor needs to know in case of an emergency, the people doing this study can find out.

GROUP 1: Placebo

GROUP 2: TICE® BCG

The participants in Group 1 will receive a placebo and the participants in Group 2 will receive the TICE® BCG. A placebo is a harmless substance that looks like the study drug but should have no effect. All the people in the study, whether they received the placebo or TICE® BCG will complete the same study procedures. You will find out if you got the placebo or TICE® BCG when the study is over.

During this study, you will be asked to fill out questionnaires. These questionnaires ask about:

- How you are feeling
- Your lifestyle habits
- Medicine use
- Health care received
- Diet

- Daily activities
- How you feel about taking part in this study

These questionnaires will take about 15-20 minutes to complete.

FOLLOW UP VISITS:

Weeks 1-12 remote visits lasting about 10 minutes:

You will be asked about injection site reactions and other possible side effects weekly for the first 3 months while on study. You will be asked similar questions related to other possible side effects monthly through month 12 of the study.

You may answer these questions by completing study questionnaires on your computer, smart phone, or over the telephone. If you report problems that cause the study team concern, a study doctor will follow-up with you by telehealth (phone call or video conference) to discuss the problems with you. They may recommend additional follow-up if it is needed.

Month 2 (Day 60) In person visit lasting about 1 hour

You will be asked to visit the study center 2 months after you receive either the vaccine or the placebo and at the end of study. This study visit will include asking you some questions, a physical exam, and collection of sputum and blood samples.

Months 3-12 remote about 30 minutes

In addition to completing the study questionnaires on your computer or over the telephone, you will be asked to collect sputum samples each month and send the samples to UVA lab, using the shipping materials provided.

Months 13-24 remote about 20 minutes

You will be asked to complete a shorter study questionnaire on your computer or over the telephone, you will be asked to collect sputum samples each month and send the samples to UVA lab, using the shipping materials provided.

Study Schedule

	Screening Demographics (Day -90 to Day 0)	Baseline (Day 0)	Weekly Weeks 1-12 (+/- 1 day)	Day 60 (+/- 10 days)	Monthly Mos 3-12 (+/- 7 days)	Monthly Mos 12-24 (+/- 7 days)	End of Study
Demographics	X						
Informed Consent	X						
Record Chest CT results and sputum AFB culture results, if available	X						X
Medical History Questionnaire		X					
Urine pregnancy test if applicable		X					
Point of care HIV testing		X					
Physical exam or limited physical exam		X		X			X
Study shot: TICE® BCG or Saline intradermally		X					
Visual analog pain scale		X					
Blood collection		X		X			X
Collect and Return Sputum for AFB Culture		X		X	X	X	
Adverse Event Triage Survey		X	X		X		
Quality of Life-Bronchiectasis Respiratory questionnaire		X			X	X	
Questionnaire for Respiratory illness		X		X	X	X	
Study Location	Remote (R)	In-person (I)	R	I	R	R	I

END OF STUDY:

When you have completed your other study activities, we will ask you to have a final blood draw and brief physical exam with the study doctor.

After you have completed the study, you will be referred to your doctor. They may decide if you need to resume taking the medication to treat your MAC lung disease.

What are your responsibilities in the study?

You have certain responsibilities to help ensure your safety.

These responsibilities are listed below:

- Complete each study visit.
- Be honest about your health history.
- Follow the instructions given by the study doctor/staff.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.
- Answer study-related questionnaires and surveys truthfully.
- Inform the study doctor or study staff as soon as possible if you have to take any new medications.

Blood Testing

We will take (or "draw") up to total amount of 7 teaspoons for this study. Blood will be drawn at 3 time points.

Day 0: 3 teaspoons
Day 60: 2 teaspoons
End of study: 2 teaspoons

The blood we take will be tested to measure how your body is reacting to the study agent (vaccine or placebo).

If you want to know about the results before the study is done:

During the study, your study leader will let you know of any test results that may be important to your health. In addition, as the research moves forward, your study leader will keep you informed of any new findings that may be important for your health or may help you decide if you want to continue in the study. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time, you can ask for more information about the study results, and placebo recipients can ask whether there are options to receive BCG vaccine

During the study, blood will be collected to see if your body has had an immune response to the study agent (TICE® BCG or placebo). This test will not be done right away, and its results will not change anything about your medical care.

What are the risks of being in this study?

A risk of allowing us to collect information about you is a potential loss of privacy. The University of Virginia will do its best to protect your records so that facts about you and your health will be kept private. The chance that information identifying you will be given to someone else is very small. However, we cannot *guarantee* it will be safe.

Risks and side effects related to the TICE® BCG include:

Likely:

- Injection site pain
- Redness
- Papule formation (small raised area of skin)
- Itching

Less Likely:

- Fever
- Muscle pain
- Headache
- Weight loss
- Lymph node enlargement

Rare but serious:

- Infection with BCG
- Lesions on your body near injection site
- Allergic reaction
- Scar formation
- Cardiac event

Severe reactions are rare, even in an elderly population. Severe reactions can be treated with antibiotics and/or anti-inflammatory medications.

Risks from Placebo:

There is the risk that the placebo injection will lead to injection site pain, redness, papule formation, or itching.

Risks from Completing Questionnaires

Some of the questions asked may be upsetting, or you may feel uncomfortable answering them. If you do not wish to answer a question, you may skip it and go to the next question.

Risks of having your blood drawn:

Having blood drawn may cause:

- ✓ pain (common),
- ✓ a bruise (sometimes),
- ✓ fainting or passing out (not very often), and

- ✓ infection (rare).

If the people doing the study are exposed to your blood or body fluids in a way that could give them a disease, your blood may be tested. The tests might check for:

- ✓ hepatitis,
- ✓ HIV (Human Immunodeficiency Virus), or
- ✓ other infections.

You and the person exposed would be told the test results. However, your name would be kept private. If your test is positive for hepatitis or HIV or any other infection that may affect your clinical care, we will tell you the results and help you understand what the results mean for you.

Other unexpected risks:

You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems and they will schedule a telehealth.

Could you be helped by being in this study?

You may not directly benefit from being in this study. However, the information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

You do not have to be in this study to be treated for your illness or condition. You can get the usual treatment even if you choose not to be in this study. The usual treatment would include antibiotic treatment if recommended by your doctor

Will you be paid for being in this study?

You will be paid up to $550 if you finish the entire study. You will be paid $25 after each follow-up that includes a monthly sputum sample (months 2 through 24). In order to be paid, you will be need to register with UVA Payment Works. The study team will request payment to you when they receive the sputum sample. You should get your payment about 30 days after the request is made either by check or direct deposit. The income may be reported to the IRS as income.

By agreeing to be in this study, you are donating your blood and sputum for research, and giving up any property rights you may have to these specimens or the results of the research. The results of this research using your donated materials may have commercial value. However, you will not receive any payments.

Will being in this study cost you any money?

The following procedures/tests, which are being done for research purposes, will be provided at no cost to you or your health insurance:

- Vaccine injection (placebo or TICE® BCG)
- Blood collection
- Pregnancy test if applicable
- Physical exam by study doctor
- HIV test
- Questionnaires

You and/or your insurance company must pay for any tests or care given beyond what is required in this study. In addition, you and/or your health insurance may also have to pay for other drugs or treatments that are given to help you control any side effects. You will have to pay for any costs not covered by your health plan. You may be responsible for any co-payments or deductibles. You may wish to ask your insurance company for an estimate of what these costs might be or if pre-approval is required.

You will be responsible for the cost of travel to come to any study visit and for any parking costs.

What if you are hurt in this study?

You do not give up any legal rights, such as seeking compensation for injury, by signing this form. If you feel you have been injured as a result of this study, you may contact the Principal Investigator or the IRB (phone numbers are located near the end of this form). If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover.

What happens if you leave the study early?

You can change your mind about being in the study at any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include:

a) You do not follow your doctor's instructions
b) The study sponsor closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to let us know.

Any data collected about you up until the time you leave the study must be kept in order to determine the results of the study.

How will your personal information be shared?

The UVA researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

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.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form or complete the "Leaving the Study Early" part of this form and return it to the researchers. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

A copy of this consent form will be put in your medical record. (This is not the same as the record of this research study.) This means that everyone who is allowed to see your medical records will be able to find out that you are in this study. This is done so your regular doctors will know what you receive as part of this study. If you have other health problems during the study, they will be able to treat you properly.

Please contact the Principal Investigator listed BELOW to:

- Obtain more information about the study and ask any questions regarding study procedures or study treatments/interventions.
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Eric Houpt
University of Virginia Division of Infectious Disease
Box 801340
Charlottesville, Virginia 22908
Telephone:(434) 982-1700

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22903 Telephone: (434)924-2620

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the UVA Study Tracking Number (at the bottom of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

You may also report a concern anonymously by calling the UVA Compliance Hotline phone number at 1-800-235-8700.

Would you like the study team to communicate with you by email or text message?

If you choose to communicate with the study team by unsecure email (email that is not encrypted) or text message to your personal phone, there is some risk that your health information could be read or accessed by someone else while the information is sent or saved by your email or phone provider.

Your personal email or phone provider may also share or release your information because they do not have to follow the privacy laws that UVA follows. Sometimes email and phone providers release information to marketing companies for use in direct advertising. If you choose to communicate by email or text messaging, UVA cannot control this potential loss of privacy but we want to tell you about this possible risk.

You do not have to agree to communicate with the study team by email or text message to be in this study. If you agree to texting or emailing, the study team will collect your phone and/or email address from you that you would like them to use to contact you. Please note, if you agree to text messaging, charges may apply depending on your data/text plan with your phone provider.

You do not have to agree to use email or text message to be in this study.

PLEASE INDICATE YOUR CHOICE BELOW:

Yes_____ I agree to be contacted by email or text.

If you agree to texting or emailing, the study team will collect your phone and /or email address that you would like them to use. Please note, if you agree to text messaging, charges may apply depending on your data/text plan with your phone provider.

No_____ I DO NOT agree to be contacted by email or text.

Would you like to be contacted about future studies?

The researchers in this study would like to know if you wish to be contacted regarding participation in additional studies that may be appropriate for you. By agreeing to be contacted, you will allow a qualified member of the study team to contact you in the future to ask if you want to participate in additional studies. You have no obligation to participate in any study.

Declining will have no influence on your present or future status as a patient in this clinic. You will receive the same care as any other patient seen in this clinic. There will be no penalty or loss of benefits to which you are otherwise entitled. Your clinic records will indicate that you do not want to be asked about future research by or through anyone but your treating physician.

Participation in research may involve some loss of privacy. However, your records will be handled as confidentially as possible. Access will be limited to the study team organizing the study. No information will be used for research without additional permission. Your contact information will not be shared with anyone outside of UVA without your permission.

You do not have to agree to be contacted about future research to be in THIS study.
PLEASE INDICATE YOUR CHOICE BELOW if you are willing to be contacted about any future research studies.

____ Yes, I agree to be contacted about future research studies.

____ No, I do not want to be contacted about future research studies.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form, it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

Person Obtaining Consent

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Notification of My Health Care Provider

Your health care provider will be notified of your participation in this study if your healthcare provider is at UVA.