Title of Study: The Effect of Chlorhexidine on the Oral and Lung Microbiome in Chronic Obstructive Pulmonary Disease

Principal Investigator: Chris Wendt, MD **VAMC:** Minneapolis 618

INTRODUCTION

It is important that you read and understand the following explanation of the proposed research study before you agree to participate. This consent form describes:

- The purpose,
- The description of the study,
- The benefits,
- The risks and/or discomforts (including any potential for pain),
- Steps taken to decrease or eliminate the risks, discomforts, or possible pain,
- Any other treatments that may be available, and
- Confidentiality and use of research results.

Whether you decide to participate or not, treatment at the VA for which you are eligible will not be affected.

This consent form may contain words you do not understand. Please ask the study doctor or the study staff to explain any words or information unclear to you.

PURPOSE OF THE STUDY

You are being asked to voluntarily participate in a research study to determine if a medicated mouth rinse called chlorhexidine will help improve the mucus in your airways. You have been asked to participate in this study because you have chronic obstructive pulmonary disease (COPD) and chronic cough with phlegm production. Your participation in the study will last 8 weeks, and for this study you will participate 2 days. Up to 50 people will be in the study at this site. Our goal is to determine if the mouth rinse chlorhexidine changes the secretions in the lung by lowering the number of bacteria in those secretions.

DESCRIPTION OF STUDY

The following information describes what will happen while you participate in the study.

Screening Exams

If you agree to participate in the study, we will check to see if your medical condition matches our study entry criteria. To determine if you are eligible to participate, you will

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come to the clinic for a screening visit that will last a couple of hours. During this visit, the following will happen:

- You will be asked questions about your health, your medical history and the medications you are taking.

- You will have a limited physical exam that will include measurement of vital signs. Your heart, lungs and mouth will also be examined.
- You will be asked to perform breathing tests (spirometry). These tests measure your lung function.
- You will be asked to fill out research questionnaires about your breathing and other respiratory related symptoms. There will also be questions concerning your overall quality of life.

Research Treatment

If you qualify for the study, you will be assigned at random (like flipping a coin) to one of two groups of patients. One group will rinse and spit the mouth wash, chlorhexidine, twice a day. The other group will take identical looking wash that is a placebo (no active medication).

Patients in both groups will rinse their mouth with approximately 2 tablespoons of liquid twice daily for 8 weeks. You will be instructed not to eat or brush your teeth for one half hour before and one hour after the rinse and to not use other mouth rinses. We will also ask that you not receive a routine dental appointment with teeth cleaning while participating on this trial. You will be asked to keep a daily diary of symptoms by answering 3 simple questions related to breathlessness, cough and sputum. Your chance of getting chlorhexidine is 50%, which is the same chance of you getting the placebo. You will not know, until the end of the study, which rinse you are taking. The doctors and clinic staff will not know this either, though it will be possible for them to find out quickly in an emergency.

All patients will continue on previously prescribed COPD treatments.

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After you are assigned to a group you will have the following procedures performed twice, once prior to starting the study medication and again during the last week of study medication:

- You will have blood samples (approximately 15 ml or 1 tablespoon) taken to measure an inflammation markers in your blood.
- You will rinse your mouth with approximate 1 ounce of sterile water and spit into a cup. This will be used to identify the bacteria in your mouth.
- You will undergo a test called an 'induced sputum': You will be asked to fast for at least 2 hours prior to the study. Prior to the sputum test you will be treated with an inhaler, albuterol, to open your airways and be given approximately one ounce of sterile water to gargle and spit. We will then treat you with a nebulizer treatment containing a high concentration of sterile saline, or salt water for 20 minutes. This solution will loosen your sputum in your airways and may make you cough. We will stop the nebulizer every 2 minutes to encourage you to cough up sputum and check your lung function with a quick handheld breathing test. If your breathing test should drop by more than 20% or you feel short of breath, we will stop the sputum collection. You can eat immediately following the test. The fluid will be tested for bacteria. None of your genetic material will be extracted or used for analysis. These results will not be available to you or your family and will be used for this study only.

Phone call during treatment phase:

Approximately 4 weeks after you start the study medication the study team will call to see how you are doing. You may call at any time during the study if you have questions or concerns.

- You will be asked a few questions to see if you are having any side effects from the study medication.
- You will be asked if you have had any problems with taking the medication.
- You will be asked about medication use over the proceeding weeks, such as antibiotics, prednisone and mouth washes.
- You will be asked about clinic visits or hospitalizations related to your COPD.

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Final Clinic Visit
Eight weeks after starting the study, you will have your final study visit. You will need to come to the study site and this visit will take a couple of hours. You will repeat the tests described above. In addition, we will ask you to bring all of your unused study medication. The visit will include:

- You will have a limited physical exam that will include your heart, lungs and mouth will be examined.
- You will be asked to fill out a research questionnaire about your breathing and other respiratory related symptoms. There will also be questions concerning your overall quality of life.
- You will be asked a few questions to see if you had any side effects from the study medication.
- You will need to bring in any remaining study medication that you have in your home.
- You will be asked if you had any problems taking the study medication.
- You will undergo an oral rinse and induced sputum (described above).

RISKS AND/OR DISCOMFORTS

Induced Sputum
The procedure may involve risks and/or discomforts. Although the procedure has been performed safely in hundreds of individuals as part of research studies and routine clinical care, it is not a trivial undertaking.
Common risks:

- There can be some discomfort due to coughing and some mild shortness of breath.

Uncommon risks:

- A medication that can open your airways will be used to open your airways. This medication, albuterol, is often used to treat people with COPD. Albuterol sometimes increases heart rate or causes jitteriness or shakiness, but these effects usually disappear quickly.
- Shortness of breath. On occasion the saline and coughing can induce significant

shortness of breath and wheezing. To prevent this we will monitor your breathing every 2-4 minutes during the test and stop the test if your breathing function drops by more than 20%. If you should have persistent shortness of breath, it may require a second treatment with an inhaler, such as albuterol.

Although the complications of induced sputum that are listed above have been reported with the procedure in the past, the principal investigator does not consider any of these complications as being likely (1) because the screening procedure will eliminate from this study individuals at particular risk of these complications and (2) because the physicians performing the procedures will be experienced.

Breathing tests (spirometry)
This testing may make you feel short of breath. On rare occasions, people feel dizzy or faint. A medication that can open your airways (albuterol) can give the side effects described above.

Blood draws
Blood testing will be done during the research study. Blood draws may cause mild discomfort and bruising. Very rarely, fainting, blood clots, or an infection at the site can occur.

Questionnaires and Daily Diary
You may be uncomfortable sharing information about your symptoms and how they affect your life. Questionnaires you complete will stay with your study file in the study doctor's office. Only your study identification, not your name, will be recorded with the answers you provide on these questionnaires and diary. You have the option of leaving answers blank if they make you feel uncomfortable. There are no right or wrong answers. You should answer the questions based on how you feel.

Risks of Chlorhexidine mouth rinse
There have been multiple studies published using Chlorhexidine for a variety of dental conditions and a study to prevent lung infection. These studies did not report an increase in side effects with Chlorhexidine compared to placebo.

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There have been rare reports of irritation of the lining of the mouth, and some have reported allergy. However, this has not been more than placebo. A small number of people report a decrease in taste sensation that is temporary. This is less than 4 out of 100 people. Also, people that drink tea and use chlorhexidine report a small increase in discoloration of their teeth. For this reason, we will ask you to avoid drinking tea while on the study medication.

Risks Associated with Confidentiality
Participation in any research carries the risk of breach of confidentiality because participants provide health information. We will do our best to protect your confidentiality. All paper documents with information obtained as part of this study will be secured in a locked file behind a locked door at all times. Only study staff will have access to this information. Electronic information will be kept in a password protected file on secured VA computers. Only study staff will have access to this information.

Unforeseen Risks
In addition to the risks listed above, there may be uncommon or previously unrecognized risks that could occur during the study.

There may be other unknown side effects that could occur.

FUTURE USE OF SPECIMENS

The specimens are being sent to an outside lab, (removed of all identifiers), and then the unused portion will be returned to the VA lab for banking, for future research related to COPD for 10 years. The specimens will be stripped of all identifiers, and dates, and held at the VAMC laboratory of Dr. Chris Wendt. Only Dr. Wendt and her research personnel will have access to the specimens. The specimens will be de-identified for long-term storage and will be labeled with a unique code that does not include your name, date of birth, social security number or other information linked to you.

EMPLOYEES AS RESEARCH SUBJECTS

If you are a VA employee you are considered a special class of research subject who deserves special protections: 1) your decision to participate in this study

should be free from pressure or coercion to participate; and 2) the VA research team will work to secure your information according to VA data security and privacy policies and every effort will be made to keep your information from your supervisor and co-workers. However, accidental disclosure or release of your private information could occur during the conduct of this study.

BENEFITS

There may be no direct benefit to you from being in the study. If you do experience some improvement in cough and phlegm production and/or shortness of breath while taking the study drug, any symptom benefit would likely not last beyond the time you are in the study. The knowledge gained from this study may benefit others in the future.

COMPENSATION

You will be paid $50 per visit (2 visits) for your participation for a possible total of $100. You will be given $5 in the form of a coupon to buy lunch in the cafeteria at each visit (2 visits) In addition, if you are traveling over 50 miles one way to come to the Minneapolis Veterans Administration Medical Center for this study, you will be paid $0.415 (41.5 cents) per mile for your travel expenses. You will receive your payment within 6 weeks of completing the study.

ALTERNATIVES (OTHER AVAILABLE TREATMENTS)

The medication being studied will be added to your other breathing medications. Your usual breathing medicines will not be altered as part of this study. There are multiple inhaled and oral medications that are used to treat chronic obstructive pulmonary disease (COPD). The medication Chlorhexidine should not interfere with your existing COPD therapies.

CONFIDENTIALITY AND USE OF RESEARCH RESULTS

The results of this study may be published or presented but your identity and records will not be revealed unless required by Federal Law. A Federal Law allows the U.S.

Food and Drug Administration, Office for Human Research Protections, Government Accountability Office and other Federal agencies, the Research and Development Committee and/or the Institutional Review Board (IRB)/Human Studies Subcommittee of the VA Medical Center to review records. Because of the need for these inspections, absolute confidentiality cannot be guaranteed.

COSTS TO YOU FOR PARTICIPATING

There is no cost to you for taking part in this study. All the study costs, including any study medications provided by the sponsor, will be paid for by the VA Medical Center. **Veterans who must make a co-payment for their usual medications or treatments will continue to be required to make such a co-payment for non-study related drugs.** There should be no additional medical costs to you for taking part in this study. However, frequent clinic visits may result in transportation costs and possible wages lost due to time missed from work.

MEDICAL CARE IF YOU ARE INJURED

In case you are injured from this research study, treatment will be available, including first aid, emergency treatment and follow-up care, as needed, by the VA Medical Center. In the event you cannot reach a VA facility, the VA will pay for necessary medical care for any injury or illness directly related to your participation in this research study. If you receive this type of medical care, you must contact the Research Investigator for this study. You can find contact information in the section of this consent titled “Compensation for Any Injuries”.

COMPENSATION FOR ANY INJURIES

You have not released the VA Medical Center from liability by signing this form. This includes but is not limited to: 1) free medical care other than as described in this consent form, 2) payment of lost wages, or 3) compensation for pain and suffering. Compensation for those items from the VA may be available under applicable Federal Law. You should immediately report any injuries resulting from your participation in this

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study to Dr. Chris Wendt at (612) 467- 4400 during the day and during the evenings or week-ends, by calling the VA operator at (612) 725-2000 and ask to have the Pulmonologist on call paged. Tell the operator you are in a research study. (If you do not live in the metropolitan area, you may call the toll-free number: 1-866-414-5058.)

NEW INFORMATION

You will be given any new significant information that is discovered during the course of this study which may influence your willingness to continue the study.

OTHER INFORMATION

Reasons for Removal from the Study

The study doctor can end your participation in this study if you do not take your study medications as prescribed, if you miss scheduled study visits, or if s/he determines that it is in your best interest to end your participation. In addition, you may be removed from the study by the doctor if you do not follow the study plan, have a study-related injury, if it is believed that being in the study may cause you harm, for administrative reasons, or for any other reason.

If You Want to Withdraw From the Study

At any point during this study, you can decide that you no longer want to participate. If you no longer want to participate, you should notify the study coordinator, Ms. Sue Johnson (612) 629-7492 or Dr. Chris Wendt (612) 467-4400. You will continue to get your usual care at the VA regardless of your study participation. If desired, you can request that your specimens be destroyed.

RESEARCH SUBJECT'S RIGHTS:

I have read or have had read to me all of the above.
_____ has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available.

Printed name and **last 4 of SS# (If addressograph label is used, please mask all other information)**	This section for completion by IRB only Approval date: 02/27/2017 Expiration date: 02/26/2018

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I have been informed that because this study involves articles regulated by the FDA (Food and Drug Administration), the FDA may choose to inspect research identifying me as a subject of this investigation.

I understand that I do not have to take part in this study and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published but my identity and records will not be revealed unless required by law. We do not anticipate any commercial benefits from this study and you will not receive any additional benefits other than what is stated in this form.

I authorize the use of my bodily fluids (blood sample, oral wash and sputum).

In case there are medical problems or questions, concerns, or complaints, I have been told I can call Dr. Chris Wendt at (612) 467-4400 or Sue Johnson at (612) 629-7492 during the day and the VA operator at (612) 725-2000 after hours and ask to have the Pulmonologist on call paged. I will tell the operator I am in a research study. (If I do not live in the metropolitan area, I may call the toll-free number: 1-866-414-5058.)

If any medical problems occur in connection with this study the VA will provide emergency care.
If I have any questions about the rights of a research subject, or would like to:

- obtain information
- discuss problems or concerns, or have questions about this study
- offer input regarding this research study

and would like to speak to an individual who is not part of the research team of this study, I may contact the Patient Representative at (612) 725-2106. If I wish to verify the validity of the study and its authorized contacts, I may call the patient representative or contact the IRB office at 612-467-2800.

Printed name and **last 4 of SS# (If addressograph label is used, please mask all other information)**	This section for completion by IRB only Approval date: 02/27/2017 Expiration date: 02/26/2018

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My questions have been answered and I voluntarily consent to participate in this study. By signing this form, I have not given away any of my legal rights, which I have as a subject of this research study. I will receive a signed copy of this consent form.

_____ _____
Subject's Signature Date

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name Of Person Obtaining Consent

Printed name and **last 4 of SS# (If addressograph label is used, please mask all other information)**	This section for completion by IRB only Approval date: 02/27/2017 Expiration date: 02/26/2018