INFORMED CONSENT FORM

# A Blinded, Randomized, Placebo-Controlled, Influenza Challenge Study in Healthy Adult Volunteers Using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), Clade 3C3a) Influenza Challenge Virus

NCT # 06476275

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**Consent to Participate in a Research Study**
**ADULT**
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**KEY INFORMATION SUMMARY**

This is a research study to understand what happens when a person is infected with an influenza ("flu") strain and how the body responds to the dose received. To do this, we will infect ("challenge") healthy participants with a strain of the flu and follow them to see what symptoms occur and when they occur. Some participants will receive a challenge with a placebo (no actual flu virus). We will collect blood samples, nasal swabs, nasal washes, nasal absorptive matrices, saliva, and exhaled breath samples. Participants must consent to storage and future research use of their blood, nasal, saliva, and breath samples if they would like to take part in this study. We will also collect samples from the surfaces and air in your confinement room.

If you agree to take part in this study, your involvement will last for approximately 2 1/2 months, including screening. This study will require a confinement stay of at least 10 days, or perhaps longer. After you leave the confinement unit, there will be 2 more clinic visits with blood, nasal, and saliva sample collections, which will take about 45 minutes for each visit.

Genetic testing may be performed on your samples collected during this study after the study is over. You will not be given the results of these tests. If you do not agree to the use of your samples for such tests, you should not participate in this study.

The risks involved in participating in this study are described in detail below. Some of the more common risks include symptoms of flu illness (mild fever, tiredness, body aches, chills, headache, blocked or runny nose, sore throat, cough and sneezing), minor pain and bruising with blood draws, and discomfort in the nose or gagging with nasal sample collection.

If you are interested in learning more about this study, please continue reading below.

Research studies are voluntary. You do not have to agree to be in this study. Please read this consent form carefully and take your time making your decision. The study team will discuss the study with you. Please ask about any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you

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decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below and will be reviewed with you by the study team.

Please tell the study doctor or study staff if you are taking part in another research study.

Dr. Christopher W. Woods, MD, MPH will conduct the study. The study is co-sponsored by Owlstone Medical Limited and Darwin Biosciences Inc. These diagnostic companies received funding from the Defense Threat Reduction Agency (DTRA), which is part of the Department of Defense (DoD), and the companies will pay Duke University to perform this research. These funds may reimburse part of Dr. Woods' and his team's salary.

**Who will be my doctor on this study?**
If you decide to participate, Dr. Woods will be your doctor for the study. They will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

**Why is this study being done?**
The purpose of this study is to understand what happens when a person is infected with the flu and how the body responds to the dose received and to identify elements or certain markers in your breath, saliva, and blood that may predict when you are getting sick.

**How many people will participate in this study?**
Up to 100 people may sign consent for this study at Duke to ensure that up to 40 participants complete the inpatient viral challenge.

**What is involved in the study?**
Screening Clinic Visit(s) - approximately 3 hours:
At the screening visit, we will give you information about the study. We will ask you to read the consent and we will answer your questions. After you have had time to think about whether to participate in the study and have discussed it with your family, friends or doctor, and if you agree to take part in this study, you will be asked to sign and date this consent form. Eligible participants will also be asked to consent to a separate biorepository protocol (Pro00109993) for the use of leftover samples and associated information (data) for the purpose of future research. More information regarding this biorepository is below in the section regarding future use.

If you agree to take part in the study, the following screening procedures will be done to see if you are eligible for this study. These procedures may be done all in one visit, or you

Duke University Health System

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may be asked to return on another day for certain parts of the screening process (for example, the chest x-ray):

- You will be asked about your complete medical history including any medications you are taking or have recently taken, vaccinations you have received, smoking history (including e-cigarettes), and past and current alcohol and drug use.
- We will collect your sex, date of birth, ethnicity, and race.
- We will collect your Flu and COVID-19 vaccination history.
- We will measure temperature, pulse, breathing rate, blood pressure and a measure of the oxygen in your blood (using a pulse oximeter device on your finger).
- We will measure your height and weight.
- You will have a physical examination.
- If you are a woman who is able to become pregnant, you must use an acceptable method of birth control for at least 30 days before the flu virus is given until the end of the study. Women will have a blood pregnancy test at this visit and a urine pregnancy test before the flu virus is given. Women with a positive pregnancy test at any time before the flu challenge will not be able to continue in the study.
- We will collect approximately 27 mL (about 2 tablespoons) of blood from a vein in your arm (venous blood) for laboratory tests, including blood counts, blood chemistry tests, and a flu antibody test. This will also include tests to see if you are infected with hepatitis B, hepatitis C, or HIV.
    - As part of this protocol, you will be tested for HIV (human immunodeficiency virus, which is the virus that causes the acquired immunodeficiency syndrome [AIDS]). You will also be tested for hepatitis B and C, which causes liver damage and liver failure. You will be notified of the results of the testing, and counseled as to the meaning of the results, whether they are positive or negative. If the test indicates that you are infected with HIV or hepatitis B or C, you will receive additional counseling about the significance of your care and possible risks to other people. We are required to report all positive results to the North Carolina Division of Public Health. The test results will be kept confidential to the extent permissible under the law. If you do not want to be tested for HIV or hepatitis B and C, then you should not agree to participate in this study.
- You will have a urine drug test for amphetamines, cocaine, and opiates now and on admission to the confinement unit.
- You will have an electrocardiogram (ECG) performed.
- You will have a chest x-ray performed. Women of childbearing potential will have to have a negative serum pregnancy test before having a chest x-ray. If

you are planning to get your chest x-ray directly after your screening visit or if more than 7 days have passed since the negative serum pregnancy test, we will do a urine pregnancy test to ensure women are not pregnant before having a chest x-ray.

- You will be provided with some wearable devices, a Garmin VivoSmart wristband and an Oura ring to wear at home before you come into the confinement unit. The Garmin, and Oura Ring wearable device will measure certain physiologic responses (for example, heart rate, oxygen saturation, electrical activity of the heart) after challenge with the flu virus. The Garmin VivoSmart is worn on your wrist and monitors heart rate and activity. The Oura Ring is worn on your finger and monitors heart rate, activity, and body temperature. You will also be provided with a phone that links to the devices via various apps. If these devices are not available at screening, they will be shipped to you before confinement, or you may receive that at the confinement visit. If there are any problems with connectivity between the phone app and the devices prior to confinement, we may schedule a phone call or zoom meeting with you.
- You will be provided with a small portable electronic device called the OMED Health® breath analyzer (OMED device) and asked to exhale a single breath into the device so that we can measure the amount of hydrogen and methane in your breath. You will also be provided with some essential safety and handling instructions prior to use. The OMED device will connect via Bluetooth® to its OMED Health smartphone app in order to record your readings. You will be provided with a mobile phone with the OMED Health app already installed and your study user account created (registered to Duke University email address using only participant ID), along with login details. You will be asked to provide a fasted breath sample before breakfast, before lunch, before dinner and 2-4 hours after dinner each day as an inpatient. All information collected by the OMED device will be digitally recorded (and stored in the cloud through Amazon Web Services (US)) using the OMED Health app associated with your study user account and will be processed and automatically received by the study team at Owlstone. You should not enter any other, in particular personal, details into the app to avoid unintended personal data being collected. This device may be sent to you a week or two prior to the start of the confinement period in order to collect baseline data during your normal routine at home.
- An online training session may be scheduled before the confinement period, so that the study team can teach you how to use the Oura, Garmin and OMED devices.

Duke University Health System

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**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

If any of the above screening tests are abnormal and the study doctor decides they are clinically important, you will not be able to continue in the study. Abnormal test results will be provided to you for follow-up with your provider.

After the screening visit(s), if you are eligible to participate in the study, you will be scheduled for the confinement challenge part of the study. We will inform you of the medications that you should not use within 7 days of your confinement stay.

Eligible participants will be randomly assigned (like drawing straws) to receive either the active virus or a placebo. A placebo is an inactive substance (no flu virus is included) given in the same form as the active virus. You have approximately a 1 in 7 (15%) chance of receiving placebo and a 6 in 7 (85%) chance of receiving active virus. The virus/placebo will be administered into your nose.

Confinement Challenge Stay (minimum 10 days):
You will be admitted to the confinement unit 2 days before we plan to give the flu virus or placebo. You may be required to share a room with one other participant of the same sex. In order to ensure we challenge our goal number of subjects with influenza virus, some subjects may be chosen to serve as backups. We will discuss with you whether you have been chosen as a backup prior to the confinement period. Subjects agreeing to serve as backups will either be admitted to the confinement unit or confined in an alternate location under respiratory isolation. Backup subjects confined in an alternate location must agree to stay in that location and abide by isolation and infection control precautions, unless transported to the study clinic for study-related procedures as outpatients. Backups not chosen for the influenza challenge will be discharged to home without having received the viral challenge on Day 1. Backups chosen for the influenza challenge will continue as inpatients on the confinement unit.

Every day while you are inpatient:

- You will be asked about any current or new medications you are taking or have recently taken.
- Your temperature, pulse, breathing rate, blood pressure and a measure of the oxygen in your blood (using a pulse oximeter device on your finger) will be taken approximately every 8 hours while you are awake.
- You will have a brief physical examination.
- You will be asked about any flu symptoms you might have.
- You will be asked to complete a food diary.
- You will be trained on and complete the flu patient-related outcomes (FLU-PRO) questionnaire and diary that you will fill out around the same time each day to record your body's reaction to flu virus.

Duke University Health System

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**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

- You will be given a Faros device to monitor your heart's activity and this will be worn on your chest.
- In the event the OMED Health breath analyzer is not available for use in this study, a separate breath sample may be collected using a specialized collection kit for measuring hydrogen and methane levels. This collection kit consists of a collection straw and breath collection tube. You will breathe through the collection straw and into the collection tube for 3-5 seconds. For this measurement, your breath will be collected at least once each day, with a second breath collection taking place on each of the first two days after receiving active virus or placebo.
- You will have your breath collected so we can analyze the volatile organic compounds (VOCs) in your exhaled breath. The study team will obtain this sample by asking you to wear a nose clip and breath normally through your mouth into a tube for 15-20 minutes.
- You will be asked to spit into a collection tube to collect your saliva up to four times approximately 4-5 hours apart for baseline immune tests. Saliva will be collected before meals and before you go to bed at night.
- You will have a small device called a TAP device placed on your upper arm for 5 minutes. It will collect approx. 1/8 teaspoon (0.5ml) of capillary blood.
- The Garmin VivoSmart and Oura Ring will transfer your data via Bluetooth to a smartphone where the compatible app has been installed. These apps will then upload the data to cloud-based servers maintained by the individual device manufacturers.
- A machine will be placed in your room to collect samples of the air, and a study team member will swab some of the surfaces in your room.

<u>Inpatient Day 1 (Study Day -2):</u>

- You will be asked if you want to continue in the study.
- You will be asked about your medical history.
- Women who are able to become pregnant will have a urine pregnancy test. If this is positive, they will not be able to continue in the study.
- You will have a urine drug test for amphetamines, cocaine, and opiates. If this is positive, you will not be able to continue in the study, unless the study doctor agrees it is safe for you to do so.
- You will have about 20 mL (1.5 tablespoons) of blood taken for baseline immune tests. Blood will be collected from a vein in your arm and a small amount will be collected from your upper arm (capillary blood).
- You will have a nasal swab to be sure you do not already have flu illness or any other respiratory virus, including COVID-19. If this is positive, you will not be able to continue in the study.

Duke University Health System

**Consent to Participate in a Research Study**
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**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

- You will have a nasal absorptive matrix collected for baseline immune tests. The study team will obtain this sample by inserting a thin flexible, textured strip into your nose and waiting 2 minutes for it to absorb nasal mucus.
- You will have a nasal wash with a saltwater solution (saline) for baseline immune tests. The study team will obtain this sample by gently squirting saline into your nose through a syringe while having you hold a specimen cup under your nose as the fluid flows out of your nose for the nasal wash sample collection.
- You will be asked to spit into a collection tube to collect your saliva up to four times approximately 4-5 hours apart for baseline immune tests. Saliva will be collected before meals and before you go to bed at night.

<u>Inpatient Day 2 (Study Day -1):</u>

- You will be asked if you want to continue in the study.
- You will have a nasal swab to be sure you do not already have flu illness or any other respiratory viruses, including COVID-19. If this is positive, you will not be able to continue in the study.
- You will have a nasal absorptive matrix and nasal wash collected for baseline immune tests.
- You will have about 75 mL (5 tablespoons) of blood taken from your arm (venous blood) and about 0.5 mL (1/8 teaspoon) will be taken from your upper arm (capillary blood) for baseline immune tests.
- Your exhaled breath (VOCs) will be measured once in the afternoon.

<u>Inpatient Day 3 (Study Day 1 – the day flu virus is given):</u>

- You will be asked if you want to continue in the study.
- Backup subjects who do not receive the viral challenge will be discharged to home.
- Your exhaled breath (VOCs) will be measured once in the morning.
- If you agree to continue in the study:
    - We will give you about 1 mL of fluid containing the flu virus or placebo, about 1/2 mL (less than 1/8 teaspoon) in each nostril via nasal spray.
    - We will monitor you and check the following 3 times per day while you are awake during the day: temperature, pulse, breathing rate, blood pressure and a measure of the oxygen in your blood (using a pulse oximeter device on your finger).
    - You will be asked if there have been any changes in your health.
    - You will have 5ml (1 teaspoon) of blood taken from your arm (venous blood) and about 0.5mL (1/8 teaspoon) will be taken from your upper arm (capillary blood)

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

Inpatient (Daily) Days 4-10 (Study Days 2-8):

- You will have a nasal swab to see if you have flu illness or any other respiratory viruses.
- You will have a nasal absorptive matrix collected for immune tests.
- You will have a nasal wash with a saltwater solution (saline) for immune tests.

Inpatient Day 4 (Study Day 2):

- About 50 mL (3 tablespoons) of blood will be taken from your arm (venous blood) for safety tests and immune tests.
- About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from your upper arm for immune tests.
- You will be asked to spit into a collection tube to collect your saliva four times approximately 4-5 hours apart for immune tests; before meals and at bedtime.
- Your exhaled breath (VOCs) will be measured twice, once in the morning and once in the afternoon.

Inpatient Day 5 (Study Day 3):

- You will have about 20 mL (2 teaspoons) blood taken from your arm (venous blood) for immune tests.
- About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from your upper arm for immune tests.
- You will be asked to spit into a collection tube to collect your saliva four times approximately 4-5 hours apart for immune tests; before meals and at bedtime.
- Your exhaled breath (VOCs) will be measured twice, once in the morning and once in the afternoon.

Inpatient Day 6 (Study Day 4):

- About 50 mL (3 tablespoons) blood will be taken from your arm (venous blood) for safety tests and immune tests.
- About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from your upper arm for immune tests.
- You will be asked to spit into a collection tube to collect your saliva four times approximately 4-5 hours apart for immune tests; before meals and at bedtime.
- Your exhaled breath (VOCs) will be measured once in the afternoon.

Inpatient Day 7 (Study Day 5):

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

- About 20 mL (2 teaspoons) blood will be taken from your arm (venous blood) for immune tests.
  About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from your upper arm for immune tests.
- You will be asked to spit into a collection tube to collect your saliva four times approximately 4-5 hours apart for immune tests; before meals and at bedtime.
- Your exhaled breath (VOCs) will be measured once in the afternoon.

Inpatient Day 8 (Study Day 6):

- About 40 mL (2 tablespoons) blood will be taken from your arm (venous blood) for immune tests.
- About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from your upper arm for immune tests.
- You will be asked to spit into a collection tube to collect your saliva four times approximately 4-5 hours apart for immune tests; before meals and at bedtime.
- An ECG will be performed.
- Your exhaled breath (VOCs) will be measured once in the afternoon.
- If there is still virus found in your nasal swab, you will be provided a treatment course of baloxavir marboxil or oseltamivir. These are two different antiviral drugs used to treat flu. The study doctors will decide which to treat you with, at their determination.

Inpatient Day 9 (Study Day 7):

- About 20 mL (2 teaspoons) blood will be taken from your arm (venous blood) for immune tests.
- About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from your upper arm for immune tests.
- You will be asked to spit into a collection tube to collect your saliva four times approximately 4-5 hours apart for immune tests; before meals and at bedtime.
- Your exhaled breath (VOCs) will be measured once in the afternoon.

Inpatient Day 10 (Study Day 8):

- We will collect about 80 mL (about 5 1/2 tablespoons) blood from your arm (venous blood) for safety and immune tests.
- About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from upper arm for immune tests.
- You will be asked to spit into a collection tube to collect your saliva up to four times approximately 4-5 hours apart for immune tests; before meals and at bedtime.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

- If you meet discharge criteria (two consecutive tests 12 hours apart with nasal swabs negative for flu virus, no fever, no symptoms, and are clinically stable for two days), you will be discharged from the confinement unit. The Faros device will be removed. You will be able to keep the Oura Ring and Garmin VivoSmart devices if you wish.
- If there is still virus found in your nasal swab, you will not be discharged.
- If you do not have virus found in your nasal swab, but still have fever or are clinically ill, an evaluation including a physical exam and lab tests will be done and you will not be discharged.

Inpatient Day 11 – Day 14 (Study Days 9-12 if you are not discharged on Study Day 8):

- If you remain in confinement, physiological responses from wearable devices will be assessed.
- You will have a nasal swab approximately every 12-24 hours to see if you have flu illness or any other respiratory viruses.
- About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from your upper arm for immune tests.
- You will be asked to spit into a collection tube to collect your saliva four times approximately 4-5 hours apart for immune tests; before meals and at bedtime.
- Procedures to be followed will be the same as Study Day 8 with the exception of blood collections. You only have additional blood taken if clinically indicated.

Post-Discharge (after you leave the inpatient unit through Study Day 15):

- You will complete the FLU-PRO questionnaire and diary in the late afternoon at approximately the same time daily.

Post-discharge Clinic Visit 1 (Study Day 15) – approximately 45 minutes:

- About 60 mL (4 1/2 tablespoons) of venous blood will be taken from your arm for immune tests.
- About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from your finger for baseline immune tests.
- We will collect the FLU-PRO questionnaire and diary.
- You will be asked about any flu illness symptoms you might have.
- You will be asked about any current or new medications you are taking or have recently taken
- You will have your temperature, pulse, breathing rate and blood pressure taken.
- You will have a physical examination.
- You will have a nasal absorptive matrix and nasal wash collected for immune tests.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

- You will be asked to spit into a collection tube to collect your saliva for immune tests.

Post-discharge Clinic Visit 2 (Study Day 29) – approximately 45 minutes:

- About 60 mL (4 1/2 tablespoons) of blood will be taken from your arm for immune tests.
- About 0.5mL (1/8 teaspoon) blood (capillary blood) will be collected from your finger for baseline immune tests.
- You will be asked about any current or new medications you are taking or have recently taken.
- You will have your temperature, pulse, breathing rate and blood pressure taken.
- You will have a physical examination.
- You will have a nasal absorptive matrix and nasal wash collected for immune tests.
- You will be asked to spit into a collection tube to collect your saliva for immune tests.

Early Termination Visit – approximately 45 minutes:

If you decide to leave the study early, we will ask you to complete a final study visit. At this visit, the following may be done:

- You will be asked about your current health and any changes in your medications.
- We may ask you about the FLU-PRO questionnaire and diary.
- We may ask you about your flu illness symptoms.
- You may have a physical examination based on your current health.
- You may have your vital signs taken - temperature, pulse, breathing rate and blood pressure.
- We may collect blood, nasal absorptive matrix, saliva, or nasal wash samples for immune or safety tests.
- A treatment course of oseltamivir or baloxavir marboxil will be offered to all subjects who do not have two tests 12 hours apart with nasal swabs negative for flu virus (on Study Day 6 or thereafter or if early termination occurs prior to Study Day 8).

Unscheduled Study Visits – approximately 30 minutes:

Unscheduled visits may occur for further evaluations. At these visits, the following may be done:

- You will be asked about your current health and any changes in your medications.
- We may ask you about the FLU-PRO questionnaire and diary.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

- We may ask you about your flu illness symptoms.
- You may have a physical examination based on your health.
- You may have your vital signs taken - temperature, pulse, breathing rate and blood pressure.
- We may collect blood, nasal absorptive matrix, or nasal wash samples for immune or safety tests.
- Other assessments may be done depending on when this visit occurs during the study period.

**What Are My Responsibilities if I Take Part in This Research?**

If you take part in this research, you will be responsible to do the following:

- Come to all study visits as scheduled.
- Agree to remain in the confinement unit until all discharge criteria are met (unless you decide to leave the study early).
- Complete the FLU-PRO questionnaire and diary as instructed.
- Complete the food diary as instructed.
- Avoid deleting any information recorded by the OMED device and app or the study user account created for you.
- Avoid receiving a licensed or investigational vaccine within 30 days before the flu virus challenge.
- Avoid receiving the 2024/2025 seasonal influenza vaccine within 4 months prior to or during the study.
- If you are a woman of childbearing potential, avoid pregnancy by practicing true abstinence or by using at least one acceptable primary form of birth control from at least 30 days before the flu virus challenge until the end of the study. Acceptable primary forms of birth control include a monogamous relationship with a partner who has had a vasectomy for 180 days or more before receiving the influenza challenge virus, intrauterine devices, birth control pills, and injectable/implantable/insertable hormonal birth control products.
- Abstain from alcohol use 7 days before confinement, and throughout the confinement stay.
- Avoid using prohibited medications 7 days before and during your confinement stay.
- Avoid eating or drinking anything hot or cold within 10 minutes prior to oral temperature being taken.
- Abstain from donating blood for 2 months before and for the duration of the study.

**Sample Storage for Future Use**

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

As part of this study, we are obtaining blood, nasal, saliva, and breath samples from you. However, we may not need all of the samples that we collect for this research study.

Future research is research that is not part of this flu study but will be performed in the future. You will not be told about the future research or any results. Types of research include new or different immunological laboratory tests to provide information for the development of new flu vaccines or new flu test methods, or to better understand flu virus or other infections. New genetic testing, including DNA testing, may occur. The tests we might want to use to study your blood, nasal, saliva, and breath samples may not even exist at this time.

At the time of screening, eligible participants will be required to consent to a separate biorepository protocol for the use of leftover samples and associated data (information) in future research. This will not include protected health information, such as your name, date of birth or medical history. If you do not want your leftover samples to be used for future research, you should not agree to participate in this study.

Leftover samples will be labeled only with a code (a unique tracking number) to protect your confidentiality. The codes may stay on the samples and be stored indefinitely or used for future research. Personnel at the storage facility and research testing lab will not know your identity. However, the researchers who enrolled you will keep in a secured area a "key" that could connect the codes or tracking numbers to identify you, if needed.

By signing this consent form, you are agreeing to the collection, storage and future research use of your blood samples and information for research, excluding your protected health information. Stored extra/leftover blood and nasal samples will be used for research purposes only. At any time during this study or after this study is over, stored extra/leftover blood, breath, saliva, and nasal samples may be shared with other investigators, institutions or drug companies. The samples will not be sold or used directly for production of any commercial product. However, the research studies in the future could indirectly lead to a commercial product that protects against flu viral infection or disease. Although the results of any future research may be patentable or have commercial profit, you will not receive payment if this happens.

There are no benefits to you in the collection, storage, and future use of your blood, breath, saliva, and nasal samples. The results of any future research will not be available to you or your regular doctor and will not be placed in your medical record. Future research tests may benefit others by leading to new approaches in the development of vaccines, new tests, or treatments for flu illness.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

The results of any future testing will be kept confidential in the same way as the results of other testing done for this study. If these samples are tested in the future, the results may be published. You will not be identified in such publications.

Please feel free to ask the study staff any questions you may have about how your samples may be used.

**Genetic Testing**
We may perform genetic testing, including whole genome sequencing, on your blood and nasal samples in this study. The genetic studies described are for research purposes only. Therefore, you will receive no results from this study. It is not the purpose of this study to look for or provide you with any medical information or diagnoses relating to your present condition or any other disease or illness. The research tests are not being used as diagnostic tests for any disease or illness. Your participation in this study is not a substitute for your regular medical care or check-ups.

Through this research, we may find that you have an abnormal gene or gene product (RNA or protein) which indicates a risk for developing a disease at some time in the future. It is also possible that the research results may indirectly provide unexpected personal information about you or your family (such as ethnic/racial background or an unknown genetic relationship between family members). Please talk with the study doctor if you have any questions or concerns about the genetic testing being done in this research study. He may also refer you to a genetic counselor for further information.

It is possible that this study will identify information about you that was previously unknown, such as disease status or risk. There are no plans to provide this information to you or your physician unless the information indicates that you may be at risk for a serious illness known at the time of testing to be treatable. In that case, we will attempt to notify you using the contact information you have provided, so that you can speak with Dr. Christopher Woods. Duke University staff will not provide this information in a voice mail, email, or otherwise prior to contacting you. Please notify us of any change in your contact information.

If you do not want to be notified of any incidental findings, please initial below.

_____ "Please do not notify me of any incidental findings obtained from this research."

If you prefer, we can ask you at the time of notification whether or not you want to receive incidental findings information. In this case, please initial below.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

_____ "Please ask me at the time of notification whether or not I want to receive incidental findings information."

If at any time during or after the study you change your mind about whether or not you would like to be notified, you can contact us at (919) 668-7174.

After providing the information to you, Dr. Woods may arrange for you to meet with him and/or a genetic counselor or refer you to another appropriate health care provider to review the incidental findings information with you or your physician.

**Potential Risks and the Genetic Information Non-Discrimination Act (GINA):**
There is a potential risk of loss of confidentiality. Every effort will be made to protect your confidential information, but this cannot be guaranteed. The genetic information obtained as a result of your participation in this research will not be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location at DUHS, accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law.

The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:

- Health insurance companies and group plans may not request genetic information from this research;
- Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
- Employers with 15 or more employees may not use your genetic information when deciding to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Since your genetic data and health information may be stored and shared with other researchers, there may be a risk that data from genetic testing could be misused for discriminatory purposes. However, state and federal laws provide protections against genetic discrimination. If you have any questions, please ask the Investigator. Researchers who will have access to genetic information about you will take measures to maintain the confidentiality of your data as described above. Risks may also result if you

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

disclose information yourself or give separate consent to have your research records released.

**Will I be given research results that may affect my medical care?**
Clinically relevant results of this research will be communicated to you by the study staff at that time. This could include abnormal laboratory, ECG, or other clinically significant results. The study doctor may recommend that you follow-up with your physician or he may refer you to an outside physician, if indicated.

**How long will I be in this study?**
Your participation in this study will last up to 74 days (approximately 2 1/2 months), including up to a 45-day screening period and a 29-day follow-up period (includes the confinement stay). The confinement stay will last between 10 to 14 days, depending on when you meet the discharge criteria (two consecutive tests 12 hours apart with nasal swabs negative for flu virus, no fever, no symptoms, and are clinically stable for two days).

You can stop participating at any time without penalty. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

**What are the risks of the study?**
You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be risks in this study that are not yet known. The potential risks of participating in this study are those related with having blood drawn, receiving a flu virus in your nose, and having other procedures performed.

As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose.

<u>Risks of receiving flu virus in the nose</u>
You are likely to experience symptoms from the flu virus given in your nose. Typical symptoms include mild fever, tiredness, body aches, chills, headache, diarrhea, difficulty swallowing, eyes sensitive to light, feeling dizzy, lack of appetite, swollen lymph nodes, nausea, sore or painful eyes, teary or watery eyes, blocked or runny nose, sore throat, cough, chest tightness/congestion, and sneezing. These symptoms usually last for 3-4 days. Symptoms may last for up to two weeks, but this is unusual.

The challenge flu virus has been made specifically for human infection under the strictest conditions. It has been carefully tested to ensure it is free from bacteria or other viruses.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

Guillain-Barré syndrome (GBS) is a rare disease of the nerves that causes weakness, below normal or no reflexes, and a high amount of protein in the cerebrospinal fluid (fluid found in the brain and spinal cord). Influenza virus infection has been associated with GBS. Most people get better completely, but some people can be paralyzed for a long time. Anyone can develop GBS, but people older than 50 are at greatest risk.

While rare in healthy persons, natural flu virus may cause more moderate illness such as a sinus or ear infection or more severe illness, including high fever, bronchitis, prolonged coughing illness, pneumonia, respiratory distress, heart problems including inflammation of the heart muscles (myocarditis), neurological complications, and even death. The risk of death from influenza among healthy adults is about 1 in 1 million. You will be followed closely with attention to these possible risks. If there is still virus found in your nasal swab on Inpatient Day 8, you will be offered one dose of baloxavir or oseltamivir (approved antiviral drugs used to treat the flu), and you will not be discharged until you test negative for the flu or the study doctor determines that you are no longer infectious. If you do not have virus found in your nasal swab but you still have fever or are clinically ill, an appropriate work-up will be done, and you will not be discharged until the study doctor determines you are stable. The study doctor may also treat your symptoms with over-the-counter medications, as needed. If you develop severe flu symptoms or complications during the confinement period and meet criteria for escalation of care, you will be referred to a non-study physician at Duke University Medical Center.

<u>Risks related to blood draws</u>
The risks of drawing blood include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

<u>Risk related to nasal swabs, nasal matrices, or nasal washes</u>
Obtaining a nasal swab, matrix, or wash can cause discomfort in the nostrils, a gag reflex, bleeding from the nose, watery eyes, or coughing at the time of collection.

<u>Risk related to saliva collection</u>
Saliva collection will involve spitting into a tube. Saliva collection involves drooling or collecting saliva that naturally pools in your mouth. The risk of interacting with the saliva collection kit is minimal; there is a preservative contained sealed in the lid of the collection tube. Once the collection tube lid is closed, the preservative is mixed with your saliva.

<u>Risks related to breath collection</u>

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

For the breath sample you will be asked to breathe normally into a mouthpiece whilst wearing a nose clip for 14-16 minutes (up to a maximum of 30 minutes). You can breathe normally into the mouthpiece (inhale and exhale) without using your nose. The air you breathe in will be filtered by a machine to make sure substances that circulate around in the room do not change the signal. Your breath will be collected into 4 small tubes and stored for further analysis.

There is a risk of some discomfort from use of the nose clip and mouthpiece when providing a breath sample. After sampling when removing the mouthpiece, there may be a build-up of saliva and this might be unpleasant or appear unhygienic.

Risks of the OMED and hydrogen and methane collection devices
There is a risk of feeling lightheaded after the breath collection.

Risks from Imaging Tests That Use Radiation
If you take part in this research, you may have one or more chest x-rays, which use radiation. To give you an idea about how much radiation you will get each time a chest x-ray is done, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year called the 'natural background'. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. The chart below the amount of time in the natural background that gives an amount of radiation that is about equal to the amount of radiation each time you have the test.

A possible health problem seen with radiation exposure is the development of cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research is also shown in the chart. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

| Test | 'Natural Background Time' Equivalent for Each Time This Test is Done | Extra Cancer Risk Each Time This Test is Done |
|---|---|---|
| Chest X-ray | 3 Weeks | Minimal |

You may have a number of medical imaging exams that are part of the regular care for your condition, and you would have them whether or not you participate in this research. These studies will not add to the risk of the research. However, if you have concerns about the overall radiation exposure, you should discuss them with your physician.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

There is a greater risk to a developing fetus. Female subjects will have either a serum or urine pregnancy test before chest x-ray, depending upon the study visit window. Pregnant and breastfeeding women may not participate in this study.

Risks of electrocardiogram (ECG)
The electrodes of an ECG may feel cold when applied; in rare cases, a rash, itching, redness or skin irritation develops where the patches are placed. This type of irritation usually resolves by itself, but topical medication is occasionally required.

Risks of oseltamivir and baloxavir marboxil antivirals
Adverse events reported in at least 1 out of 100 (1%) of adult and adolescent subjects treated with oseltamivir or baloxavir marboxil included diarrhea (3 out of 100 or 3%), bronchitis (2 out of 100 or 2%), abdominal pain (2 out of 100 or 2%), dizziness (2 out of 100 or 2%), a cold (1 out of 100 or 1%), headache (1 out of 100 or 1%), nausea (1 out of 100 or 1%), a cough (1 out of 100 or 1%), fatigue (1 out of 100 or 1%), and insomnia (1 out 100 or 1%). The flu virus we are using is sensitive to these medicines.

Risks of delaying influenza vaccine receipt
In the US, routine annual influenza vaccination is recommended for all persons, with an emphasis placed on vaccination of high-risk groups and their caregivers. To participate in this study, you are asked to delay the 2023-2024 influenza season vaccination through 30 days after the flu virus challenge. The flu vaccine takes approximately two weeks to be protective. If the influenza season begins before this time, you will be at increased risk of developing flu illness. Flu illness is described above.

Risks of wearable devices (Faros, Garmin and Oura Ring)
The **Bittium Faros 180** (referred to as Faros) is an FDA approved Class II medical device designated for research use in adults. As long as the exclusion criteria are met (excluding those subjects with pacemakers or other implanted electronic medical devices), there are no known physical risks associated with wearing the Faros 180. Long-term ECG monitoring is an established procedure that carries minimal risks. Holter monitors, which are ambulatory ECG devices, are often worn for days or weeks to monitor heart rhythm. The only known physical risk related to wearing these types of sensors relates to skin irritation caused by the electrodes. The electrodes have a clear tape that allows for visual monitoring of skin condition. The participant will be instructed to temporarily remove the device if any redness or irritation develops because of sensitivity to the adhesive.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

There are minor risks associated with the Garmin wearable device in this study. For the **Garmin Vivosmart 4** (referred to as Garmin)**,** subjects with pacemakers or other internal electronic devices should consult a physician before using a heart rate monitor. This study excludes people with internal cardiac devices, minimizing this risk. The Garmin also emits green light and flashes occasionally. Subjects with epilepsy or sensitive to flashing lights should also consult their physician before use. The device operating temperature is -4 to 122°F while charging temperatures are 32 to 113°F. These temperature ranges should be observed in order to minimize heat and/or fire associated battery risks. Lithium-ion batteries should not be disassembled, removed or modified. They should not be exposed to fire or explosions, or there is a risk of fire, chemical burn, electrolyte leak, and/or injury.

There are minor risks associated with the **Oura Ring** wearable device in this study. The rings are provided by Oura Ring, Inc., a private corporation registered in the state of Delaware. Oura Ring created an online platform where data from the ring is uploaded and made accessible to ring wearers. Duke will create a mock account for information from your ring, so that the data is deidentified and your identity withheld. You will have access to your mock account. Duke will have access to your mock account, so that Duke can conduct the research. Duke will aggregate the deidentified data uploaded from the rings onto the platform, and Duke will make the deidentified and aggregated data available to Oura Ring for its own purposes, which includes commercial use. Subjects with pacemakers or other internal electronic devices should consult a physician before using a heart rate monitor. This study excludes people with internal cardiac devices, minimizing this risk. The Oura Ring also emits green light and flashes occasionally. Subjects with epilepsy or sensitive to flashing lights should also consult their physician before use. Lithium-ion batteries should not be disassembled, removed or modified. They should not be exposed to fire or explosions, or there is a risk of fire, chemical burn, electrolyte leak, and/or injury.

A small loss of privacy is possible with the use of these devices due to how the information is stored. We will do our best to make sure that information collected about you on these devices is kept confidential, but we cannot guarantee total confidentiality.

<u>For women participating in the study</u>
A pregnancy test will be performed on all women of childbearing potential at the first screening appointment, before the chest x-ray, and when admitted to the confinement unit. Pregnant and breast-feeding women may not participate in this study, as pregnant women, the developing fetus and newborns are at increased risk of complications from flu virus infection. You must confirm to the best of your knowledge that you are not pregnant and do not intend to become pregnant.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

If you are a woman who could possibly become pregnant (you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed), and you have a partner who is able to father children, you must agree to either abstain completely from vaginal intercourse for 30 days prior to the flu virus challenge until one week after discharge from the confinement unit, or use at least one acceptable primary form of contraception for the same length of time. Your doctor will review birth control methods to make sure that the one you are using meets the level of effectiveness required by this study.

**Unforeseeable Risks:** There may be risks, discomforts, drug interactions or side effects that are not yet known.

**Are there benefits to taking part in the study?**
You will receive no direct benefit from taking part in this study. There may be benefits to society through the improvement of our understanding of flu infection, how humans are protected from flu virus, and the immune responses that occur after flu infection.

**Will my information be kept confidential?**
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of this study, results of your study-related laboratory tests, x-rays, and procedures may be reported to the Department of Defense. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include:

- representatives from the Food and Drug Administration,
- representatives of the Department of Defense,
- the Duke University Health System Institutional Review Board,
- and others as appropriate.

If any of these groups review your research record, they may also need to review your entire medical record.

The study results will be retained in your research record for at least six years after the study is completed. At that time, either the research information not already in your medical record may be destroyed or information identifying you will be removed from

such study results at DUHS. Any research information in your medical record will be kept indefinitely.

This information may be further disclosed by the cosponsors (Owlstone Medical, Ltd. and Darwin Biosciences, Inc.) of this study or to outside reviewers for audit purposes. If disclosed by either sponsor or outside reviewers, the information is no longer covered by federal privacy regulations.

Breath, saliva and blood samples and study data collected during the course of the study will be shared with the co-sponsors and their affiliates. However, your samples and data will be coded so your name, address, medical record info and other personal information will be protected securely in a locked office at Duke University and not be shared.

Owlstone Medical are based in the United Kingdom (UK) and any information about you held at Owlstone Medical will be stored securely in accordance with applicable data protection legislation, as set out in their Privacy Policy which can be accessed using this link: https://www.owlstonemedical.com/privacy-policy/.

**Further scientific research by Owlstone Medical**: Owlstone may process some of the data about you obtained through this research project for additional scientific or statistical research purposes which are compatible with the purposes of this study and where Owlstone has a legitimate interest to do so. Owlstone will be a data controller for this processing. This may include adding data to Owlstone's scientific database, Breath Biopsy VOC Atlas® (Atlas), as permissible under local data protection legislation which applies to Owlstone. It will not be possible to identify who you are through the data used in this database. Atlas is a scientific database about breath-related molecules and their context (such as disease, location and many others). The information in Atlas may be further shared with third party research and academic institutions and scientists to aid public research. Owlstone will also use data processors to perform some services on its behalf with regards to Atlas, such as for data storage and technology support purposes. Any third parties that have access to Atlas will be contractually bound to robust data protection and confidentiality obligations, including any appropriate safeguards required when transferring data outside of the UK. Owlstone will retain data in Atlas for as long as it is legally able to do – but has set an initial retention period of 10 years from the date of transfer to Atlas. Retention will be under periodic review and consideration as to its value and need to extended retention. OML has robust technical and organizational measures in place to protect your data held in Atlas.

You may have the right to access, restrict, rectify or erase the data Owlstone processes for further scientific research, and you can opt-out at any time. Should you have a

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

complaint regarding Owlstone's processing of your data you can raise it with the Information Commissioner's Office (ICO), which regulates data protection and privacy matters in the UK (https://ico.org.uk/for-the-public). If you wish to enforce these rights or for more information you can contact us or our Data Protection Officer via Privacy@Owlstone.co.uk.

Darwin Biosciences, Inc. is based in the United States and any information about you held at Darwin Biosciences will be stored securely in accordance with applicable data protection legislation. Darwin Biosciences will use your saliva samples, blood samples, and data collected during this study to support their research and development on RNA biomarkers found in blood and saliva to identify potential biomarkers of infectious disease. If you have any questions or concerns in relation to this, please email: Clinical@darwin.bio

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain confidential. If you decide to share your information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other people not connected with the study.

To help protect your confidentiality, we will use participant ID numbers on research data. The data will be stored in locked cabinets and/or offices when not in use. Only research team members who are involved in the conduct, oversight or auditing of this study will have access to the research data.

Electronic data, including the information collected from the wearable devices, will be stored in password protected computers and databases behind Duke firewalls.

For this study, each blood, saliva, and nasal sample will be labeled with a barcode and a unique tracking number to protect your confidentiality. Personnel at the central storage and testing lab will not know your identity.

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

Duke University generally requires that we document in your medical record chart that you are participating in this study. If you do not have a medical record in the Duke University Health System, then we will create one for you. The information included in the chart will provide contact information for the research team and information about the risks associated with this study. A copy of your signed Informed Consent Document will be uploaded in your medical record chart.

**Will it cost me anything to be in the study?**
It will not cost you anything to take part in this study. You will not have to pay for any study procedures, the study confinement unit or alternate location, oseltamivir and baloxavir marboxil antivirals if needed, or any study visits.

**Will I be paid to be in the study?**
You will receive up to $3500 for your participation. You will receive $100 for the screening visit, $2500 ($250 per day) for the confinement stay, $300 ($17.50 per day) for FLU-PRO and food diary completion, and $600 ($300 per visit) for follow-up clinic visits. You will only receive compensation for the study activities that are completed. If necessary, you will also be provided with a parking voucher.

Payment for participation in research is considered taxable income and Duke University is required in many cases to report this information to the Internal Revenue Service (IRS).

Duke University requires that you provide your name, mailing address, and social security number for this tax reporting purpose before payment can be issued. If you do not want to provide this information, you cannot be paid but you can still take part in the research study.

Research subject payments to a non-employee of Duke University adding up to $600 or more during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the individual and a copy sent to the IRS.

Research participant compensation made to a Duke University employee at any time during the calendar year will result in a 1099 (Miscellaneous Income) form being issued to the employee and a copy sent to the IRS regardless of the total amount paid.

**What about research related injuries?**
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., your Duke physicians, US Department of Defense (DoD), Darwin Biosciences Inc., or

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

Owlstone Medical Limited, to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Christopher Woods at (919) 668-7174 during regular business hours and at (919) 451-9795 after hours and on weekends and holidays.

**What if I want to withdraw from the study?**
If you agree to be in the study, you may withdraw from the study at any time. However, we strongly discourage you from withdrawing after challenge with the flu virus, before the required confinement stay is completed. This is because leaving the unit when you may be infected with flu virus is a risk to you and to others. You could become sick with flu illness, and we would not be there to follow you closely for signs of more serious illness. In addition, if you still have flu virus in your nose, you could spread that flu virus to others, including those who may be more likely than a healthy adult to get very sick from the flu virus. We will ask you to sign a form acknowledging these risks if you choose to leave the confinement unit before we discharge you. We will encourage you to take a treatment course of the antiviral medication, baloxavir marboxil or oseltamivir. We will encourage you to avoid contact with anyone who could be at high risk of flu complications.

If you withdraw from the study, no new data about you will be collected for study purposes unless the data concerns an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled and will not affect your access to health care at Duke. If you do decide to withdraw, or if you have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the investigator Dr. Christopher Woods at (919) 668-7174 or his research team at (919) 971-5649.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

If you agree to allow your leftover blood, nasal, saliva, and breath samples to be kept for future research with identifying information that could link your sample to you, you are free to change your mind at any time. We ask that you contact Dr. Christopher Woods in writing and let them know you are withdrawing your permission for your identifiable

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

samples to be used for future research. Their address is 310 Trent Drive, Box 90519, Trent Bldg 205, Durham, NC 27708 or email chris.woods@duke.edu. At that time, we will ask you to indicate in writing if you want the unused identifiable samples destroyed or if your samples (having all identifying information removed that would link the sample to you) could be used for other research.

The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples other than what is described in this consent form.

A description of this clinical trial will be available on https://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.

**Whom should I call if I have questions or problems?**
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Christopher Woods at (919) 668-7174 during regular business hours and at (919) 451-9795 after hours and on weekends and holidays.

You can call the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111 if:

- You have questions about your rights as a research participant
- You wish to discuss problems related to the research
- You have any concerns or suggestions related to the research
- Want to obtain information or offer input about the research

Duke University Health System

**Consent to Participate in a Research Study**
**ADULT**
**A Blinded, Randomized, Placebo-Controlled Influenza Challenge Study in Healthy Adult Volunteers using a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus**

**STATEMENT OF CONSENT**

"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

| _____ | _____ | _____ |
|---|---|---|
| Signature of Participant | Date | Time |

| _____ | _____ | _____ |
|---|---|---|
| Signature of Person Obtaining Consent | Date | Time |