Duke University Health System

Consent to Participate in a Research Study
ADULT
A Multicenter, Blinded, Randomized, Placebo-Controlled, Dose-Ranging Influenza Challenge Study in Healthy Adult Volunteers to Determine the Optimal Infection Dose and Safety of a Recombinant H3N2 (A/Texas/71/2017 (H3N2), clade 3C3a) Influenza Challenge Virus
DMID 20-0005
Version 5.0 14APR2022

CONCISE SUMMARY
This is a research study to understand what happens when a person is infected with one of three different doses of an influenza ("flu") strain and how the body responds to the dose received. To do this, we will infect healthy participants ("challenge") 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 draw blood, perform nasal swabs, nasal scrapings, and/or nasal washes. Participants must consent to storage and future research use of their blood and nasal samples if they would like to take part in this study.

If you agree to take part in this study, your involvement will last for approximately 3 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 3 more clinic visits with blood draws and nasal washes and/or nasal scrapings which will take about 45 minutes each.

Genetic testing, including HLA typing, 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 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. There is also a risk of exposure to COVID-19 during the confinement period.

There are no direct benefits to you from participating in this study. There may be benefits to society through the improvement of our understanding of flu infection with different doses of this flu strain, how humans are protected from flu virus, and the immune responses that occur after flu infection.

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

You are being asked to take part in this research study because you are in good health and are aged 18 to 45 years. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to

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take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

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

The National Institute of Allergy and Infectious Diseases (NIAID), which is part of the National Institutes of Health (NIH), is funding this research study. This means that Duke University is receiving payments from NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from NIH for conducting this study. The study will help to support their salary.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, ***Dr. Christopher W. Woods, MD, MPH*** and ***Dr. Emmanuel "Chip" Walter, MD, MPH*** will be your doctors for the study and 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 research study is to try to determine the best dose of a flu challenge strain to be given in future studies for testing new and improved influenza vaccines. We will also do studies to understand what happens when a person is infected with the flu virus (how you feel and how your body reacts), and how the immune system responds to infection with the flu virus (what antibodies are formed or increased after you get the flu virus).

The influenza virus is a germ. The "flu" virus causes influenza illness or "flu" illness, an infection of your nose, throat, windpipe and your lungs. The flu virus is spread from person-to-person mainly through coughing, sneezing, and touching/or contaminated surfaces. When someone has flu illness they usually have a mild fever, tiredness, body aches, chills, headache, blocked or runny nose, sore throat, cough and/or sneezing. While in most healthy people, the flu virus causes illness that often looks like the "common cold" and gets better on its own, it can become more serious. Children younger than 5 years of age, adults older than 65 years of age, pregnant women and people of all ages with chronic medical illnesses are more likely to have complications of flu illness and to have a higher risk of death from flu-related illnesses. Flu-related illnesses cause an average of 20,000-40,000 deaths each year in the United States (US), and most of these deaths occur in people over 65 years of age.

When the flu virus infects your body, the immune system in your body makes proteins, including antibodies, and recruits other immune cells to help your body fight the infection. Later, if you are

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exposed to the flu virus, your antibodies and immune cells will help attack and kill the virus. With these antibodies and cells, you may not get sick at all, or you may have a much shorter or milder illness.

By the time we are adults, we have been infected with the flu virus many times. While we have learned a lot about how the flu virus infects people, it is hard to know exactly when someone is infected by the flu virus, and what happens early on after they are exposed to the flu virus but before they become sick. Flu "challenge" studies, where we give a strain of the flu virus to a participant, allow us to follow people closely before and after infection. We learn about the flu virus and the body's reaction to it. This may help us to design better flu vaccines or better drugs to treat flu illness.

Flu illness can be caused by different types of flu viruses. One of those flu viruses is called influenza A/H3N2. In this study, we will challenge participants with an H3N2 strain that has not widely circulated and to which people do not have many antibodies. This is investigational, as this strain has not been used in challenge studies before. In this study, we will infect healthy participants ("challenge") 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 1X SPG, sucrose-phosphate buffer (placebo) instead and not the flu strain. The first group of participants to be infected with the flu virus will receive the lowest of the three doses to be tested. This group is called Cohort 1. If not enough participants have symptoms and the dose is considered to be safe, the next group of participants will receive a higher dose. The dose will be increased up to two times until enough of the participants in a group exhibit mild flu illness symptoms (Cohorts 2 and 3). We will do this study to determine which dose of this strain causes enough mild flu illness symptoms in people who receive it. The dose, which causes enough mild symptoms without causing severe symptoms, will be selected for use in future studies of new and improved flu vaccines.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
This study will be done at 2 sites in the US, and we anticipate that up to 114 people will be challenged with different increasing doses of the flu virus or placebo (an inactive substance) as part of this study, with up to 57 participants at each site.

WHAT IS INVOLVED IN THE STUDY?
Screening Clinic Visit(s) - approximately 4 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 (Pro00104290) for the use of leftover samples and

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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 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, birthdate, ethnicity, and race.
- We will collect your COVID-19 vaccination history. You must have received a full dose of a COVID-19 vaccine at least two weeks prior to admission to the confinement unit.
- 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 up to two more urine pregnancy tests 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 for laboratory tests, including blood counts and blood chemistry tests. This will also include tests to see if you are infected with hepatitis B, hepatitis C, or HIV, the virus that causes AIDS. As part of this protocol, you will 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 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 hepatitis B and C, then you should not agree to participate in this study. The study doctor or study staff will provide pre-test counseling for the HIV/AIDS tests so you will have information about the risks and benefits of being tested. 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, you will receive additional counseling about the significance of your care and possible risks to other

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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, then you should not agree to participate in this study.

- In rare cases, an HIV test result may be 'indeterminate', which means that it is not possible to say if it is positive or negative. This can occur for a number of reasons and most people with indeterminate tests do not have HIV. Indeterminate tests are not notifiable conditions and this information is not reported to the local health department.
- 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 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 doing a chest x-ray.
- You will have a nasal swab performed to test for SARS-CoV-2, the virus that causes COVID-19.

If any of the above screening tests are abnormal, 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 or visits, 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 a 12 in 13 (92%) chance of receiving active virus if you participate in cohorts 1 or 2. You have a 17 in 18 (94%) chance of receiving active virus if you participate in cohort 3. The virus/placebo will be administered into your nose.

<u>Confinement Challenge Stay (minimum 10 days)</u>
You will be admitted to the confinement unit 2 days before we plan to give the flu virus or placebo. In order to ensure we challenge our goal number of subjects with influenza virus, some subjects will 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

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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 up to every 8 hours while you are awake.
- You will have a brief physical examination.
- You will have nasal samples collected to test for COVID-19, with the exception of Study Day 1. Should your COVID-19 test become positive, you will be discharged to home for isolation and close observation.
- 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.
- You will be asked about any flu symptoms you might have.
- You will be given a Faros, Garmin and/or Oura Ring wearable device to wear for the length of your inpatient visit to measure certain physiologic responses (e.g., heart rate, oxygen saturation, electrical activity of the heart) after challenge with the flu virus. The Faros is a device to monitor your heart's activities and will be worn on your chest. The Garmin is worn on your wrist and it, too, monitors heart rate and activity. The Oura Ring is worn on your finger and monitors heart rate, activity, and body temperature.

<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 drug is deemed acceptable by the study doctor.
- You will have about 10 mL (2 teaspoons) of blood taken for baseline immune tests.
- You will have a nasal swab and nasal scraping 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. The study team will insert a probe and gently scrape the inside of your nose so as to collect nasal samples.

- 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.
- The Garmin and Oura Ring will transfer the subject's data via Bluetooth to the 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.

Inpatient Day 2 (Study Day -1)

- 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 wash with a saltwater solution (saline) for baseline immune tests.
- You will have about 82 mL (5 1/2 tablespoons) of blood taken for baseline immune tests.

Inpatient Day 3 (Study Day 1 – the day flu virus is given)

- 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.
- 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.

Inpatient Day 4 (Study Day 2)

- About 42.5 mL (3 tablespoons) of blood will be taken from your arm for safety tests and immune tests.
- You will have a nasal swab to see if you have flu illness or any other respiratory viruses, including COVID-19.
- You will have a nasal wash for immune tests.

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Inpatient - Daily Days 5 through 10 (Study Days 3 through 8, and Days 9 through 14 as needed)

- You will have a nasal swab to see if you have flu illness or any other respiratory viruses, including COVID-19.
- You will have a nasal wash for immune tests.

Inpatient Day 5 (Study Day 3).

- You will have about 10 mL (2 teaspoons) blood taken from your arm for immune tests.

Inpatient Day 6 (Study Day 4)

- About 42.5 mL (3 tablespoons) blood will be taken from your arm for safety tests and immune tests.
- 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 7 (Study Day 5)

- About 10 mL (2 teaspoons) blood will be taken from your arm for immune tests.

Inpatient Day 8 (Study Day 6)

- About 34 mL (2 tablespoons) blood will be taken from your arm for immune tests.
- An ECG will be performed.

Inpatient Day 9 (Study Day 7)

- About 10 mL (2 teaspoons) blood will be taken from your arm for immune tests.

Inpatient Day 10 (Study Day 8)

- We will collect about 110.5 mL (about 7 1/2 tablespoons) blood from your arm for safety and immune tests.
- 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, Oura Ring and Garmin devices will be removed. 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.

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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.
- Procedures to be followed will be the same as Study Day 8 with the exception of blood collections. You will not have any more blood taken unless 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 54 mL (3 1/2 tablespoons) of blood will be taken from your arm for 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 wash and nasal scrapings for immune tests.

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

- About 68 mL (4 1/2 tablespoons) of blood will be taken from your arm for 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 wash and nasal scrapings for immune tests.

Post-discharge Clinic Visit 3 (Study Day 57) – approximately 45 minutes

- About 44 mL (3 tablespoons) of blood will be taken from your arm for 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 wash and nasal scrapings 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:

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- 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 or nasal washes and nasal scrapings 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 terminates study 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 any current or new medications you are taking or have recently taken.
- 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 health.
- You may have your vital signs taken - temperature, pulse, breathing rate and blood pressure.
- We may collect blood or nasal washes and nasal scrapings for safety or immune tests.
- Other assessments may be done depending on when this visit occurs during the study period.

BLOOD AND NASAL SAMPLE STORAGE FOR FUTURE USE
As part of this study, we are obtaining blood and nasal samples from you. However, we may not need all of the blood or nasal samples that we collect for this research study. At the time of screening, eligible participants will be required to consent to the 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.

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 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 and nasal samples may not even exist at this time.

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.

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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 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 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 or treatments for flu illness.

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 blood 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 blood samples may be used.

GENETIC TESTING
We will perform genetic testing 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

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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.

_____ "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.

Future genetic testing with your leftover samples may include DNA testing.

Following genetic testing, your genetic testing information may be shared with other researchers. We may share your genetic information (data) through a "closed" database, also called a restricted data repository. NIH gives permission to other researchers to use your genetic information for research. To qualify, researchers must receive approval from NIH to access and use the research information. Types of future research using your data may be related to the research in this study or other types of research. Your individual data will not contain information that can easily identify you. It may be possible to

identify you with your DNA; however, the researchers must follow rules specifically to not identify you. If you change your mind and want to remove your data from the database, you should contact the research site that collected your information and specimens. If possible, your information can be removed for future research. Your data cannot be removed if it has already been used.

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 Duke University, 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. 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.

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

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

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- 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.
- avoid receiving a licensed or investigational vaccine within 30 days before the flu virus challenge.
- avoid receiving the 2021/2022 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.

HOW LONG WILL I BE IN THIS STUDY?

Your participation in this study will last up to 102 days (approximately 3 1/2 months), including up to a 45-day screening period and a 57-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 choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. 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.

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Risks of receiving flu virus in the nose
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.

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. You will be followed closely with attention to these possible risks.

Risks related to blood draws
Having blood taken from your arm can cause temporary pain and discomfort, bruising, and fainting with a rare risk of clotting, excess bleeding, and infection. A possible risk of giving blood may be a low blood count (anemia); however, the total amount for this study is lower than donating a unit of blood so the risk of anemia is low.

Risk related to nasal swabs, nasal scrapings or nasal washes
Obtaining nasal fluid or a nasal swab or scraping can cause discomfort in the nostrils, a gag reflex, bleeding from the nose, watery eyes, or coughing at the time of 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.

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 2021-2022 influenza season vaccination through 60 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 exposure to COVID-19
The risk of being exposed to COVID-19 is increased due to confinement in the confinement unit for an extended period of time. Though all participants will be vaccinated and tested for COVID-19 infection upon study entry and daily while inpatient, it is possible that the test is incorrect. Symptoms and complications of COVID-19 illness include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea, respiratory failure, blood clots, and even death. You will be followed closely with attention to these possible risks.

Risks of wearables (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.

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.

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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, or in other words, has all identifiable information removed 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 group all subjects' deidentified data uploaded from the rings onto the platform, and Duke will make the deidentified and grouped 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.

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.

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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 with different doses of this flu strain, 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 study and may be seen by people including those collaborating, funding, and regulating it. We will share only the minimum necessary information in order to conduct this study. Personal information will be shared with other investigators at Duke University who need to contact you about your interest in participating in a new research study. 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 National Institute of Allergy and Infectious Diseases (NIAID) and its affiliates. 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 and affiliates of National Institute of Allergy and Infectious Diseases (NIAID), 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 Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);
2) you have consented to the disclosure, including for your medical treatment; or
3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

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You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

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 Duke University. Any research information in your medical record will be kept indefinitely.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

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 Duke University, we cannot guarantee that it will remain private. If you decide to share private 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.

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.

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people, such as those indicated below, may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you. Reviewers may include:

- federal government regulatory agencies,

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- the U.S. Food and Drug Administration,
- the National Institutes of Health (NIH) and those contracted by the NIH, such as EMMES Corporation and Technical Resources International (TRI) pharmacovigilance and study monitoring groups
- auditing departments of Duke University, and
- The Duke University Health System Institutional Review Board (a committee that reviews and approves research studies) and other representatives of this organization.

To help protect your confidentiality, we will use 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 Faros, Garmin and/or Oura Ring devices, will be stored in password protected computers and websites. For this study, each blood and nasal sample will be labeled with a barcode and a unique tracking number to protect our confidentiality. Personnel at the central storage and testing lab will not know your identity or the volunteer ID assigned to you for the study.

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. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

WHAT ARE THE COSTS TO YOU?
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.

WHAT ABOUT COMPENSATION?
You will be reimbursed up to $3370 for your expenses related to your participation (parking, gas, and time). You will receive $100 for the screening visit, $2500 ($250 per day) for the confinement stay, $170 ($10 per day) for FLU-PRO and diary completion, and $600 ($200 per visit) for follow-up clinic visits. You will only receive compensation for the study activities that are completed.

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Payment received as compensation for participation in research is considered taxable income to the research subject. If payment to an individual totals $600 or more in any one calendar year, Duke University is required to report this information to the Internal Revenue Service (IRS). 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.

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., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury. In addition, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH or the Federal government.

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 ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, 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, or 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.

Not taking part in the study or stopping your participation in the study will involve no penalty or loss of benefits to which you are otherwise entitled, and will not affect your access to health care at Duke. If you decide to stop taking part, or if you have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the investigators, Dr. Christopher Woods at (919) 668-7174, Dr. Chip Walter at (919) 620-5346, or their research team at (919) 971-5649.

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If you withdraw from this study, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, these data will be handled the same as research data.

You will be told of any significant new findings that develop during the study which may affect your willingness to participate in the study.

When the study results are available, after the study is completed (generally at least several months after your last visit), a summary of the study results will appear on http://www.ClinicalTrials.gov, as required by U.S. law. Learning about study results can cause people to become upset, especially if the results are different from what you expected. If you have any questions or concerns about the results, please contact the Investigators, Dr. Christopher Woods, at (919) 668-7174, or Dr. Chip Walter at (919) 620-5346.

CAN I BE REMOVED FROM THE RESEARCH?
Your doctor may decide to take you off this study if your study doctor determines that it is no longer in your best interest to continue. Possible reasons for removal include the following:

- Reasons related to you (for example, if you move to another city, do not agree to refrain from alcohol and drugs during the confinement stay, or do not follow study-related directions).
- Reasons related to your health (for example, if you may be at risk for complications of flu due to a new medical condition).
- We have too many participants for the confinement part of the study.
- Because this entire study is stopped (the sponsor may stop this study at any time).
- If you do not later consent to any future changes that may be made to how this study is done.
- If you become pregnant.

The sponsor, the study doctor, or the Institutional Review Board (IRB) can also end the research study early. The study doctor will tell you about this and you will have the chance to ask questions if this were to happen.

WHOM DO 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 may also contact Dr. Chip Walter at (919) 620-5346 during regular business hours.

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For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

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 Subject	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time