Safety of Simultaneous versus Sequential Administration of mRNA COVID-19 Vaccines and Quadrivalent Inactivated Influenza (IIV4) in Adults, Adolescents and Children: A Randomized Observer Blinded Study

NCT #: NCT05028361

Version Number: 10/18/2022

Duke University Health System

Consent to Participate in a Research Study
Simultaneous mRNA COVID-19 and IIV4 Vaccination Study
for Participants Receiving a booster dose of mRNA COVID-19 Vaccine
as Part of Routine Care

CONCISE SUMMARY

This is a research study to test the safety of receiving a quadrivalent inactivated influenza (flu) vaccine and an mRNA COVID-19 vaccine on the same day or two weeks apart in individuals 5 years or older. If you would like to participate in the study, you will come into a clinic for 4 study visits and participate in one phone visit. This will occur over the course of 4 months. You will also have a total of 3 blood draws during this time.

Participants in this study will be randomly assigned (like flipping a coin) to one of two groups. Participants in Group 1 will be assigned to receive the flu vaccine on the same day they receive a booster dose of mRNA COVID-19 vaccine administered as part of routine care. Group 2 will be assigned to receive the flu vaccine two weeks following receipt of their booster dose of mRNA COVID-19 vaccine. Participants will not know which group they are assigned to and may receive an mRNA COVID-19 vaccine according to what is currently recommended or authorized by the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA). All participants will answer questions about their health, quality of life and vaccination history and side effects following vaccination.

There are risks associated with the flu vaccine that are described in this document. Some risks could include: redness, swelling, or pain where the shot was given, fever, body aches, headache, or fatigue, nausea, cough or hoarseness, sore, red or itchy eyes, and itching.

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 at least 18 years old and are receiving or have received a booster dose of mRNA COVID-19 vaccine today as part of your routine care and are interested in receiving a seasonal flu shot. 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 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.

This research is supported through a contract with the Centers for Disease Control and Prevention (CDC). The CDC will pay a portion of Dr. Emmanuel Walter's, Dr. Kenneth Schmader's and their research team's salaries to conduct the study.

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WHO WILL BE MY DOCTOR ON THIS STUDY?

If you decide to participate, Dr. Emmanuel Walter will be your doctor 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?

Vaccines work by causing the body to make proteins called antibodies that fight infection. Vaccination is the most effective way to prevent infections such as influenza (flu) and COVID-19. Emergency Use Authorizations (EUAs) were granted for the Moderna and Pfizer-BioNTech booster mRNA COVID-19 vaccines. Once authorized or approved, a booster dose of mRNA COVID-19 vaccine will be distributed for use. There is potential for these vaccines to be administered at the same time as the seasonal flu vaccine in order to provide protection against both the flu and COVID-19. The current recommendations from the CDC state that COVID-19 vaccines can be given with other vaccines on the same day but it is unknown whether this will affect reactions that may occur after vaccination. To date, there are no other studies looking into the safety of receiving both a flu and mRNA COVID vaccine on the same day.

The purpose of this study is to learn more about the safety of administering a flu vaccine and an mRNA COVID-19 vaccine on the same day or 14 days apart in individuals 5 years or older. Our plan is to administer a flu or placebo in the opposite arm that you did or will receive the mRNA COVID-19 vaccine on Visit 1. The placebo, which is an inactive substance also given as a shot in the arm, will contain saline (salt water). Those participants who received placebo the first day will then receive flu vaccine and those who first received flu vaccine will then receive placebo at Visit 2, 14 days later. Around 28 days after Visit Day 1, you will have your blood collected. The study team will monitor you for adverse reactions (bad effects) throughout the study and ask questions regarding your quality of life after Visit 1.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 450 people will take part in this study at 3 different hospitals and medical facilities, and approximately 200 people will take part at Duke.

WHAT IS INVOLVED IN THE STUDY?

If you agree to be in this study, you will be asked to sign and date this consent form. If you do not sign this consent form, you will continue to receive care, but not as a part of this study. Refusal to participate will involve no penalty or loss of benefits.

Visit 1 Study Day 1 (Clinic Visit): Study staff will review this consent form with you as well as the study eligibility criteria to make sure you qualify. If you qualify and agree to participate in this study you will have the following tests and procedures:

- Study staff will ask questions about your health, current medications, demographics and your flu and COVID-19 vaccination history.

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- If you are a woman of childbearing potential, study staff may assess the likelihood of pregnancy by asking additional questions.
- You will be asked about your quality of life.
- Study staff will take your temperature.
- A blood sample of 10 mL (2 teaspoons) will be taken to test for flu and COVID-19 antibodies. These samples will be used for future, yet unknown, testing. This is described later in this form.
- You will be randomly (like flipping a coin) assigned to receive either flu vaccine and mRNA COVID-19 vaccine or placebo and mRNA COVID -19 vaccine. You will receive either a flu vaccine or a placebo.
- You will receive an mRNA COVID-19 vaccine per local standard of care within 8 hours of the study visit (on the same day)
- You will receive a Vaccine Information Sheet (VIS) for the flu vaccine, which will give you information about the flu shot.
- A study staff member will give you a paper memory aid or send you an electronic memory aid, thermometer, ruler and go over instructions for these items.
- You will be assessed for any immediate symptoms.

Study Day 1-7 Post Visit 1: You will complete an online or paper symptom diary and Quality of Life assessment each day at around the same time each day. You will receive either electronic and/or telephone reminders for completing the symptom diary.

Visit 2 Study Day 15 (Clinic Visit): You will come into the clinic on day 15 and the following tests and procedures will occur:

- Study staff will review eligibility criteria
- Study staff will record any adverse events (bad affects) within the first 7 days post-vaccination
- You will be asked to update the list of current medications you are taking.
- Study staff will obtain your temperature.
- You will receive either flu vaccine or placebo and be given a VIS and other appropriate information sheets.
- You will receive a flu vaccine verification document stating you have received your seasonal flu vaccine. You may share this with your healthcare provider and employer, as appropriate.
- A study staff member will give you a paper memory aid or send you an electronic memory aid through email, thermometer (if needed), ruler (if needed) and go over instructions for these items.
- You will be assessed for immediate symptoms

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Study Day 1- Day 7 Post Visit 2: You will complete an online or paper symptom diary each day at around the same time each day. You will receive either electronic and/or telephone reminders for completing the symptom diary.

Visit 3 Study Day 29 (Clinic Visit): You will come into the clinic on day 29 and the following tests and procedures will occur:

- Study staff will record any adverse events (bad effects) you experienced within the first 7 days post-vaccination
- You will be asked to update the list of current medications you are taking.
- 10 mL (2 teaspoons) of blood will be drawn to test for antibodies.

Visit 4 Study Day 43 (Clinic Visit): You will come into the clinic on day 43 and the following tests and procedures will occur:

- Study staff will record any adverse events (bad effects)
- You will be asked to update the list of current medications you are taking.
- 10 mL (2 teaspoons) of blood will be drawn to test for antibodies.

Visit 5 Study Day 121 (Phone Visit): This visit will occur over the phone and you will be asked about the following items:

- Study staff will record any adverse events (bad effects)
- You will be asked to update the list of current medications you are taking.

You may be asked to return for an Unscheduled Visit, should you have an adverse reaction to the vaccine(s) and you need to be assessed by the study team.

Unscheduled Visits (Clinic Visit): You will come into the clinic if this visit is needed. The following tests and procedures will occur.

- Study staff will record any adverse events (bad effects).
- You will be asked to update the list of current medications you are taking.
- Study staff will obtain your oral temperature.

Laboratory Testing of Blood Specimens
The blood specimens collected from you will measure levels of antibodies to COVID-19 and to influenza (flu) virus strains contained in the vaccine you receive. Giving blood samples for these tests will not benefit you. The results of these tests are useful only for research purposes. Your individual influenza antibody results will not be available to you or your regular doctor. Your baseline COVID-19 antibody results may be made available to you during the course of the study but not immediately.

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Blood specimens for the research tests will be sent to a central testing laboratory. Those blood specimens will not be identified by your name or other identifying information. They will be labeled only with a barcode and a unique tracking number in order to help protect your confidentiality. Personnel at the central testing laboratory will not know your identity, or even the ID code you were assigned for the study.

A part of each coded blood sample may be stored indefinitely at a site determined by the sponsor, the CDC. The stored samples will be labeled only by study subject number and will not be labeled with your name or initials, or any other information that could identify you readily, and will be kept confidential to the best of the sponsor's ability within state and federal law.

There is the possibility that these stored samples may be useful for future research and they will be stored indefinitely. These samples might be used in new or different laboratory tests, to provide information for the development of new vaccines, or for studies of influenza virus, coronaviruses or other infections. The samples may be shared with researchers at other institutions. All serum samples will be used only for research purposes; the samples will not be sold or used directly for production of any commercial product. Serum samples obtained in this study may result in the development of a product that could be patented or licensed. There are no plans to provide financial compensation to you should this occur. No genetic testing will be performed. There are no benefits to you in the collection, storage and future research use of specimens. The results of any future testing will be kept confidential in the same way as the results of testing done for this study, which you will read about later in this form in the section titled "Confidentiality."

If you do not want your blood to be used as described in this section, you should not participate in this study.

HOW LONG WILL I BE IN THIS STUDY?
You will be in this study for approximately 120 days or around 4 months. 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?
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.

Blood Draw Risks
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely. Staff will apply direct pressure to the blood draw site to reduce any bruising. Sterile techniques will be used to prevent infection at the site where blood will be drawn.

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Influenza Vaccine Risks

With every medicine, including vaccines, there is a chance of side effects. There may also be risks, discomforts, drug interactions or side effects from these vaccines that are not yet known.
During this study, you will receive a flu shot (either a quadrivalent inactivated influenza (IIV4) or (quadrivalent high dose inactivated influenza (IIV4HD) if you are 65 years of age or older) that is licensed and recommended for use in the United States. The potential side effects from these study vaccines will not be different from what you would experience if you received these vaccines as part of your regular care.

Possible risks with receiving the flu vaccine include:

- Redness, swelling, or pain where the shot was given
- Fever, body aches, headache, or fatigue
- Nausea
- Cough or hoarseness
- Sore, red or itchy eyes
- Itching

More serious risks include a small increased risk of Guillain-Barré syndrome (GBS). GBS is a rare but serious condition that can occur after certain infections or after receiving certain vaccines such as the flu vaccine. There is a small increased risk of GBS (about 1 or 2 additional cases per million people vaccinated) after vaccination with flu vaccine. GBS causes inflammation and damage to the nerves in your body. Minor symptoms such as muscle tiredness or more severe symptoms, such as paralysis (weakness, or inability to move certain parts of the body) may occur.

Very rarely, occurring in about 1 in every 1 million vaccine doses administered, there can be a serious allergic reaction to any vaccine. These reactions can cause skin rash (hives), difficulty breathing, swelling around the mouth, throat, or eyes, a fast pulse, sweating, or loss of blood pressure, and would happen within a few minutes to a few hours after the vaccination. If these reactions occur, they can usually be stopped by the study staff giving emergency medications. If you experience these reactions away from the study site, you should get immediate medical care and then contact the study doctor.

Delay of Flu Vaccine

There is a potential risk of a short delay in protection against the flu by delaying the flu vaccine by two weeks. If you develop flu like symptoms, you should consult with your health care provider. Your health care provider may order tests to see if you have the flu. If it is determined that you have the flu, your health care provider may prescribe medication to treat it.

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Placebo Risks
As the placebo injection contains salt-water and no active ingredients, the chances of having the side effects mentioned above are less likely. In other studies using the same placebo, some people who received the placebo injection reported pain, bruising, swelling and redness at the site of injection.

Shot Risks
Some people feel faint or actually faint after having received a shot. Also, some people get severe pain in the shoulder and have difficulty moving the arm where a shot was given. This happens very rarely. As with any vaccine or medication, there is a very small chance of a fatal reaction, although researchers do not expect this to occur.

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

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may be direct medical benefit to you. Study participation will confirm that you receive the recommended flu vaccination. The flu vaccine has been shown to prevent flu infection in adults. As with any licensed vaccine, protection may not occur in 100% of vaccinated persons. However, you may develop protective antibodies against the flu. Information learned from this study may also help researchers understand if the flu and mRNA COVID-19 vaccines are safe to be administered on the same day.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?
The flu vaccine is available outside of this study. Please talk to your doctor about these and perhaps other options.

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 the study, results of your study-related laboratory tests, and procedures may be reported to the CDC and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the CDC, the Duke University Health System (DUHS) 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.

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This study is supported by the CDC. Because of this support, your study information is protected by a Certificate of Confidentiality.

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 CDC or for information that is required by the Food and Drug Administration (FDA).

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

Some information collected in research studies is maintained in your medical record. However, for this study that information will be inaccessible until the end of the study, unless your physician(s) decide that it is necessary for your care.

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.

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While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name, email 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 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.

WHAT ARE THE COSTS TO YOU?
You will receive the flu vaccine at no cost. There are no additional costs to you associated with this study. However, routine medical care (care you would have received whether or not you were in this study) will be charged to you or your insurance company. You may wish to contact your insurance company to discuss this further. In order to make sure that tests and studies done solely for research purposes are charged correctly, we will carefully monitor your Duke Hospital and Clinic charges as long as you are participating in this study. These tests and studies are not a part of routine care, and people who are not part of the study do not usually have them performed. Please ask Dr. Walter if you would like to know more about which tests and studies are being done solely for research purposes.

WHAT ABOUT COMPENSATION?
All study participants will be compensated $50 (cover costs associated with parking, gas, and time) after completing each Research Clinic Visit, $25 for the Phone Visit and $25 for each completed symptom diary (2 in total) for a maximum amount of $275 for all completed study activities.

If an unscheduled visit is needed to assess any adverse reaction to the vaccine(s), you will receive an additional $25 for completion for that visit.

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.

For questions about the study or research-related injury, contact Dr. Chip Walter at 919-620-5346 during regular business hours and at 919-970-5720 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. If you withdraw from the study, no new data about you will be collected for study

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purposes unless the data concern 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 CDC.

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 including receiving the flu or COVID-19 vaccine. If you do decide to withdraw, we ask that you contact Dr. Walter in writing and let him know that you are withdrawing from the study. His mailing address is DVTU-RTP Parmer Duke University PO Box 106008, Durham, NC 27710-6008.

Your blood samples may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.

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 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. Chip Walter at 919-620-5346 during regular business hours and at 919-970-5720 after hours and on weekends and holidays. You can also reach the study team at 919-971-5649.

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.

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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