Informed Consent Form for Research Subjects
AND
Authorization to Use and/or Disclose Identifiable Health Information for Research

Study Title: INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated heart failure (INVESTED)

Study Investigator(s): Insert site investigator(s) name(s)
Sponsored by: National Institutes of Health

Name of Subject: _____

Introduction

You are invited to take part in a research study. You have been asked to participate in this research because you have had a heart attack or have heart failure.

Being in this study is voluntary. Whether or not you decide to take part in this research study is completely up to you. The information in this informed consent form will help you decide if you want to be part of the study or not. You should read the information in this form carefully before you make a decision. Ask the study investigator or staff as many questions as you wish about this consent form and what will happen to you as part of this research study.

If you decide you do not want to sign this consent form, you cannot take part in this research study. Other options besides participating in this study are available to you (see the section in this form called, "**Are there any alternatives to participating in this study?"**). If you decide not to participate in this study, your relationship with the study site and any study staff (including any of your health care providers) will not change.

What is the purpose of this study?
Influenza infection ("the flu") is known to be associated with a higher risk for heart problems. The purpose of this study is to see if an investigational high-dose influenza ("flu") vaccine is able to safely reduce heart or lung-related problems compared to the standard-dose flu vaccine. Both the high dose and standard dose flu vaccines called Fluzone® are being provided for use in the study by Sanofi Pasteur, which manufactures the vaccines. The standard dose vaccine is approved by the Food and Drug Administration (FDA) for protecting against influenza disease caused by influenza A and influenza B viruses. The high dose vaccine is approved by the FDA for the same reason, but only for adults who are at least 65 years old. Thus its use with adults younger than 65 in this study is investigational.

Who is sponsoring or supporting this study?
The National Heart, Lung, and Blood Institute of the National Institutes of Health is sponsoring this study. Sanofi Pasteur, the company that manufactures the flu vaccines used in this study, is supplying the vaccines for the research study.

How many people will take part in this study?
This study will involve about 9,300 participants from about 180 sites across the United States and Canada, with about 500 participants at approximately 30 sites in the first year.

What will my participation in this study involve?
Study activities are described below. If you decide to take part in this study today, you will have the screening/baseline visit today. If you need more time to think about participating, you may come back to complete the visit at another time.

<u>Screening/Baseline Visit</u>
The screening/baseline visit will take about 90 minutes. At this visit, we will do the following:

- Review your medical records and ask you about your medical history and the medications you are taking. After this review the study investigator will decide whether you qualify and can safely participate in the study. If so, we will continue with the rest of the procedures (if you would like to do the rest of the procedures another day, we can arrange that).
- Ask you to provide the following information about yourself: date of birth, gender, race, ethnicity, mailing address, email address, phone number, social security number, smoking status, alcohol use, level of education, a questionnaire about your health, and living arrangements. You will be asked to sign a Release of Information form to assist with collecting information in regards to possible adverse events, hospitalizations, etc.
- Ask you for contact information for two family members or friends that we can contact if we cannot reach you during the study.
- Randomly assign you, like by flipping a coin, to receive one of the following vaccines by a shot given into the muscle of the arm:
    1) Fluzone® trivalent **high-dose** (180 micrograms) – trivalent means it contains 3 types of influenza viruses
    2) Fluzone® quadrivalent **standard-dose** (60 micrograms) – quadrivalent means it contains 4 types of influenza viruses

    Neither you nor your doctor will know whether we give you the high-dose or standard-dose vaccine. However, in the case of an emergency, this information will be available. Regardless of which group you are in, you will continue to receive your current treatment for your heart condition.
- Have you stay for 20 minutes so we can watch for any reactions you might have to the vaccination.
- Give you a 7-day diary and teach you how to use it to record any side effects that you might experience from the vaccine.

- Schedule a 1-week follow-up phone call so we can collect your diary information.

Follow-Up Contacts
We will contact you 3 times, for about 10 minutes each time:

- One week after your vaccination, we will call you to collect your 7 day diary information. If we cannot reach you at one week, we will try again to contact you at 2 weeks.
- During the influenza season we will call you to ask whether you have been hospitalized. If so, we will ask for the name of the hospital, and the date(s) and reason(s) you were in the hospital.
- The summer following influenza season we will call you to ask about hospitalization again. We will also ask if you would like to receive the study vaccine in the next influenza season. Depending on the year you are enrolled in the study, you may receive the study vaccine for up to 3 years.

If you are hospitalized in between these contacts, we would like you to call and tell us.

If we are not able to reach you for any of these follow-up contacts after trying a few times, we will contact the family member or friend that you provided to us at the beginning of the study.

When we talk with you in the summer, if you choose not to receive a vaccine in the upcoming study years, we will check your medical record for hospitalizations once each year instead of calling you.

If we learn that you are no longer living, we will search public death records to confirm this information and to collect cause of death. This search will require the use of your social security number.

Visits in the Next Season(s)
If you decide to receive a study flu shot in the 2nd and/or 3rd years of participation, you will have a visit lasting about 60 minutes. This visit will be similar to the 1st year baseline visit and we will do the following:

- Review your medical records and ask you about your medical history and the medications you are taking. After this review the study investigator will decide whether you can continue to safely participate in the study. If so, we will continue with the rest of the procedures.
- Update your contact information and that of two family members or friends that we can contact if we cannot reach you during the study.
- Give you the study flu shot. We will give you the same vaccine that you received in the 1st year. As with that shot, neither you nor the study team will know which vaccine you receive, but in an emergency this information will be available.
- Give you a 7-day diary to record any side effects that you might experience from the vaccine. We will follow up in the same way as in the 1st year.
- Schedule a follow-up phone call so we can collect your diary information.

You will have follow-up contacts in the same way you had them during the 1st year, as described above.

Because it is not known if the high dose vaccine may be harmful to an unborn child, if you are a woman who has not yet gone through menopause, we will ask if you are pregnant or breastfeeding before we give you the vaccine. Women who are pregnant or breastfeeding at the time of vaccination cannot be in this study.

How long will I be in this study?
If you choose to participate in this study, your participation will last up to 3 years. You will have a single 90-minute visit (applicable to the first year you participate; the single visit during years 2 and 3 will last 60 minutes) and 3 10-minute follow up contacts over about 1 year (across a flu season).

Depending on the year you start the study, you may receive vaccination and have the visits and contacts described above each year for up to 3 years. If you choose not to continue receiving vaccinations each year, we will collect hospitalization information from your medical record rather than contacting you.

The whole study, outside of the time you will directly participate, is expected to last for 10 years.

What are the risks to me from participating in this study?
While you're in this study, you may experience the following risks associated with your participation:

Flu Vaccine
Mild soreness at the injection site, headache, and muscle aches are the most commonly reported symptoms following influenza vaccination. As with all vaccines, there is a slight risk of severe allergic reaction. Signs of serious allergic reaction can include breathing problems, hoarseness or wheezing, hives, paleness, weakness, a fast heartbeat, or dizziness. If reactions like this occur, it is within a few minutes to a few hours after the vaccine. If you have a severe egg allergy or a history of severe reactions to previous flu shots, you should discuss these reactions with the study team prior to vaccination.

There is some evidence of a link between some influenza vaccines and Guillain-Barré syndrome (GBS). GBS is a disease that can cause serious and even permanent damage to the nervous system. About 1 in 100,000 people per year develop GBS, a small number of these cases may be triggered by influenza vaccines. If you have a history of this disease, you should discuss this with the study team prior to vaccination.

We will monitor you for at least 20 minutes after you receive the vaccine to check your injection site and any allergic reactions you may have. We will give you a diary to record any reactions you have for a week, and we will contact you at the end of that week to see how you are doing.

Random assignment (like flipping a coin) to high or standard dose vaccine
In studies of different influenza vaccine doses, adults receiving higher doses had more reports of pain, redness and swelling at the injection site, and muscle aches; but there were no differences in allergic reactions or lasting muscle aches.

Reproductive risks
We do not know if the high dose vaccine is harmful to an unborn child or a nursing infant. If you are pregnant or nursing at the time of study vaccination, you cannot be in this study.

Breach of Confidentiality
It is possible that your study information could become known to someone who is not involved with the study. We have measures in place to protect against this - see the section of this form called "**How is my health information protected?**"

We are collecting your email address so we can email reminders or other information during the study. Email is generally not a secure way to communicate about your health as there are many ways for unauthorized users to get access to emails. You should avoid sending sensitive, detailed personal information by email. Email should also not be used to convey information of an urgent nature. If you need to talk to someone immediately, you should contact local site insert your investigator's name and phone number.

Are there any benefits to me from participating in this study?
You are not expected to benefit directly from participating in this study. It is possible that if you receive a higher dose of vaccine, you could have a stronger immune response, which may protect you more against the flu. This cannot be guaranteed – it is one of the things we are studying with this research. No matter which dose you get, receiving the flu vaccine has been shown to help lower the chance of getting the flu.

Are there any alternatives to participating in this study?
You may choose not to participate in this study. You do not have to participate in this study to receive the flu vaccine. Alternatives to participating in this study include asking your doctor for a flu vaccine. The standard dose is used in routine clinical practice. If you are over 65 years old you may be able to get a high dose vaccine if you specifically request it from your doctor.

What are the costs to me for participating in this study?
You and/or your health insurer are responsible for paying the costs of the routine standard of care for your existing heart and medical conditions. The vaccine will be provided at no cost by the drug manufacturer. If there are any local site charges to subjects, e.g. pharmacy dispensing fees please revise the following sentence accordingly - There will be no costs to you as a result of participating in this study.

Will I be paid for taking part in this study?

Local sites – revise to reflect the subject payment amounts for your sites:
You will receive $25 per season, for a maximum of up to $75 over 3 seasons.

Local sites – revise to reflect the subject payment method/timing for your site:
Subjects will receive payment via a check mailed to them at the end of each season.

What if I am hurt or injured by taking part in this study?
[Local site to include appropriate compensation for injury language.]

How Will My Privacy Be Protected and Who Will Use My Health Information?
This research involves the use and sharing of your health information. Your health information is protected by a federal privacy law called Health Insurance Portability and Accountability Act (HIPAA).

Health information is considered "protected health information" (PHI) when it may be possible to figure out who the person is. For example, when a person's health information is combined with identifiers like name, address, phone number and social security number, then the information is considered PHI.

Federal law requires that PHI be kept secure and private. Federal law also gives you the right to decide who can see your protected health information.

Taking part in the research will require the researchers to have and use private information about you and your health. It will also be necessary for the researchers to permit other groups to see records that contain information about you and your health. The federal privacy regulations only permit the researchers to collect, use, or share your identifiable health information if you give them your permission to do so.

This form describes how the information collected about you for this research will be used and shared with others if you choose to participate in research.

By signing this form, you are allowing us to:

1. Access your health information (like your medical record);
2. Record your collected health information in a separate research record;
3. Share the collected health information for research purposes with people and/or entities doing this research study.

Will my information be held in confidence?
The National Institutes of Health have provided a Certificate of Confidentiality for this research. This means the researchers may not share or use information or documents that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, unless you have consented for this use. Researchers also may not use information or documents that may identify you as evidence, for example, if there is a court subpoena. Researchers cannot share information or documents protected by this Certificate with anyone else who is not connected with the research unless:

- there is a federal, state, or local law that requires such sharing – for example to report child abuse or communicable diseases.
- you have consented to the sharing, including for your medical treatment.
- it is used for other scientific research, as allowed by federal regulations protecting research subjects.

Researchers cannot use the Certificate to refuse a request from the National Institutes of Health for information that is needed for auditing or program evaluation or to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you 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.

When you sign this form, any sharing or use of information or documents that you have consented to in this form will still happen even with the Certificate of Confidentiality.

What information about me will be accessed, collected and recorded in the research record?
The following information about you and your health will be used for this research:

- Your demographic information like date of birth, gender, race, ethnicity, and social security number;
- Your smoking status, alcohol use, level of education completed, and living arrangements;
- A survey about your health;
- Your medical history;
- Your medications;
- Your hospitalizations and health status;
- Your test results; and
- Other diagnostic and medical procedures done as part of your clinical care.

Your health information may be identified by including your name, medical record number, address, phone number, email address, or other identifiers.

Who will be allowed to access and record my health information in the research record?
The following people will have access to your health information and use your PHI for the research purposes described in this form:

- The research team and their collaborators who may work with our researchers in conducting the research and analyzing or publishing the research data

- The National Institutes of Health (the sponsor), and the people or groups they hire to help perform this research. The sponsor may review your health information to assure the quality of the information used in research.

- Regulatory and research oversight boards and offices and research support personnel at the University of Wisconsin-Madison and other participating institutions. This includes the Institutional Review Board (IRB) at the University of Wisconsin – Madison. This group is a reviewing body responsible for the protection of human subjects rights and welfare. Members and staff of this reviewing body may review your health information to monitor the progress of the research.

- Government/regulatory agencies, such as the Office for Human Research Protections, whose job it is to protect human subjects and oversee the conduct of research.

- Representatives of the Food and Drug Administration (FDA) or its international equivalent. The FDA may monitor the research to confirm compliance with laws and regulations. The FDA may photocopy your health information to verify information submitted to the FDA by the Sponsor. Representatives of domestic and foreign governmental and regulatory agencies may be granted direct access to your health information for oversight, compliance activities, and determination of approval for new medicines, devices, or procedures.

- Members of the Data Safety Monitoring Board. This group oversees the data and safety of this research.

- The data coordinating center, that collects the data for the trial, or their collaborators may review a copy of your signed consent form. They will see your name and the date you signed the consent.

- Members from organizations that provide independent accreditation and oversight of hospitals and research.

- Holders of public records. If we learn from your medical record or through contact with the friend or family member you provided to us that you are no longer living, we will use your social security number to search public death records for confirmation and cause of death.

- The research team may disclose your participation in the trial to your Primary Care Provider to prevent you from getting double vaccinated.

When possible, the identifiers will be removed from your health information before sharing. In addition, the researchers might use information learned from this study in scientific journal articles or in presentations. None of this information will identify you personally.

Once the study is completed, all of the data that is collected during the study will be shared with the study sponsor, the National Institutes of Health (NIH), in a way that will not identify you personally. Data shared with NIH may be used by other researchers outside of insert local site, but only data that cannot identify you personally will be provided to other researchers. There are no limits on who might use these data or how the data may be used in the future.

A copy of the data de-identified will also be kept by researchers at the University of Wisconsin-Madison (UW-Madison), Brigham and Women's Hospital, the University of Minnesota, and the University of Toronto for an indefinite period of time (meaning they have no plan to destroy the data). The banked data at these institutions will only be used by researchers at these institutions for studies about influenza and/or heart disease.

As none of the data that may be provided to other researchers and used for future research will contain any of your identifiable information, there will be no way for you to withdraw your data from being used in the future. The primary risk of having your data banked and shared is from a breach of confidentiality, but because no identifiable information will be shared the likelihood of this happening is very small.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

How is my health information protected?
Absolute confidentiality cannot be guaranteed because persons outside the research team may need to look at the research records that include your identifying information.

We will:

- Collect and use only the minimum amount of PHI necessary to complete this research;
- Store your data in a secured way using normal business practices (like using password protected computers, limiting the number of authorized personnel who can see your identifiers, using a code number instead your name, or removing your identifiers when possible to do so);
- Share your health information only when we must;
- Share only the information that is needed to satisfy the request;
- Ask anyone who receives your health information from us to protect your privacy

However, once your information is shared, we cannot promise that it will remain private. Some people or groups who get your identifiable health information might not have to follow the same privacy rules that we follow. They may pass information on to other groups or individuals not named here.

This research requires the use of your health information. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in this research.

If you choose not to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related.

What if I agree to allow the use and sharing of my information but later change my mind?

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the research and decide to stop early.

You may withdraw your permission for us to use your health information for this research study by sending a written notice to:

Local site insert PI Name
Local site insert PI Address

If you cancel your consent to use and share your information, you may no longer participate in this research. The researchers will stop collecting any additional information about you unless they need information about a side effect of the vaccination.

However, we may still use and share information that was collected before receiving your cancellation. Also, if we have sent your health information to a third party, such as the research sponsor, or we have removed your identifying information, it may not be possible to prevent its future use.

Will information from this study go in my medical record?

Some of the information that we collect about you for this study will be put in your medical record. This includes that you received the flu shot. Both you and your insert local site health providers will be able to see this information.

Can you ask to see the PHI that is collected about you for this research?

The federal rules say that you can see the health information that we collect about you and use in this research. Contact the research team if you would like to review your PHI.

While you are participating in this research, you may see and copy any research information that is placed in your medical record. However, some research information is kept only by the researcher. The records kept only by the researcher may not be available to you until the end of the research.

How long will my PHI be used and shared?

If you do not cancel your consent, your PHI may continue to be recorded until the entire study is finished. This may take years. Your permission to use and share your health information will not expire unless you cancel it.

Any research information that is placed in your medical record will be kept indefinitely.

If I have questions about the study, who should I contact?
[Local site to include appropriate contact information language.]

If I have questions about my rights as a research subject, who should I contact?
If you have any questions about your rights as a research subject or have complaints about the research study or study team, contact the University of Wisconsin Hospital and Clinics Patient Relations Representative at 608-263-8009. These Patient Relations Representatives work with the Institutional Review Board overseeing this study to help address safety concerns about the study.

You may also contact Local site insert appropriate patient relations contact information for your site.

Optional Data Collection to Follow Health Status

The trial investigators wish to ensure complete clinical follow up of your health status during and after the clinical trial. For this purpose, we will collect your health plan beneficiary numbers, which will be kept with your other study data as already described. A file with your health plan beneficiary numbers, name, and date of birth will be shared with the following additional organizations:

- The Centers for Medicare and Medicaid (CMS). This is to collect information about you regarding any hospitalizations, emergency room visits, outpatient visits, or medication use that occur after or outside of the trial.
- The people or groups that Brigham and Women's Hospital hires to help collect and use information from CMS. They may review your health information to assure the quality of the information used in research.

Your health information obtained from CMS will be securely transferred to Brigham and Women's Department of Pharmacoepidemiology and Pharmacoeconomics and linked to your other study data to create a centralized database hosted at Brigham and Women's Hospital. All data will be coded after the linkage to maintain participant confidentiality prior to data analysis.

Your health information will be followed up to 10 years following your baseline study visit with research staff.

Please mark below whether or not you agree to participate in the optional data collection to follow your health status:

We will collect health information from your insurance records to follow your health status during and after the clinical trial.

___No I do not agree to have my health information reviewed for up to ten years after my first study visit.

___Yes I agree to have my health information reviewed for up to ten years after my first study visit.

Signature

I have read the information in this consent and authorization form, reviewed any questions, and I voluntarily agree to participate in this study. I will receive a signed copy of this form.

Signature of research subject **Date**

Printed name of research subject

Signature of person obtaining informed consent **Date**

Printed name of person obtaining informed consent