UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

IRC 002, Version 6.0, 26 AUG 2013:
A Randomized, Open-Label, Phase 2, Multicenter Safety and Exploratory Efficacy Study of Investigational anti-Influenza Immune Plasma for the Treatment of Influenza

CONSENT TO PARTICIPATE IN A RESEARCH STUDY AND RESEARCH SUBJECT HIPAA AUTHORIZATION

Your contacts for this study at the Hospital of the University of Pennsylvania [HUP] are:

Principal Investigator:	Pablo Tebas, MD	(215) 349-8092
Investigators:	Donald L. Siegel, PhD, MD	(215) 662-3441
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Address: 502 Johnson Pavilion, Philadelphia, PA 19104
24 Hour Emergency Number (215) 662-6059 Ask for the Immunodeficiency Program Doctor on call

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Introduction:
We invite you to take part in a research study. This study is funded by the National Institutes of Health (NIH). The doctor in charge of this study at this site is Pablo Tebas, MD and will be paid by the NIH to conduct this research study. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will be offered a signed copy of the consent form prior to any study-related evaluations to keep.

First, we want you to know that:

Taking part in NIH-funded research at the University of Pennsylvania is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.

You may receive no benefit from taking part in this study. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your University of Pennsylvania doctors or research team before you agree to the study.

Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at University of Pennsylvania, or with family, friends, or your personal physician or other health professional. This consent form may contain words you do not understand. Please ask the study doctor or the study staff to explain any words or procedures that you do not clearly understand.

Anti-Influenza Immune Plasma for the Treatment of Influenza

Why Is This Study Being Done?

Influenza (flu) is a virus (a type of germ) that can cause infections in people. Most people infected with this virus have mild symptoms including fever, cough, muscle aches, diarrhea, and headaches. Some people get very sick from this virus. These people tend to be older and have chronic (ongoing) medical problems, but it can affect younger people too. It is estimated that 30,000 people in the United States die each year from influenza. You may be eligible to participate in this study because you may have been infected with influenza.

Currently treatments are available for influenza, but there is concern that the rate of death is still high even with treatment, and that these treatments may no longer work against the virus (resistant to the treatment).

The purpose of this study is to develop a possible new treatment for influenza. This new treatment uses antibodies against this virus. Antibodies are natural proteins made by the body that attack influenza and other germs. These antibodies are found in plasma, the yellow, clear part of the blood. There have been other studies using plasma to treat other types of viruses that showed some positive results. We have collected plasma from people who had high levels of the antibodies either because they have been infected with the influenza virus or because they have been vaccinated against the infection. This study is being done to see if transfusing this plasma (and therefore antibodies) into people currently infected with influenza, in addition to standard anti-influenza medications, will help them improve moe than if just standard treatment is given.

How Many People Will Take Part in This Study?

About 100 volunteers across all sites will take part in this study. About 10-15 people are expected to participate at the University of Pennsylvania. The study will last for 28 days for each volunteer.

Criteria to Take Part in This Study

To participate in this study you must be hospitalized with influenza. You will not be able to receive any unlicensed medications for influenza (those not approved by the FDA), though you will receive standard medications for influenza as part of this study (such as oseltamivir, zanamivir, peramivir, or other medications). This study will infuse blood products (about 500 mls of plasma in two infusions), so you will not be able to participate if you have had allergic reactions to blood products, or your doctors think giving you this amount of blood product would be dangerous to you.

What Do I Have To Do If I Am In This Study?

Screening

If you agree to join this study, you will be asked to sign this consent form. After you have signed this form, you will be asked some questions and will undergo some tests to see if you can take part in this study. The screening visit will take about 45 minutes to one hour.

At the screening visit, we will go over with you the criteria to take part in this study.

- We will ask you about your health and any medicines you are taking.
- You will have a complete physical examination where the site staff will check your vital signs such as weight, height, temperature, blood pressure, breathing, and pulse.
- We will take about 2-4 tablespoons of blood for routine safety tests and to determine your blood type and also to check flu antibody levels.
- For females we will also do a pregnancy test.

- We will swab your nose and the back of your throat to ensure that you have influenza. If you are on a breathing machine, we will obtain the sample of secretions from your windpipe.

Once we have the influenza test results, we will ensure that you meet the other requirements to participate in the study.

On-study evaluations

Once we determine that you qualify for this study, we will collect some baseline information about what symptoms you have, your vital signs (temperature, pulse, respiration rate, and blood pressure), and some other clinical information (such as whether you require any supplemental oxygen and whether you are in the ICU). We will also need to collect some blood from your arm. We will then administer the study treatment (see below).

We will take your vital signs during and after the treatment, as well as collect about 2 tablespoons of blood during the treatment

At 1, 2, 4, 7, 14, and 28 days after you are enrolled in the study we will evaluate you. If you are no longer in the hospital, we will need you to return to the clinic for these visits. Each visit should only take about 1 hour. At each of these time points, we will check your vital signs, perform a brief exam, ask questions about your symptoms, and collect some clinical information. On Day 2, 4, 7 and 28 we will collect about 4 tablespoons of blood at each time point for safety tests and other research tests. We will also swab your nose and the back of your mouth at each visit, except on Days 14 and 28.

If you are pregnant, in addition to the above, we will want to contact you each month until your delivery to ask about the health of your child and any complications during pregnancy or delivery.

Study Treatment

All participants will receive treatment for influenza with standard anti-influenza medications. The choice of the medication is up to your doctor. In addition to this, we may give you study treatment as part of this study. You will be assigned randomly (like flipping a coin) to receive either routine care or the plasma containing high levels of antibody against the influenza virus in addition to routine care. If you receive study treatment, it will be given through an IV catheter (tube) placed in a vein. You will receive 2 doses of the study treatment, separated by a few hours.

The plasma was collected from people who either recovered from the flu or were vaccinated against the flu. Some of the donors may have been compensated for the time they spent donating the plasma. All of the plasma has been tested to ensure it has high titers of anti-influenza antibodies. All of the plasma has also been tested for the infectious diseases that can be transmitted in blood, including HIV, hepatitis, and syphilis. The plasma used in this study has been tested in similar ways and meets the same standards as plasma used in any hospital blood bank.

Special Concerns

If you are pregnant, you still can participate in this study. Due to the severe disease seen in pregnant women, we are including them in this study (after we have looked at how some non-pregnant adults do with the plasma). We will enroll pregnant women at this center.

Stored Samples and Future Research

Some of the blood work we are taking is for additional research laboratory testing. The research tests we will use may not be like medical tests. We may not know how the results relate to your care. Therefore we may not put future test results in your medical record. However, if you ask,

someone on the study team will discuss the test results with you. We will not share these test results with your private doctor unless you ask us to do so.

Future Studies

Other investigators may want to study your stored samples. If so, the University of Pennsylvania study team may send your samples to them, without any information that can be traced to you. The study team may also share information such as your gender, age, health history, or ethnicity. In some cases, an Institutional Review Board (IRB) will review new research that uses your samples. The IRB is a committee that oversees medical research studies to protect volunteers' rights and welfare.

Investigators will only use your samples for research. We will not sell them. Future research that uses your samples may lead to new products, but you will not receive payment for these products.

Samples will not be stored for genetic testing.

Why Would The Doctor Take Me Off This Study Early?

As previously discussed, you may withdraw from the study at any time. You will not be asked for further information or samples.

The study doctor may need to take you off the study early without your permission if:

- the study is cancelled by the U.S. Food and Drug Administration (FDA), National Institutes of Health (NIH), or the University of Pennsylvania's Institutional Review Board (IRB).
- you are not able to attend the study visits as required by the study.

The study doctor may also need to take you off the study without your permission if:

- continuing the study may be harmful to you
- you need a treatment that you may not take while on the study

What Are The Risks Of The Study?

Risk of Treatment with Plasma:

It is not known whether you might benefit from receiving plasma therapy. Most risks associated with plasma therapy are those that occur regardless of the type of antibodies in the plasma. Fevers, rashes, hives, or headaches occasionally happen with plasma infusions. More rare side effects would include serious allergic reactions including anaphylaxis, which can be life threatening. Infections may also occur. Rarely, bacterial infections can occur if bacteria contaminate the bag of plasma. Viral infections like Hepatitis B, Hepatitis C, and HIV may occur despite our screening for these diseases.

A type of lung injury has been seen with transfusions. This transfusion-related acute lung injury (TRALI) has been shown to be related to antibodies against your cells that come from other people's plasma. TRALI is characterized by a clinical constellation of symptoms including shortness of breath, hypotension (low heart rate) and fever. This has mainly been shown to come from plasma from women who have had children (antibodies presumably generated during pregnancy). In this study, the risk is minimized by only using male donated plasma. However, this may not eliminate the risk entirely. The risk of TRALI is reported as 1 out of 5000 transfusions. If this happens it could make it hard to breathe, or you may have to be put on a breathing machine.

There is also the risk that the proteins in the plasma will cause blood clots to form. These blood clots could go to your heart or lung making it difficult to breathe. This is not specific to this study

and can occur during transfusions of blood products. if this should happen to you the usual measures for treatment will be used.

The plasma volume is roughly 500 mL (2 cups) for adults. There is a risk that if you cannot tolerate this amount of volume it may become harder to breathe or put a strain on your heart. People that are known to have conditions that would not tolerate this volume of blood are excluded from the study. However, this condition could still occur.

If you are randomized to receive the plasma, you should wait at least 5-6 months before receiving any influenza vaccine or live attenuated (weakened) virus vaccines such as those given against measles, rubella, mumps, and varicella (Chickenpox). This is because the plasma may temporarily interfere with the body's ability to mount as good of an immune response to those vaccines as desired. If there is a need to receive ANY vaccine within 7 months of receiving the study drug, you should make sure your health care provider is aware of your participation in this study and the date you received plasma.

There is the risk that plasma could make either the infection, or the inflammation associated with the influenza infection worse.

If you are pregnant, there may be additional risks. Plasma is routinely used during pregnancy, so we do not anticipate any additional risk with this plasma, but we do not know for certain. There is the risk that the plasma could cause premature labor, complications after the child is born, or spontaneous abortion.

Risk of Blood Draw:
You may feel some pain at the needle entry site. There is a slight risk of bleeding around the site. This is not dangerous, but it could result in a bruise. Some people feel lightheaded or dizzy after having blood drawn. To reduce the risk of injury because of a fall, you will be closely monitored and asked about these symptoms before you are allowed to stand up. There is also the possibility of infection at the site where the needle went in, but this rarely happens.

Risk of Throat Swabs, Nasal Swabs, and Nasopharyngeal Aspirate:
Generally these procedures are well tolerated. They may cause discomfort, though we try to minimize it the best we can. Occasionally these procedures can cause you to cough or gag, and rarely vomit. The nasal swab and nasal wash can irritate the lining of the nose and rarely may cause a minor nosebleed.

Risk of endotracheal aspirate
The aspirate from your windpipe (only done if you are on a breathing machine) can make you cough, and rarely can irritate the lining of your wind pipe or cause a small amount of bleeding.

Are There Benefits to Taking Part in This Study?

You may not receive any direct benefit for participating in this study. The benefits of treating with plasma in patients actively infected with influenza are unknown. It is possible that receiving plasma in addition to standard antiviral therapy will make the infection resolve faster.

What Other Choices Do I Have Besides This Study?

The alternative is not to participate in this study. You can also just receive current standard of care treatment for influenza.

You have the right to agree or refuse to participate in this research. If you decide to participate and later change your mind, you are free to discontinue participation at any time. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. Refusal to participate will not affect your legal rights or the quality of health care that you may receive at this center. You will be given any new information that becomes available during your participation in the research that may affect your willingness to continue in the study.

If you agree to participate in this study, you agree to let us store your samples for future research. No matter what you decide, you may still participate in other studies at the University of Pennsylvania. However, your refusal to let us store your samples may lead to your withdrawal from this specific study.

What About Confidentiality?

The greatest risk is that someone may take information from your medical records without your permission. The chances of this happening are very low. If this information becomes available, you may face discrimination when you apply for insurance or a job. You may also have similar problems if you share the information yourself or let us release your medical records.

Confidentiality and Labeling of Samples

We will label your samples with a code that only the study team can link to you. We will keep any information that can be traced back to you private to the extent permitted by law.

Information about you (such as your name, address, and telephone number) will be kept separate from the results of research tests we perform. Research information will be kept in a password-protected computer file that only the study investigators can view. If we learn anything of importance to our research from this testing, we may publish the results in a medical journal. However, you will not be identified in such an article.

When results of a University of Pennsylvania research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the University of Pennsylvania will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the University of Pennsylvania will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your University of Pennsylvania medical records. However, you should know that the Act allows release of some information from your medical record without your permission; for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

HIPAA AUTHORIZATION

The authorization part of the consent gives more detailed information about how your personal health information may be used and disclosed by the University of Pennsylvania Health System (UPHS), the School of Medicine and the individual Principal Investigator, subject to University of Pennsylvania procedures.

What personal health information is collected and used in this study and might also be disclosed?
The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number, date of birth
- Personal and family medical history
- SSN: will be collected if it is expected you will receive more than $600 for study participation in a given year
- Current and past medications or therapies.
- Results of tests and procedures you will undergo during this research study

Why is your personal contact and health information being used?
Your personal contact information is important for the research team to contact you during the study. Your personal health information and results of tests and procedures are being collected as part of this research study. In some situations, your personal health information might be used to help guide your medical treatment.

Which of our personnel may use or disclose your personal health information?
The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the Investigator's study team
- Authorized members of the workforce of the UPHS and the School of Medicine, and University of Pennsylvania support offices, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring, to provide treatment, to manage accounting or billing matters, etc.).

Who, outside of UPHS and the School of Medicine, might receive your personal health information?
As part of the study, the Principal Investigator, the study team and others listed above, may disclose your personal health information, including the results of the research study tests and procedures. This information may be disclosed to those listed below:

Individuals or organizations responsible for administering the study:

- Frontier Science Technology Research Foundation (FSTRF): Data for this study will be recorded on case report forms, keyed into a central database and electronically submitted to the Data Coordinating Center. The data will be cleaned and stored at this facility until it is ready to be analyzed.
- Government Agencies: Data from this study will be made available to the Food and Drug Administration and to the National Institutes of Health/National Institute for Allergy and Infectious Disease (NIAID), for them to evaluate the safety and efficacy of the treatments being used in this study.

- Monitors and Auditors: The study records will be assessed by a contract monitoring agency to assure that all assessments and evaluations are being conducted appropriately for the study. These persons will have access to your clinical trial medical chart for these purposes.

Regulatory and safety oversight organizations

- The Food and Drug Administration
- The Office of Human Research Protections

Once your personal health information is disclosed to others outside of UPHS or the School of Medicine, it may no longer be covered by federal privacy protection regulations. Data are reported to the sponsor on Case Report Forms that identify you by your unique study number and not your name, date of birth or medical record number. Information regarding your health, such as side effects of the study vaccine you experience will be reported only by code number. All samples collected for analysis will be labeled with your study number, visit number and date of your visit.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may UPHS and the School of Medicine be able to use or disclose your personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research repository (database). However, UPHS and the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization to do so
- The University of Pennsylvania's Institutional Review Board grants permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

Can you change your mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study. You will also be given the UPHS and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your personal health information.

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any results of procedures performed as part of this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Results of research procedures performed as part of your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

Will I Receive Any Payment?

You will be compensated $25.00 for travel costs associated with coming to the outpatient study visits. You will not be compensated while you are an inpatient. The total amount of compensation for the study will vary from $25 to $150 depending on when you are discharged from the hospital.

Please note that if you receive more than $600.00 compensation in one year for participation in research studies at the University of Pennsylvania, you must provide a Individual Tax Identification number or Social Security Number for tax purposes.

What Are the Costs To Me?

The study medication, visit and procedures are provided without charge to you. Any procedures done specifically for the study will not be billed to your insurance.

What Happens If I Am Injured?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through the University of Pennsylvania or the NIH. You will not be giving up any of your legal rights by signing this consent form.

What Are My Rights As a Research Subject?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your healthcare provider will treat you the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

Clinical Trials Listing

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 any information that can identify you. At most, the Web site will include a summary of the results of this research. You can search this Web site at any time.

What Do I Do If I Have Questions Or Problems?

By agreeing to participate in this study, you do not waive any rights that you have regarding access to and disclosure of your records.

For questions about this study or a research-related injury, contact:

- Pablo Tebas, MD (215-349-8092)
- Clinical Trials Unit (215 349-8092)

For questions about your rights as a research subject, contact:

- Director of Regulatory Affairs at the University of Pennsylvania by phoning (215) 898-2614

CONSENT

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you. You will also be given the University of Pennsylvania Health System and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your health information.

Name of Subject (Please Print)	Signature of Subject Date
Participant's Legal Guardian (print) (As appropriate)	Legal Guardian's Signature and Date
Name of Person Obtaining Consent (Please Print)	Signature Date