HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

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

Protocol Title:	IRC-003, PROTOCOL VERSION 7 – FEBRUARY 1, 2016 A Randomized, Double-Blind, Phase 2 Study Comparing the Efficacy, Safety, and Tolerability of Combination Antivirals (Amantadine, Ribavirin, Oseltamivir) versus Oseltamivir for the Treatment of Influenza in Adults at Risk for Complications
Principal Investigator:	Pablo Tebas, MD 502 Johnson Pavilion, Philadelphia PA 19104
Contact for Staff	**(215) 349-8092**
Lead Study Nurse:	Yan Jiang, RN, BSN, MSN
Research Team:	Joseph Quinn, RN, BSN Uzair Ashraf, MD Salma Zeb, BA
24 hr. Emergency Contact:	Immunodeficiency Program Doctor on call (215) 662-6059

Introduction:

We invite you to take part in a research study. This study is funded by the United States (U.S.) 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 get a copy to keep.

First, we want you to know that:

- Taking part in NIH research 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. 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 the University of Pennsylvania doctors or research team before you agree to take part in 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.

Why Is This Study Being Done?

Influenza 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 medical problems. It is estimated that 30,000-50,000 people in the U.S. die each year from influenza. You may be able to be part of this study because you may be infected with influenza, and you have medical problems that may put you at higher risk for severe infection with influenza.

There are treatments currently available for influenza. The treatment of influenza is complicated and no one knows yet the best way to treat it. Oseltamivir (Tamiflu) is used most often to treat influenza, but there are still many hospitalizations, complications, and deaths even with treatment. There is also concern that currently available treatments may not work against the virus in the future. We want to see if we can find a better treatment for people who are at high risk for complications.

Our goal is to develop a possible new treatment for influenza by using several anti-virus medications instead of just one (which is usually what is given). Studies in animals suggest that treating influenza with a combination of medications (oseltamivir, ribavirin, and amantadine) will make the virus go away faster. We are investigating whether these medications together can slow down the spread of the influenza virus in your body. Prior to this study, this combination of medications has been used in fewer than 32 people with influenza and in 42 healthy people.

The current flu virus is resistant to one of the drugs used in the combination (amantadine). However, studies in animals suggest that when used in combination, this is still an important component of the combination.

How Many People Will Take Part in This Study?

About 700 volunteers across all sites will take part in this study. About 15-30 people are expected to participate at the University of Pennsylvania.

Criteria to Take Part in This Study

In order to be in this study you must be at least 18 years of age, have one or more medical conditions like heart or lung disease that may cause you to have complications from influenza, and have an influenza-like illness for no more than 96 hours or about 4 days.

If you take certain medications or if you have certain laboratory findings that may increase your risk from the medications being used in this study, you will not be able to be in the study. You can't have received a live virus vaccine within 3 weeks prior to starting the study. You must be willing to let us store samples of your blood and influenza virus.

Lastly, you cannot be in this study if you were in another study and took a study drug within 30 days before starting this study (or sometimes longer depending on the drug). While you are on this study, you cannot be in any other study that takes more than 7 tablespoons (100 mL) of blood in any 4-week period of time or a study that gives any unlicensed drug, vaccine, or other investigational treatment for influenza.

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 60 minutes.

At this visit, we will:

- Take a brief medical history and then perform a physical examination.
- Take approximately one tablespoon (16 mls) of blood to examine your chemistries, liver and kidney function, and cell counts.
- Test for influenza by swabbing the back of your nose and/or the back of your throat.
- For females we will also do a pregnancy test.

On-Study Evaluations

If you qualify for the study, you will be randomly assigned (in a manner similar to flipping a coin) to take either oseltamivir alone (the current standard treatment for influenza) or to take oseltamivir, amantadine (Symmetrel) and ribavirin (brand names include Rebetol, Ribasphere, and Virazole). Half of the people in this study will take oseltamivir alone, and the other half will take the combination of medications. Everyone will receive a study medication kit showing three medications so that neither you nor your doctors will know which treatment you will receive. A drug company, Adamas Pharmaceuticals, is supplying the amantadine and ribavirin, and the NIH is supplying the oseltamivir for this study.

Once you have been randomized, we will collect pre-treatment data. We will take your vital signs. We will then provide you with a book of diary cards and explain how to complete them. These diary cards will be used to understand your symptoms and your activity limitations. We will ask you to complete the first diary card entry with the study staff. You will take the diary home, and complete the diary twice a day for the first 7 days. You should also check your temperature twice a day, and capture the highest temperature in the diary. On Day 8 through Day 14 you need to complete the dairy just once a day. You should bring the diary back at each visit.

We will also take approximately one tablespoon (17 mls) of blood that will be used for research tests to see how your body responds to influenza. We will insert another swab into the back of your nose to test for the amount of influenza virus. All of these samples are sent to a central lab, and we will not have the results until the end of the study.

We will then give you the study medication kit. You will take the medication home and take the medication twice a day for 5 days. Each time you will be taking 5 capsules with food to decrease the chance of an upset stomach. You should bring the medication kit with you to each visit.

We will ask you to return to the clinic on Days 3, 7, and 28. The first visit may take 2-3 hours, but each subsequent visit should take approximately one to two hours. At each visit we will review the information on your diary, perform nose swabs (through Day 7), and take blood approximately one tablespoon (16 mls) for testing your chemistries, liver and kidney function, and cell counts (Days 3, 7, and 28).

The total amount of blood drawn for this research study is approximately 132 mls or about 9 tablespoons. If you are also enrolled in other protocols, the total amount of blood collected for all studies cannot be more than the allowed limits. At each visit, you will be asked about new symptoms

and side effects you have experienced as well as any medications you are taking. You must notify the study staff if you are enrolled in any other research studies.

After Day 28, women of child bearing potential will need to return to the clinic every month for a urine pregnancy test for approximately 6 months after stopping the study treatment. For men that are capable of having children, we will contact you by phone every month for 6 months so we can remind you about the importance of not getting your partner pregnant.

Study Treatment

- Oseltamivir is already approved (licensed) to treat influenza.
- Ribavirin is a licensed drug, but it is not licensed for the treatment of influenza. Ribavirin is frequently used to treat hepatitis C.
- Amantadine is also approved to treat influenza, but by itself it is not active against current types of the virus. It seems to still work when used with other medications.

Stored Samples and Future Research

We will store blood and swab samples for future research. These samples will help us learn more about your body's response to influenza. 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 will 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.

Other investigators may want to study your stored samples. If so, the NIH study team may send your coded samples to them. The investigators will not know they are your samples. 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 participants' rights and welfare.

In general, future research that uses your samples will not help you, but it may help us learn what causes severe influenza. This research may also help us learn how to prevent or treat influenza.

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.

How Long Will I Be In This Study?

You will be in this study for 28 days. If you are a female who could become pregnant, you will have additional study visits once a month for up to six months. If you are a male who may impregnate a woman, you will have telephone contact once a month for up to six months.

Why Would the Study 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 site's Institutional Review Board (IRB).
- You are not able to attend the study visits as required by the study.
- 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?

There may be risks that are unknown at this time.

Risks of Oseltamivir

When used as part of routine medical care it can cause nausea, vomiting, and diarrhea. It is thought that using a higher dose of this drug may cause more of these symptoms. Less common side effects of this drug include dizziness (vertigo) and difficulty sleeping.

Risks of Ribavirin

Ribavirin is a licensed drug, though is not licensed for the treatment of influenza. Ribavirin is frequently used to treat hepatitis C. Ribavirin may cause birth defects and/or death of an unborn baby, so avoiding pregnancy is crucial. Ribavirin may cause anemia (low blood cell count). In studies for hepatitis C (which is longer treatment than this study), ribavirin causes anemia in 1 of every 7 people taking the drug. In cell cultures, ribavirin has been shown to affect the genetic material of cells. However the significance of this finding is unclear as ribavirin has not been shown to increase the risk of cancers in animals or people. Ribavirin can affect your other blood counts, and liver, so we will be testing your blood for these. Lastly, ribavirin when taken with other medications (including some HIV medications and azathioprine) can be dangerous, so it is important to tell us all of the medications you are taking or have taking in the last month.

Risks of Amantadine

The adverse reactions reported most frequently (5-10% of the time) are: nausea, dizziness (lightheadedness), and insomnia. Less frequently (1-5%) reported adverse reactions are: depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia (loss of coordination), livedo reticulans (purplish discoloration of the skin) peripheral edema (swelling of feet or hands), orthostatic hypotension (low blood pressure that happens when you stand up from sitting or lying down), headache, sleepiness, nervousness, dream abnormality, agitation, dry nose, diarrhea and fatigue. Amantadine can cause mental confusion, blurry vision, and it could increase seizure activity. This is more often seen in patients with psychiatric disorders or substance abuse, but can occur in anyone.

Risks of Combination Treatment

There is also a possible risk of side effects when oseltamivir, amantadine, and ribavirin are used in combination. Some adverse reactions such as nausea or confusion may be caused by more than one of these drugs. When used together these adverse reactions may be more common. In clinical practice, these medications have not been used together to treat people with influenza. In studies with healthy volunteers, there was more nausea when these drugs were taken together. There is the possibility of other side effects that we don't know about yet.

Risks 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.

Risks of Nasal Swabs
Generally, swabbing the nose is well tolerated. It may cause discomfort, though we try to make that as little as possible. The nasal swab can irritate the lining of the nose and rarely may cause a minor nosebleed.

Risks of Stored Samples
The greatest risk of allowing us to store your samples will be an unplanned release of your identification from the samples due to release of this information from the stored sample database. The chances of this happening are very low.

Are There Risks Related To Pregnancy?

If you are a female, you cannot be pregnant or breast-feeding. Because we know that one of the study drugs (ribavirin) can hurt the developing fetus, it is very important that women avoid getting pregnant during the study and for about six months afterward. During that time, women will need to visit the study clinic and have monthly urine pregnancy tests for 180 days (approximately 6 months).

Men must avoid getting their partners pregnant during the study and for about 6 months afterward. Men that are capable of having children will be called monthly for 6 months to ensure your partner(s) have not become pregnant.

Participants must avoid pregnancy by not having sex where the female partner could get pregnant, or using either oral contraceptives (the pill), other hormonal contraceptives including vaginal contraceptive rings and contraceptive patches, barrier contraceptives such as condoms, or an intra uterine device (IUD).

If you (or your partner) become pregnant during the course of the study, you must inform your doctor and study staff right away. If you become pregnant while you are on the study, your doctor will contact you about your birth outcome. With your permission, you will be asked questions about the birth outcome (length of pregnancy, type of delivery, APGAR scores). If you are unable to recall the information, you may be asked to sign a medical release for information, so that the research staff can request your records from the delivery center or your obstetrician.

If you (or your partner) become pregnant after taking study drugs, your study doctor will see if you were taking the combination of flu drugs with ribavirin, the drug that can hurt a developing baby. If you did receive ribavirin, you (or your partner) will be asked to enroll and participate in the Ribavirin Pregnancy Registry that is maintained by the ribavirin manufacturer.

This registry program is not a part of this research study but collects information to help doctors learn more about the effects of ribavirin on babies exposed to ribavirin during pregnancy. If you (or your partner) are interested in enrolling, your study team will provide you with the Pregnancy Registry information and help you register and participate in this program. Participation is completely voluntary. You can receive more information from your study doctor, or you can go to: http://ribavirinpregnancyregistry.com or call 800-593-2214.

Are There Benefits to Taking Part in This Study?

You may not receive any direct benefit for being in this study. You will be treated for influenza. The combination medication may make your symptoms resolve faster and lessen the risk of complications, but we don't know that for sure. What we learn from this study may allow us to further develop a new treatment for seasonal influenza and swine influenza.

What Other Choices Do I Have Besides This Study?

The alternative is not to participate in this study. If you decide not to participate in this study you should still seek treatment for influenza.

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.

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

Confidentiality and Labeling of Samples

We will label your nose and blood 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 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.

Access to your identifiable medical record information will be limited to investigators associated with the study and their research staff. In addition authorized representatives from the IRB and NIH authorized monitors and auditors will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the appropriate conduct of this research study, monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.

When results of an NIH 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 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. Some information including pertinent hospital or clinical records will be made available for inspection by the local IRB/IEC, the local and national regulatory authorities, the U.S. FDA, the site monitors, and the NIAID staff for confirmation of the study data.

Will I Receive Any Payment?

You will be compensated for the time and inconvenience of being in this study, and it will be based on the number of clinic visits you complete. For each of the study visits you attend (Screen, baseline, Days 3, 7, and 28) $50 compensation will be provided. If you complete all five visits you will be paid $250. Females that require pregnancy testing for 6 months will be paid $25 for each visit (Days 60, 90, 120, 150 and 180) or $125 if all visits are attended..

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 Happens If I Am Injured?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania or the National Institutes of Health to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

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).

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, email address and medical record number
- 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 (Institutional Review Board and the Office of Clinical Research), 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 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 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.

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/Time
Name of Person Obtaining Consent (Please Print)	Signature	Date