Title of study: ED Influenza Therapeutic Pilot Study: Oseltamivir vs. Peramivir

NCT number: 02609399

PI name: Richard Rothman, MD, PhD

Date of protocol: 09/26/16

Influenza Therapeutic Pilot Study

A Pilot Randomized Controlled Trial for Feasibility of Enrolling Subjects for Influenza Therapeutic Trials and Administering Influenza Antivirals in the Emergency Department to High Risk Subjects

Protocol Number: 15-001

Version: 2.0

Pharmaceutical Support Provided by: BioCryst Pharmaceuticals, Inc.

IND Sponsor: Andrea Dugas, MD, PhD

Lead Co-Principal Investigators: Andrea Dugas, MD, PhD & Richard E. Rothman, MD, PhD

IND #: 127482

09/26/2016

Influenza Therapeutic Pilot Study

Statistical Analysis Plan

Version 2.0

IND Sponsor: Richard E. Rothman, MD, PHD
Study Principle Investigator: Richard E. Rothman, MD, PHD
Study Co-Investigators: Andrea Dugas, MD, PHD
and Mustapha Saheed, MD

Prepared by:

Qilu Yu, PHD

Westat
1600 Research Boulevard
Rockville, MD 20850

5/18/2017

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: **A Pilot Randomized Controlled Trial for Feasibility of Enrolling Subjects for Influenza Therapeutic Trials and Administering Influenza Antivirals in the Emergency Department to High Risk Subjects**

Application No.: **IRB00080405**

IND Sponsor: **Andrea Dugas, MD, PhD**

Principal Investigator: **Andrea Dugas, MD, PhD**
Department of Emergency Medicine

Johns Hopkins Medical Institutions

5801 Smith Avenue

Davis Building, Suite 3220

Baltimore, MD 21209

Phone: **410-735-6400**

Fax: **410-735-6425**

Email: **adugas1@jhmi.edu**

1. What you should know about this study:

- You are being asked to join a research study. This consent form explains the research study and your part in it. Please read it carefully and take as much time as you need. Ask your study doctor or the study team to explain any words or information that you do not understand.

- You are a volunteer. If you join the study, you can change your mind later. There will be no penalty or loss of benefits if you decide to quit the study.

- During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.

- If we think your participation in this study may affect your clinical care, information about your study participation will be included in your medical record, which is used throughout Johns Hopkins. Doctors outside of Johns Hopkins may not have access to this information. You can ask the research team to send this information to any of your doctors.

- When Johns Hopkins is used in this consent form, it includes The Johns Hopkins University, The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Johns Hopkins Community Physicians, Suburban Hospital, Sibley Memorial Hospital and All Children's Hospital.

- Biospecimens will be collected in this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US 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.

- If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

2. Why is this research being done?

This research is being done to establish the use of the emergency department as a primary site for participant enrollment in research studies that look at drugs used to treat influenza ("the flu"). This will help us understand the best way to design and plan research studies that will use study drugs to treat patients who are sick with the flu.

We will be giving one of two drugs used to treat the flu to each study participant, either oseltamivir or peramivir. Both oseltamivir and peramivir are approved by the Food and

Drug Administration (FDA) to treat the flu but the use of oseltamivir and peramivir in sicker individuals is not approved and is considered investigational. The FDA is allowing oseltamivir and peramivir to be used in this study.

People with a positive flu test from their current emergency department visit may join.

How many people will be in this study?

Up to 225 adults will be in this study.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

On the Day of Enrollment:

Some of these tests and procedures are likely to be part of regular care and may be done even if it turns out that you do not take part in the research study:

- Answer questions while you are in the emergency department about your current symptoms, any medications you may be taking, and your medical history. We will also ask for some basic information about you such as your age, sex, race, and telephone number. This will take about 10 minutes to complete. We will also ask you to sign an authorization for release of health information, which will allow our research staff to review your medical records at other hospitals in the four weeks after today's visit to the emergency department.
- Have some laboratory tests, if they have not been done in the last 24 hours. This will take about 1 hour to complete:
    - Blood: we will collect 10 mL or 1 tablespoon of blood from your vein.
    - Pregnancy test (Blood or Urine): we will collect 10 mL or 1 tablespoon of blood or urine from women of childbearing potential. If you are pregnant you will not be permitted to participate in the study.

  The results of your tests will be part of your medical record and provided to your treating provider.
- Chest x-ray, if one was not done as part of your medical care in the emergency department.
- Receive a drug to treat your flu. Depending on which drug you get, this may take up to 30 minutes.
- You will be randomly assigned, like flipping a coin, to one of the two flu drugs listed below:

- One group will receive oseltamivir (Tamiflu) by mouth, which will take no more than 5 minutes.
- The second group will receive peramivir (Rapivab) through an IV, which will take about 30 minutes to complete.

- Biospecimen collection from your flu test. Any leftover specimen from the swab that was taken for your flu test will be stored and may be used for future testing.

For 1-2 weeks after enrollment:

- Complete a daily diary for 14 days. You will answer questions about how you are feeling.
  - You can complete these questions on your own over the internet or a research coordinator will help you to complete the questionnaire. If you prefer to have a research coordinator help you complete the questionnaire, this will take place over the phone or if you remain in the hospital, this may take place in person. It will take about 10 minutes each day.
- Continue to take a drug to treat your flu, depending on which drug you receive.
  - If you are taking oseltamivir, you will be asked to take the drug by mouth once or twice a day for 5 days (a total of 5 to 10 doses). This will take less than 1 minute each day.
  - If you are taking peramivir you will only receive one dose of the study drug through an IV. If you are hospitalized and your doctor wishes to continue the peramivir, this drug will be provided to you free of charge.
- Study Check-In on day 3 and day 7
  - The study team will call you to see how you are feeling and if you have any side effects from the drugs. We will also ask you about any other doctor or hospital visits you have had since you started the study. This will take place over the phone, or if you remain in the hospital, this may take place in person. This will take about 5 minutes on each day.If you are admitted to the hospital, we will collect a nasopharyngeal swab on these days. We will insert a swab into your nose in order to collect a small sample of nasal secretions. This is a biospecimen that will be saved for testing in the future to look at the amount of flu virus that you have in your body.

On Day 28 (4 weeks) after enrollment

- Answer some questions about how you have been feeling and about any other doctor or hospital visits you have had in the time since you started the study. This will take place over the phone or, if you remain in the hospital, this may take place in person. It will take about 10 minutes.

After this, the study is complete, and you will not be contacted again.

After you complete the study, we will review your medical record to see if you were treated or hospitalized for the flu.

Incidental Findings

If a chest x-ray is not done as part of your regular medical care, you will have one as part of this research study. It will be reviewed by a qualified person just as it would be if you were having the chest x-ray as part of your routine medical care.

There is a possibility that while reviewing your chest x-ray we may see an abnormality that we did not expect to see in this study. This is what is called an "incidental finding."

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail or by phone. In the case of a potential serious emergency, someone may go to your home.

A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding.

If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

- An incidental finding may cause you to feel anxious.
- Since an incidental finding will be part of your medical record, it may affect your current or future life or health insurance coverage. This risk will vary depending on the type of insurance plan involved.

The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

Request to collect and store biospecimens for future research

As part of this research study, we would like to ask you to let us store your biospecimens and health information for future research. This research could include other diseases.

The study doctor can provide you with additional information if you have questions. Also, further information about our use of your biospecimens can be found in this consent document under the heading, *What Happens to Data and Biospecimens that are Collected in the Study?*

Will you allow us to store the biospecimens we collect for this study for use in future research*? You may participate in this study even if you do not allow us to store your biospecimens.*

YES ☐ _____
Signature of Participant

NO ☐ _____
Signature of Participant

How long will you be in the study?

You will be in this study for 28 days (4 weeks or about 1 month).

4. What are the risks or discomforts of the study?

Questions

The questions that you will be asked to complete during the study may contain questions that could be embarrassing and/or make you feel uncomfortable. You may get tired or bored when we are asking you questions or when you are completing questionnaires. You do not have to answer any question you do not want to answer.

Blood draw

To draw your blood, we will place a small needle into your vein and draw 1 tablespoon of blood. This can be briefly painful, and can result in some bruising and/or infection in that area.

To minimize these risks and discomforts, a trained physician, nurse, study coordinator, or designee will collect the specimens. Care will be taken to obtain these specimens in a safe and hygienic manner. If you already have an IV line placed, we will draw the blood from the existing line if possible.

Urine collection

If you are a woman of childbearing potential you may be asked to give us a urine specimen for a pregnancy test, if a blood pregnancy test is not done. There are no risks or discomforts associated with this procedure.

Nasopharyngeal swab collection

The small swab placed in your nostril if you are in the hospital on Day 3 and/or Day 7, for future testing, may cause brief pain, and cause your nose to itch, your eyes to water or you may sneeze.

Chest x-ray

If a chest x-ray is not done as part of your medical care, we will do one for this study, which will expose you to radiation from x-rays or gamma rays. X-rays and gamma rays can damage cells, but at low doses, the body is usually able to repair these cells.

The radiation exposure that you will get in this research study is 0.01 rem (a rem is a unit of absorbed radiation). This is less than the 0.3 rem that the average person in the United States gets each year from natural sources like the sun, outer space, air, food, and soil. The risk from the radiation exposure in this research study is very small.

The radiation exposure described here is what you will get from this research study only. It does not include any exposure you may have received or will receive from other medical tests outside of this study that are a part of your medical care. Radiation risk builds up with each exposure. You should think about your own history of radiation exposure from tests (like x-rays or CT scans) in deciding about the radiation in this study. If you have questions about the total amount of radiation you will be receiving, you should ask your doctor.

Influenza drugs

This is a treatment study. Oseltamivir (Tamiflu) is the standard clinical care for the treatment of influenza. If you join this study you may receive that drug or you may receive another drug, peramivir (Rapivab), which is also used to treat for influenza. The chance of receiving the standard of care drug if you join the study will be determined by a process called randomization, which is like a coin flip.

There are some known side effects of the study drugs, oseltamivir (Tamiflu) and peramivir (Rapivab) that some people have experienced, and there may be side effects and discomforts that are not yet known. Below are known possible side effects.

- ***Oseltamivir***

  If you receive this drug you may experience nausea, vomiting, bronchitis, insomnia or vertigo.

  It is rare but serious if you experience skin/hypersensitivity reactions (a skin rash) such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, or erythema multiforme.

It is also rare but serious if you experience any neuropsychiatric events (e.g., confusion or abnormal behavior).

- ***Peramivir***
  Inserting an intravenous (IV) catheter to give you peramivir may cause pain, bruising, swelling and bleeding where the catheter is placed. There is also a risk of infection.

  If you receive this drug you may experience diarrhea.

  It is rare but serious if you experience skin/hypersensitivity reactions (a skin rash) such as Stevens-Johnson Syndrome and erythema multiforme.

  It is also rare but serious if you experience any neuropsychiatric events (e.g., hallucinations, delirium, or abnormal behavior).

There is also a risk of death from influenza

Confidentiality

Subject confidentiality will be held strictly in trust by the study doctor and staff. This confidentiality will be extended to cover testing of biological specimens in addition to the clinical information relating to subjects.

5. Are there risks related to pregnancy?
Pregnant women cannot take part in this study. If you are a woman capable of having children, you must have a pregnancy test. The results of that test must be negative for you to continue in the study. If you become pregnant (or suspect pregnancy) before the study is completed, you must inform the study doctor.

6. Are there benefits to being in the study?
There may or may not be a direct benefit to you from being in the study. If you take part in this study, you may also help others in the future.

7. What are your options if you do not want to be in the study?
If you decide not to join this study, other options are available. You do not have to join this study to get treatment. Oseltamivir is available for use outside of this research study.

You do not have to join this study. If you do not join, your care at Johns Hopkins will not be affected.

8. **Will it cost you anything to be in this study?**
You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet).

This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).
- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

9. **Will you be paid if you join this study?**

You will be paid up to $275 if you join this study:

- $100 at the completion of all enrollment activities.
- $75 if you complete at least 8 of the 14 daily diaries.
- $100 at the completion of the 4-week follow-up.

You may be required to provide your social security number to be paid for taking part in this study. Federal tax law requires that you report your research payments when you file your taxes. If your total payments from Johns Hopkins exceed $600 per year, Johns Hopkins will report these payments to the Internal Revenue Service and you will receive a 1099-MISC form from us.

10. **Can you leave the study early?**

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you leave the study early, Johns Hopkins may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

11. **Why might we take you out of the study early?**

You may be taken out of the study if:

- Staying in the study would be harmful.
- You need treatment not allowed in the study.
- You fail to follow instructions.
- The study is cancelled.
- There may be other reasons to take you out of the study that we do not know at this time.

If you are taken out of the study early, Johns Hopkins may use or give out your health information that it has already collected if the information is needed for this study or any follow-up activities.

12. **How will your privacy be protected?**

We have rules to protect information about you. Federal and state laws and the federal medical Privacy Rule also protect your privacy. By signing this form you provide your permission, called your "authorization," for the use and disclosure of information protected by the Privacy Rule.

The research team working on the study will collect information about you. This includes things learned from the procedures described in this consent form. They may also collect other information including your name, address, date of birth, and information from your medical records (which may include information about HIV status, drug, alcohol or sexually transmitted disease (STD) treatment, genetic test results, or mental health treatment).

The research team will know your identity and that you are in the research study. Other people at Johns Hopkins, particularly your doctors, may also see or give out your information. We make this information available to your doctors for your safety.

People outside of Johns Hopkins may need to see or receive your information for this study. Examples include government agencies (such as the Food and Drug Administration), safety monitors, other sites in the study and companies that sponsor the study.

If you are in a cancer study that receives federal funding, the National Cancer Institute (NCI) now requires that we report identifiable information (such as, zip code) about your participation. You may contact the NCI if you have questions about how this information is used.

We cannot do this study without your authorization to use and give out your information. You do not have to give us this authorization. If you do not, then you may not join this study.

We will use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside Johns Hopkins who receive your information may not be covered by this promise or by the federal Privacy Rule. We try to make sure that everyone who needs to see your information keeps it confidential – but we cannot guarantee that your information will not be re-disclosed.

The use and disclosure of your information has no time limit. You may revoke (cancel) your permission to use and disclose your information at any time by notifying the Principal Investigator of this study by phone or in writing. If you contact the Principal Investigator by phone, you must follow-up with a written request that includes the study

number and your contact information. The Principal Investigator's name, address, phone and fax information are on page one of this consent form.

If you do cancel your authorization to use and disclose your information, your part in this study will end and no further information about you will be collected. Your revocation (cancellation) would not affect information already collected in the study, or information we disclosed before you wrote to the Principal Investigator to cancel your authorization.

13. **What treatment costs will be paid if you are injured in this study?**

Johns Hopkins and the federal government do not have a program to pay you if you are hurt or have other bad results from being in the study. However, medical care at Johns Hopkins is open to you as it is to all sick or injured people.

The costs for any treatment or hospital care you receive as the result of a study-related injury that are not covered by a health insurer will be billed to you.

By signing this form you will not give up any rights you have to seek compensation for injury.

14. **What other things should you know about this research study?**

a. What is the Institutional Review Board (IRB) and how does it protect you?

The Johns Hopkins Medicine IRB is made up of:

- Doctors;
- Nurses;
- Ethicists;
- Non-scientists; and
- People from the local community

The IRB reviews human research studies. It protects the rights and welfare of the people taking part in those studies. You may contact the IRB if you have questions about your rights as a participant or if you think you have not been treated fairly. The IRB office number is 410-955-3008. You may also call this number for other questions, concerns or complaints about the research.

When the Johns Hopkins School of Medicine IRBreviews a study at another site, that site (institution) is solely responsible for the safe conduct of the study and for following the protocol approved by the Johns Hopkins IRB.

b. What do you do if you have questions about the study?
Call the principal investigator, Dr. Andrea Dugas at 410-735-6400 If you wish, you may contact the principal investigator by letter or by fax. The address and fax number are on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-955-3008.

c. What should you do if you are injured or ill as a result of being in this study?
If you think you are injured or ill because of this study, call Dr. Dugas at 410-735-6400 during regular office hours.

If you have an urgent medical problem related to your taking part in this study, call Dr. Andrea Dugas at 410-735-6400 during regular office hours. Or any time of day, please call Johns Hopkins Hospital at 410-955-5000 and ask them to page Dr. Andrea Dugas to your phone number.

d. What happens to Data and Biospecimens that are collected in the study?
Johns Hopkins and our research partners work to understand and cure diseases. The biospecimens and/or data you provide are important to this effort.

If you join this study, you should understand that you will not own your biospecimens or data, and should researchers use them to create a new product or idea, you will not benefit financially.

With appropriate protections for privacy, Johns Hopkins may share your biospecimens and information with our research sponsors and partners. Your name or any other identifying information will not be included.

15. **What does your signature on this consent form mean?**
Your signature on this form means that:

- You understand the information given to you in this form.
- You accept the provisions in the form.
- You agree to join the study.
- You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

Signature of Participant	(Print Name)	Date/Time
Signature of Person Obtaining Consent	(Print Name)	Date/Time
Signature of Witness to Consent Procedures (optional unless IRB or sponsor required)	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.

DOCUMENTATION OF INVESTIGATOR CONSENT

My signature below indicates that I have discussed the risks, benefits, and alternatives, answered any questions, and believe the participant is able to make an informed choice to join the study.

Signature of Investigator	(Print Name)	Date/Time
Signature of Participant	(Print Name)	Date/Time
Signature of Witness to Consent Procedures (optional unless IRB or sponsor required)	(Print Name)	Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR; A COPY MUST BE GIVEN TO THE PARTICIPANT; IF YOU ARE USING EPIC FOR THIS STUDY A COPY MUST BE FAXED TO 410-367-7382; IF YOU ARE NOT USING EPIC A COPY MUST BE PLACED IN THE PARTICIPANT'S MEDICAL RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

ONLY CONSENT FORMS THAT INCLUDE THE JOHNS HOPKINS MEDICINE LOGO CAN BE USED TO OBTAIN THE CONSENT OF RESEARCH PARTICIPANTS.

Table of Contents

1. PROJECT OVERVIEW

1.1 Project Design

This pilot study is an open-label randomized controlled clinical trial. It is designed to demonstrate the feasibility of utilizing emergency departments (ED) as a primary site for subject enrollment in clinical trials evaluating influenza therapeutics, providing pilot data for future clinical trial design and planning. Adults presenting to the ED with laboratory-confirmed influenza who meet Centers for Disease Control and Prevention (CDC) criteria for antiviral treatment will be enrolled. Subjects will be randomized to either oral (oseltamivir) or intravenous (IV) (peramivir) antiviral treatment.

1.2 Objectives

1.2.1 Efficacy

1.2.1.1 Primary Objective

To prospectively enroll high-risk subjects with laboratory-confirmed influenza into a randomized, open-label study of oral versus IV influenza therapeutic to include symptom evaluation and outcome assessments.

1.2.1.2 Secondary Objectives

Secondary Objective 1: To identify influenza-positive patients utilizing a previously established triage-based assessment and rapid testing algorithm for suspected influenza infection.

Secondary Objective 2: To retrospectively evaluate all potentially eligible patients for potential enrollment biases.

Secondary Objective 3: To create a repository of residual nasopharyngeal (NP) samples collected from ED patients with suspected influenza illness.

1.2.2 Safety

The safety will be assessed by evaluating the clinical significance of laboratory abnormalities and adverse events (AEs) and all serious adverse events (SAEs). The overall occurrences of AEs and SAEs will be reported by System Organ Class (SOC) and Preferred Term (PT). The AEs and SAEs will also be evaluated and reported by the relationship to study drug, severity and the outcome. All the results will be summarized by study arm and/or by clinical site as appropriate.

1.2.3 Pharmacokinetics

The pharmacokinetics of influenza antivirals will not be studied.

1.3 Treatments

All eligible subjects will be randomized to receive one of two treatment groups. They will receive either oral or IV antiviral treatment.

1.3.1 Treatment Assignment

Randomization will be carried out using a computerized randomization system in the ratio of 1:1. It will be performed by research staff after informed consent, laboratory results and verification of all eligibility criteria have been performed.

Subjects randomized to the oral treatment arm will receive oral oseltamivir. Subjects randomized to the IV treatment group will receive IV peramivir.

1.3.2 Selection and Timing of Doses

Influenza antivirals will be dosed based on creatinine clearance (CrCl) results, as described below. CrCl will be calculated using the Cockcroft Gault equation (see Manual of Operating Procedures (MOP)).

Treatment	CrCl Result	Dosage	Frequency/Duration
Oral Oseltamivir	>60 mL/min	75 mg	Twice daily (every 12 hours) for 5 days
	>30 – 60 mL/min	30 mg	Twice daily (every 12 hours) for 5 days
	>10 – 30 mL/min	30 mg	Once daily (every 24 hours) for 5 days
IV Peramivir	≥50 mL/min	600 mg	One time
	30 – 49 mL/min	200 mg	One time
	10 – 29 mL/min	100 mg	One time

1.4 Procedures

1.4.1 Subject Identification

Research staff will review ED adult patient charts to identify patients with a positive laboratory-confirmed influenza test during their current ED visit. If a patient appears to be eligible, research staff will approach the patient, verify that the patient meets eligibility criteria, and determine if he/she would like to participate in the study.

To be considered eligible for enrollment, a patient must meet the inclusion criteria and must not meet any of the exclusion criteria listed in the protocol at the time of screening. Screening and enrollment occur at the same visit. Screened patients who are eligible and provide written consent to participate in the study, will be randomized to a treatment arm and considered as enrolled in the study.

For secondary objective 2, research staff will identify subjects by retrospectively screening all ED records of patients who presented between November and April of the current influenza season to determine eligibility. (See Protocol).

For all eligible patients, research staff will review the ED and hospital records to retrospectively complete a set of structured clinical data forms to collect the following: basic demographic data; symptoms related to the Clinical Decision Guideline (CDG); criteria for CDC antiviral treatment; initial presentation and clinical course at the ED, including antiviral treatment, antibiotic treatment, Xpert Flu test or other influenza test information; and hospital course if subsequently admitted.

1.4.2 Randomization

Subjects will be randomized to receive one of two treatment groups using a computerized randomization system in the ratio of 1:1. Randomization will be performed at study level and not stratified by site.

1.4.3 Blinding/Unblinding

This is an open-label study, and the administration of treatments will not be blinded.

1.4.4 Replacement

No additional subjects will be recruited to replace any subjects who are lost to follow up or cannot be evaluated.

1.4.5 Data Monitoring

Data and safety will be monitored by the Safety Monitoring Committee (SMC), consisting of the IND sponsor, JHH Co-PIs, JHU Research Program Manager, Biomedical Advanced Research and Development Authority (BARDA) Medical Officer, Independent Safety Monitor (ISM), and study biostatistician (See Data and Safety Monitoring Plan (DSMP)).

2. STATISTICAL ANALYSIS CONSIDERATIONS

2.1 Sample Size and Power

The proposed sample size is at least 50 subjects per site, per influenza season. This sample size was determined, in collaboration with the Office of the Assistant Secretary for Preparedness and Response (ASPR)/BARDA, to be adequate for this pilot effort which is being conducted specifically to examine the feasibility of achieving higher recruitment rates than has historically been achieved in other clinical venues, and the ability to reliably collect useful therapeutic endpoint data from an ED enrollment site. Estimates are based on data from the JHH ED 2014-2015 influenza season using the CDG testing algorithm, where 1604 patients were tested for influenza between November 2014 and April 2015, and 311 influenza-positive patients were identified. Of those 311 patients, approximately 75% met CDC criteria for influenza treatment (i.e., potential enrollment in the study) and 40% were admitted to the hospital. As 2014-2015 was a robust influenza season, it is estimated that a routine influenza season would have approximately 25% fewer influenza-positive patients. Based on similar previous ED based therapeutic clinical trials conducted at the JHH ED, it is anticipated that 56% of eligible patients will agree to participate in the study. Therefore, assuming a routine influenza season, there will be an estimated 174 eligible patients, of whom 97 will be enrolled (58 discharged, 39 admitted). Based on these estimates, at least 50 (conservatively) and up to 225 subjects could be enrolled and followed for 28 days.

2.2 Analysis Population

The analysis population includes adults presenting to the ED with laboratory-confirmed influenza who meet CDC criteria for antiviral treatment. Detailed inclusion/ exclusion criteria are listed in the Protocol.

2.3 Data Handling

2.3.1 Outcome Measures and Predictors

Outcomes:

a. For the Primary Objective:

- The number of subjects successfully enrolled
- The proportion of subjects who received treatment with IV study drug in the ED
- The proportion of subjects who received (first dose) oral study drug in the ED
- The proportion of subjects who complete follow-up.

In addition, the following clinical measures will be evaluated for planning future clinical trial endpoints:

- For all study subjects:

- Reported symptoms (including FLU-PRO Symptom Questionnaire)
- Daily functional assessment
- Patient Global Impression of Change (PGIC) on Day 7 and Day 28
- Patient Global Impression of Severity (PGIS) at enrollment, and on Day 7 and Day 28
- Number of subsequent medical visits or hospitalizations within 28 days of enrollment
- Influenza-related complications including pneumonia, myocardial infarction, and stroke.

- For subjects initially admitted to the hospital from the ED:
  - Severity of disease based on Intensive Care Unit (ICU) admission, mechanical ventilation, or oxygen supplementation
  - Ordinal scale up to 14 days:
    - Death
    - Receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
    - In ICU (without mechanical ventilation or ECMO)
    - Non-ICU hospitalization, requiring supplemental oxygen
    - Non-ICU hospitalization, not requiring supplemental oxygen
    - Not hospitalized, but unable to resume normal activities
    - Not hospitalized with full resumption of normal activities.

b. For the Secondary Objective 1:

- The proportion of ED patients who were screened for influenza
- The proportion of screened patients who met testing criteria
- The proportion of patients who met testing criteria who were tested for influenza
- The proportion of patients tested for influenza who were positive for influenza.

c. For the Secondary Objective 2:

- The proportion of eligible patients who were enrolled
- Comparison of demographic characteristics between those who were enrolled in the study versus those who were identified to be potentially eligible through the retrospective chart review.
  - Age
  - Sex
  - Race
  - Ethnicity

d. For the Secondary Objective 3:

- The creation of a robust repository using all remnant samples of patients tested using the triage-based assessment and testing algorithm from November through April 2015 - 2017. Note that this is not a quantitative outcome.

<u>Potential predictors (independent variables) of interest:</u>

- Enrollment: We will compare demographic characteristics between those who were enrolled and randomized in the study versus those who were eligible but not enrolled (declined, screen failure etc.).
- Influenza Type: We will compare study outcomes between subjects with Influenza A and B.
- Other clinical characteristics: We will compare study outcomes by various subject demographic, historical (i.e. past medical history and co-morbidities), and clinical characteristics.
- Study site: There are 2 sites in the study. Study outcomes will be presented in total and by site. We will also compare subject characteristics by site for Secondary Objective 2.

2.3.2 Measurement Times

Subjects will be followed for 4 weeks.

2.3.3 Missing Data

We will first assess the extent and pattern of missing data for all outcomes. If data are missing for only a small proportion, or if the missing is likely to be at random, data analysis will be conducted using available observations.

If a substantial proportion of subjects have missing information, we will further explore the pattern of missing data, and assess whether missingness or loss to follow up is associated with subjects' characteristics, disease severity or any other factors.

2.4 Statistical Methods

2.4.1 General Overview and Plan of Analysis

The analysis will be performed on data collected from both study sites, JHH and MMC.

2.4.2 Hypothesis Testing

There is no hypothesis testing for the study.

2.4.3 Descriptive Statistics of All Study Variables

Descriptive statistics including mean, median, standard deviation, range for continuous outcomes and frequency/proportion for categorical outcomes will be used to characterize study outcomes.

In addition, we will compare demographic characteristics between those who were enrolled and randomized in the study versus those who were eligible but not enrolled (declined, screen failure, etc.).

2.4.4 Modeling

No statistical modeling will be performed for the study.

2.4.5 Multiple Comparisons

No adjustment for multiple comparisons will be applied.

2.4.6 Project Center Effects

There are two clinical sites in the study. We recommend exploring randomization balance by site. It may also be of interest to compare subject characteristics and the primary outcomes by site.

3. STATISTICAL ANALYSIS

3.1 Analysis of Subject Characteristics

Subject characteristics will be presented (see Tables 1 and 2). These characteristics will be summarized separately by study arm as well as combined.

3.2 Analysis of Primary Objectives

Primary Objective: To prospectively enroll high-risk subjects with laboratory-confirmed influenza into a randomized, open-label study of oral versus IV influenza therapeutic to include symptom evaluation and outcome assessments.

Analysis: Number of patients screened, enrolled and randomized will be plotted in Figure 1. Descriptive statistics including mean, median, standard deviation, range for continuous outcomes and frequency/proportion for categorical outcomes will be used to characterize study outcomes.

All results will be summarized separately by study arm as well as combined. Results will be summarized in Tables 3-7. Ordinal scale up to 14 days for subjects who initially admitted to the hospital from the emergency department, as well as Karnofsky Performance Scale will also be plotted (Figures 2 and 3).

3.3 Analysis of Secondary Objectives

Secondary Objective 1: To identify influenza-positive patients utilizing a previously established triage-based assessment and rapid testing algorithm for suspected influenza infection.

Analysis: Frequencies and proportions will be presented in Table 8.

Secondary Objective 2: To retrospectively evaluate all potentially eligible patients for potential enrollment biases.

Analysis: The analysis will involve a retrospective chart review and comparisons of subject characteristics. It is not part of Westat's scope of work, and is therefore not included in this SAP.

Secondary Objective 3: To create a repository of residual nasopharyngeal (NP) samples collected from ED patients with suspected influenza illness.

Analysis: There is no quantitative data collection for this objective. No statistical analysis will be performed.

3.4 Analysis of Efficacy and Safety

3.4.1 Efficacy

As this is an exploratory study, data analysis will be principally descriptive. Potential clinical endpoints will be described using descriptive statistics for the purposes of future trial planning, and no statistical comparisons between the oral and IV antiviral arms will be made.

3.4.2 Safety

Safety will be assessed by evaluating the clinical significance of laboratory abnormalities and AEs and all serious adverse events SAEs. The overall occurrences of AEs and SAEs will be reported by SOC and PT. The AEs and SAEs will also be evaluated and reported by the relationship to study drug, severity and the outcome. All the results will be summarized by study arm and/or by clinical site as appropriate. Results will be presented in Tables 9 - 11 and Listings 1 – 3.

4. PROPOSED SUMMARY TABLES, GRAPHS AND LISTINGS

4.1 Mock Tables

Table 1. Subject Demographics

Characteristics	Site 1			Site 2			Total		
	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)
Age									
n									
Mean (SD), Min--Max									
Sex, n (%)									
Female									
Male									
Ethnicity, n (%)									
Hispanic or Latino									
Non-Hispanic or Non-Latino									
Unknown									
Race, n (%)									
American Indian or Alaskan Native									
Asian									
Black or African American									
Native Hawaiian/Other Pacific Islander									
White									
Other									
CDC Criteria for Antiviral Treatment, n (%)									
Hospital Admission									
Complications/Pneumonia									

Characteristics	Site 1			Site 2			Total		
	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)
Age 65 or Greater									
Chronic Pulmonary									
Chronic Cardiovascular									
Chronic Renal									
Chronic Hepatic									
Chronic Hematologic									
Chronic Metabolic									
Chronic Neurologic									
Immunosuppression									
Pregnancy or Less than Two Weeks Postpartum									
Morbid Obesity									
Resides in Nursing Home									
Native American									

Study Arm:
Arm 1 = Oral antiviral treatment (Oseltamivir)
Arm 2 = IV antiviral treatment (Peramivir)

Table 2. Subject Symptom Onset and Baseline NEWS Score

N (%)	Site 1			Site 2			Total			Influenza Type	
	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	A (n=)	B (n=)
Time of Symptom Onset at Enrollment											
Within 2 Days											
3 Days											
4 Days											
NEWS Score											
Median (Min—Max)											
0											
1-3											
4-6											
>6											

Table 3. Summary of Subject Status

N (%)	Site 1			Site 2			Total			Influenza Type	
	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	A (n=)	B (n=)
Subjects Enrolled											
Subjects Completed Treatment (%) in the ED											
Subjects Completed Follow up											
Number of Doses (Median, Min—Max)		-	-		-	-		-	-	-	-
NEWS Score											
Percent Daily Dairies Completed											

Table 4. Summary of FLU-PRO Symptoms

Symptom Severity Score by Domain of Symptoms	Mean (Standard Deviation), Min-Max										
	Site 1			Site 2			Total			Influenza Type	
	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	A (n=)	B (n=)
Nose											
Throat											
Eyes											
Chest/ Respiratory											
Gastrointestinal											
Body/ Systemic											
Total											
# Days Missed Questionnaire											

Table 5. Clinical Outcomes

Outcomes	Site 1			Site 2			Total			Influenza Type	
	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	A (n=)	B (n=)
Pneumonia											
Inpatient, n (%)											
Outpatient, n (%)											
Pneumonia Severity Index (Median, Min—Max)											
Hospitalization, n (%)											
LOS (Mean, St. Dev., Min—Max)											
Hospitalization with Pneumonia, n (%) LOS (Mean, St. Dev., Min—Max)											
Karnofsky Performance Scale											
Mean, St. Dev.											
Median, Min—Max											
Patient Global Impression of Change (Median, Min—Max)											
Day 7											
Day 28											
Patient Global Impression of Severity (Median, Min—Max)											
Enrollment											
Day 7											
Day 28											

Outcomes	Site 1			Site 2			Total			Influenza Type	
	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	A (n=)	B (n=)
Number of Subsequent Medical Visits or Hospitalizations (Median, Min—Max)											

Table 6. Influenza-Related Complications

Influenza-Related Complications	# Subjects (%)										
	Site 1			Site 2			Total			Influenza Type	
	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	A (n=)	B (n=)
Pneumonia											
Myocardial Infarction											
Stroke											
Severity of Disease											
Intensive Care Unit (ICU) Admission											
Mechanical Ventilation											
Oxygen Supplementation											
Ordinal Scale (up to 14 Days)											
Death											
Mechanical Ventilation or Extracorporeal Membrane Oxygenation (ECMO)											
ICU without Mechanical Ventilation or ECMO											
Non-ICU Hospitalization, Requiring Supplemental Oxygen											
Non-ICU Hospitalization, Not Requiring Supplemental Oxygen											
Not Hospitalized, but Unable to Resume Normal Activities											
Not Hospitalized, with Full Resumption of Normal Activities											

Table 7. Characteristics of Subjects Initially Admitted to the Hospital from the ED

Characteristics	# Subjects (%)										
	Site 1			Site 2			Total			Influenza Type	
	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	Arm 1 (n=)	Arm 2 (n=)	Total (n=)	A (n=)	B (n=)
Severity of Disease											
Intensive Care Unit (ICU) Admission											
Mechanical Ventilation											
Oxygen Supplementation											
Ordinal Scale (up to 14 Days)											
Death											
Mechanical Ventilation or Extracorporeal Membrane Oxygenation (ECMO)											
ICU without Mechanical Ventilation or ECMO											
Non-ICU Hospitalization, Requiring Supplemental Oxygen											
Non-ICU Hospitalization, Not Requiring Supplemental Oxygen											
Not Hospitalized, but Unable to Resume Normal Activities											
Not Hospitalized, with Full Resumption of Normal Activities											

Table 8. Patient Screening and Testing for Influenza

	Site 1		Site 2		Total	
	N	%	N	%	N	%
Patients through ED						
Of Patients through ED, N(%) Screened with CDG						
Of Patients Screened with CDG, N(%) Who Met Testing Criteria (score ≥3)						
Of Patients Who Met Testing Criteria, N(%) Who Had Tests Ordered						
Of Patients Who Met Testing Criteria, N(%) Who Had Tests Collected and Resulted						
Of Those Tested, N(%) Positive for Influenza						
Of Those Tested Positive, N(%) Enrolled and Randomized						

Table 9. Summary of Adverse Events by System Organ Class and Preferred Term, with number (%) of subjects reporting at least one adverse event

SYSTEM ORGAN CLASS	Study Arm 1						Study Arm 2						Total					
	Grade of AE						Grade of AE						Grade of AE					
Preferred Term	1	2	3	4	5	Total	1	2	3	4	5	Total	1	2	3	4	5	Total

Table 10. Summary of Adverse Events by Relationship to Study Drug and Severity

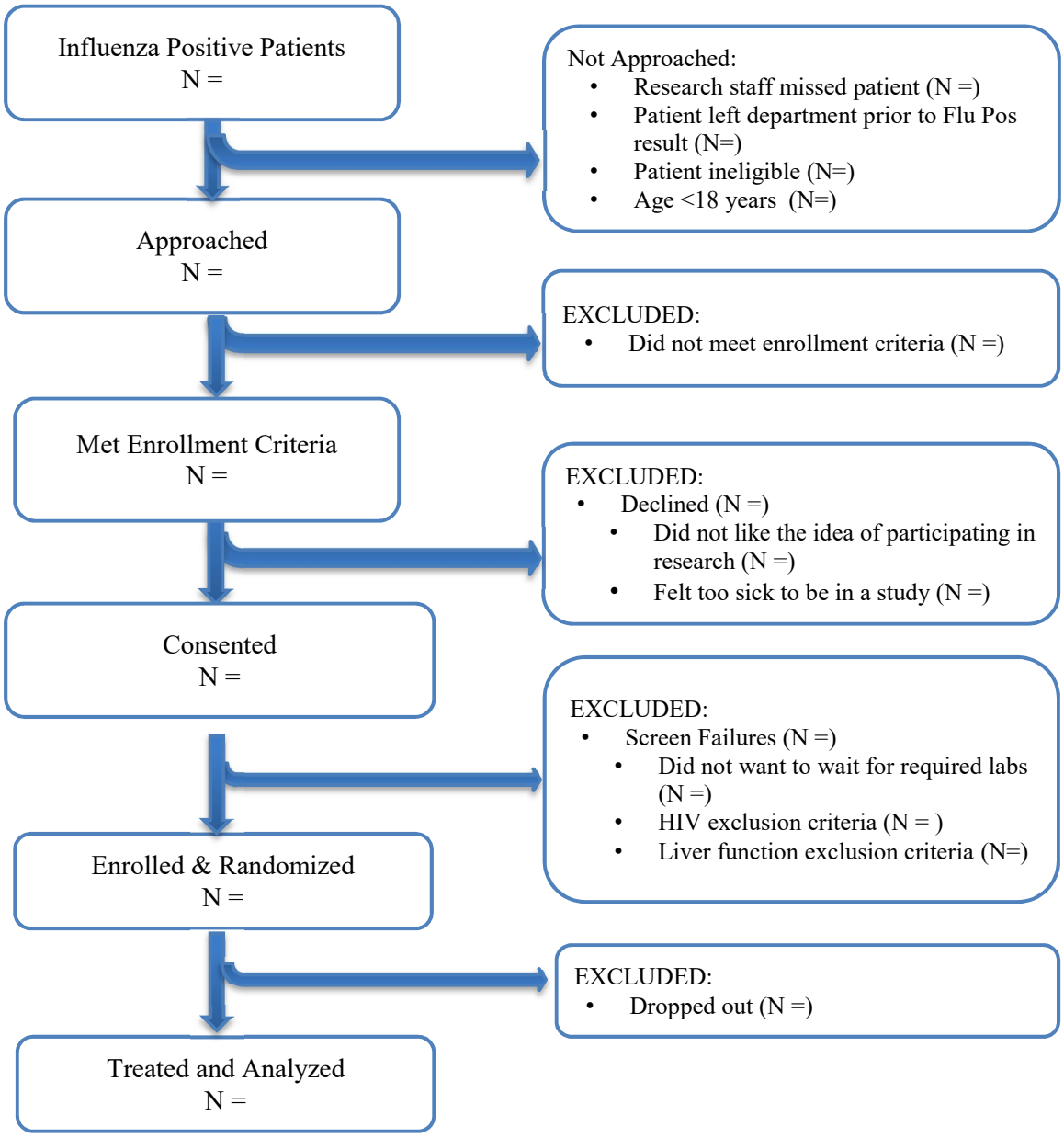
Adverse Events	Study Arm 1		Study Arm 2		Total	
	# Events	%	# Events	%	# Events	%
Total Number of Adverse Events		-		-		-
Relatedness to Study						
Not related						
Related						
Severity of AE						
Mild						
Moderate						
Severe						
Potentially Life Threatening or Disabling						
Death						

Table 11. Frequency of Protocol-Specific Adverse Event

Symptoms	AE Code (MedDRA, CTCAE)	N (%)
Allergy/Hypersensitivity Reaction		
Rash or Skin Reaction		
Altered Mental Status		

4.2 Mock Graphs

Figure 1. Study Patient Screening and Enrollment



4.3 Mock Listings

Listing 1. Patient Level Adverse Events

Patient Identifier	Site	Study Arm	Start Date	Resolution Date	AE Code (MedDRA, CTCAE)	Severity	SAE? (Y/N)	Related-ness	Hospitali-zation Type	Outcome	Comments

Severity of AE:
1 = Mild
2 = Moderate
3 = Severe
4 = Potentially Life threatening or disabling
5 = Death

Relatedness to Study Drug:
0 = Not related
1 = Related

Outcome:
1 = Ongoing
2 = Resolved without sequelae
3 = Resolved with sequelae
4 = Death**
5 = Worsened
6 = Chronic
7 = Lost to follow-up

Hospitalization:
0 = None
1 = ICU
2 = Step down unit
3 = Other

**Provide further details regarding all reported serious AEs and deaths in the SAE and Subject Deaths tables listed at the end of this section.

Listing 2. Serious Adverse Events

Patient Identifier	Site	Study Arm	SAE Onset Date	Outcome Date	Outcome	SAE Classification	Severity	Related to Study Drug	Description of Actions and Outcomes (e.g. hospitalization, withdrawn from study)

Severity of SAE:
1 = Mild
2 = Moderate
3 = Severe
4 = Life threatening or disabling
5 = Death

Relatedness to Intervention:
0 = Not related
1 = Related

SAE Classification:
1 = Death
2 = Life threatening
3 = Inpatient hospitalization or prolonged hospitalization
4 = Persistent/significant disability/incapacity
5 = Resulted in congenital anomaly/birth defect
6 = Important medical event

Outcome:
1 = Ongoing
2 = Resolved without sequelae
3 = Resolved with sequelae
4 = Death**
5 = Worsened
6 = Chronic
7 = Lost to follow-up

Listing 3. Deaths

Patient Identifier	Site	Study Arm	Age	Date Enrolled	Treatment Date	Cause of Death	Date of Death	Comments

Table of Contents

Sponsor and Principal Investigator Signatures

Sponsor Signature:

Johns Hopkins University Representative | Date

Principal Investigator Statement and Signature:

I have read and understand this protocol, agree to participate as a Principal Investigator, will ensure the protocol is followed as outlined, and will comply with applicable regulations and with Good Clinical Practice.

Principal Investigator | Date

List of Abbreviations

AE	Adverse Event/Adverse Experience
AIDS	Acquired Immunodeficiency Syndrome
ASPR	Assistant Secretary for Preparedness and Response
BARDA	Biomedical Advanced Research and Development Authority
BMI	Body Mass Index
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CDG	Clinical Decision Guideline
CFR	Code of Federal Regulations
Co-PI	Co-Principal Investigator
CQI	Continuous Quality Improvement
CrCl	Creatinine Clearance
CRF	Case Report Form
DAIDS	Division of AIDS
ECMO	Extracorporeal Membrane Oxygenation
ED	Emergency Department
EDSS	Electronic Decision Support System
EMR	Electronic Medical Record
FDA	US Food and Drug Administration
G6PD	Glucose-6-Phosphate Dehydrogenase
GCP	Good Clinical Practice
HAART	Highly Active Antiretroviral Therapy
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IATA	International Air Transport Association
ICF	Informed Consent Form
ICU	Intensive Care Unit
ID	Identification
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
IT	Information Technology
IV	Intravenous
JHH	Johns Hopkins Hospital
LAIV	Live Attenuated Influenza Vaccine
MMC	Maricopa Medical Center
MOP	Manual of Operating Procedures
NP	Nasopharyngeal
OC	Oracle Clinical

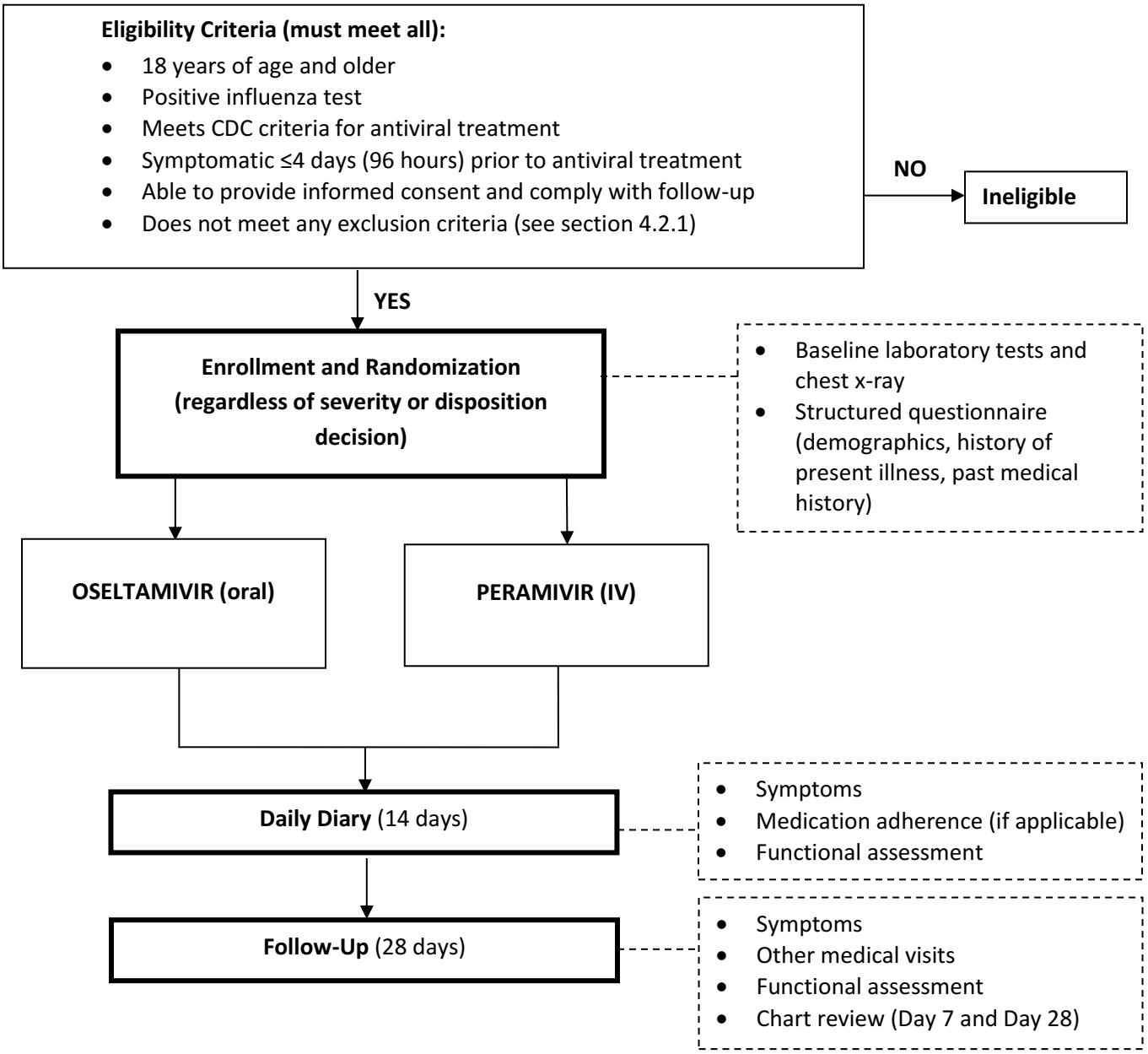
OHRP	Office For Human Research Protections
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
RCT	Randomized Controlled Trial
RDC	Remote Data Capture
SAE	Serious Adverse Event/Serious Adverse Experience
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
TAT	Turnaround Time
US	United States

Protocol Summary

Title:	**A Pilot Randomized Controlled Trial for Feasibility of Enrolling Subjects for Influenza Therapeutic Trials and Administering Influenza Antivirals in the Emergency Department to High Risk Subjects**
Population:	Adults presenting to the emergency department (ED) with laboratory-confirmed influenza who meet Centers for Disease Control and Prevention (CDC) criteria for antiviral treatment
Informed Consent:	Written informed consent
Number of Sites:	2 – large, urban, academically-affiliated, US EDs
Study Duration:	September 2015 – September 2018
Subject Participation Duration:	4 weeks
Description of Agent or Intervention:	Subjects will be randomized to either oral (oseltamivir) or intravenous (IV) (peramivir) antiviral treatment.
Objectives:	This pilot study is designed to demonstrate the feasibility of utilizing EDs as a primary site for subject enrollment in clinical trials evaluating influenza therapeutics, providing pilot data for future clinical trial design and planning. Primary Objective: To prospectively enroll high-risk subjects with laboratory-confirmed influenza into a randomized, open-label study of oral versus IV influenza therapeutic to include symptom evaluation and outcome assessments. Secondary Objective 1: To identify influenza-positive patients utilizing a previously established triage-based assessment and rapid testing algorithm for suspected influenza infection. Secondary Objective 2: To retrospectively evaluate all potentially eligible patients for potential enrollment biases. Secondary Objective 3: To create a repository of residual nasopharyngeal (NP) samples collected from ED patients with suspected influenza illness.
Description of Study Design:	This is an open-label randomized controlled clinical trial in which subjects with influenza are randomized to either oral (oseltamivir) or IV (peramivir) antiviral treatment.

Estimated Time to Complete Enrollment:	Subject enrollment will occur over two influenza seasons (November 2015 – April 2017) or longer, at the co-principal investigators' (Co-PIs') discretion, based on influenza prevalence.

Schematic of Study Design



1. Background

1.1. Scientific Rationale

Although new influenza therapeutics are needed to mediate population level morbidity and mortality associated with both seasonal and pandemic influenza, clinical trials evaluating emerging therapeutics have been challenging. One well-recognized challenge with prior large trials is that they historically have recruited otherwise healthy subjects at clinical sites with relatively low rates of recruitment, resulting in the need to engage up to hundreds of recruitment sites, and a relative lack of patients with more severe and/or complicated illness. This has introduced management challenges with trial implementation and evaluation, including high associated costs for subject recruitment and retention.

As the first line of care for many patients with influenza, and over 130 million visits/year, US emergency departments (EDs) represent an as yet untapped clinical venue for recruiting individuals with influenza into clinical trials. Notably, EDs also have the advantage of caring for patients early in their clinical course, and frequently serve as the initial site of care for those with complicated and/or severe influenza. Taken together, this creates opportunities which could be leveraged for design and implementation of more streamlined influenza therapeutic clinical trial design. We propose a pilot study to demonstrate the feasibility of utilizing EDs as primary sites for subject enrollment in clinical trials evaluating influenza therapeutics, providing data to inform future clinical trial design and planning.

1.2. Potential Risks and Benefits

The risks and benefits for subjects enrolled in this trial are appropriately balanced. All of the study interventions are consistent with recommended clinical practice. The triage algorithm for influenza testing is a standard operating procedure (SOP) in the ED from November through April. The drugs under study (i.e., oseltamivir and peramivir) have both been approved by the US Food and Drug Administration (FDA) for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days.

Additionally, the Centers for Disease Control and Prevention (CDC), Infectious Diseases Society of America, and the World Health Organization recommend antiviral treatment with a neuraminidase inhibitor as soon as possible for all persons with suspected or confirmed influenza who are at higher risk for influenza complications, or who have severe or complicated illness. These recommendations come from multiple observational studies showing reduction in morbidity and mortality. The strongest evidence remains in hospitalized patients, where both early initiation of antiviral treatment (less than two days from illness onset) and treatment up to five days after symptom onset were associated with reduced mortality, with greater benefit associated with earlier initiation of treatment. All subjects in this study will be adults at higher risk for influenza, who are recommended to receive antiviral treatment in accordance with CDC recommendations. Many of these subjects may require hospitalization for disease severity and/or underlying conditions. [http://www.cdc.gov/flu/professionals/antivirals/antiviral-use-influenza.htm]

1.2.1. Potential Risks

The risks to subjects enrolled in the study will be comparable to those encountered by similar patients receiving standard care. These risks include minor risks associated with study participation and adverse events (AEs), including reactions to the study drugs (see below).

Subjects will be carefully screened to ensure that they meet all study inclusion criteria and do not have any exclusion criteria that would put them at unnecessary risk from study participation. Subjects will be contacted for follow-up at Day 28, and will have access 24 hours a day, 7 days a week, to on-call research staff, investigators, and emergency care if questions should arise.

Minor risks associated with study participation include added time associated with completing study questionnaires, pain or discomfort during a blood draw, or unanticipated disclosure of a subject's underlying medical conditions. To minimize these risks and discomforts, trained personnel who have completed all Health Insurance Portability and Accountability Act (HIPAA) training and procedures associated with enrollment of human subjects and study related procedures, will approach, consent, enroll patients, and collect data. Further, trained personnel will only approach patients and conduct study related activities during patients' ED wait times, decreasing risk of potential increased ED care time associated with study related procedures. Baseline laboratory tests and a chest x-ray are non-invasive and standard treatment in the ED, and therefore, pose no additional study-associated risk. To minimize any potential discomfort, trained personnel will collect all specimens.

Subjects will be carefully screened for possible AEs after receiving study drug, and will be provided with information to contact the study team for any possible AE that occurs throughout the trial. Subjects with findings suggestive of possible AEs will have the appropriate investigations performed. Serious adverse events (SAEs) will be defined *a priori*, and reported to the independent safety monitor (ISM) and the Institutional Review Board (IRB) as described in section 8; subjects will be advised and provided with referral sites to seek medical treatment.

The study will be conducted in accordance with Good Clinical Practice (GCP), and full compliance with 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312; 45 CFR Part 46 (Protection of Human Subjects); and the HIPAA Privacy Rule. Procedures for managing protected health information (PHI) will be included in the written informed consent form (ICF). Numerous safeguards will be put in place to ensure the confidentiality and integrity of all data, addressing both the human and physical elements of protecting subject confidentiality. These include data management staff training in protection of human subjects and the ethical conduct of human research, systematic backup for the centralized database, use of encrypted data on durable media, and utilization of encryption and role-based access mechanisms for remote access in compliance with industry best practices and consistent with security and privacy requirements of the IRB. Any paper documentation containing PHI, such as informed consent documents, will be stored securely by research staff. See section 11.4 for further information on maintaining confidentiality to reduce PHI disclosure risks.

Depending on the randomization, a subject may receive oseltamivir or peramivir. According to the current package insert, the following warnings and precautions, drug interactions, and AEs are reported with these study drugs:

Oseltamivir (Tamiflu)

Warnings and Precautions:

Serious skin/hypersensitivity reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme: Discontinue TAMIFLU and initiate appropriate treatment if allergic-like reactions occur or are suspected.

Neuropsychiatric events: Patients with influenza, including those receiving TAMIFLU, particularly pediatric patients, may be at an increased risk of confusion or abnormal behavior early in their illness. Monitor for signs of abnormal behavior.

Drug Interactions:

Live attenuated influenza vaccine (LAIV), intranasal:

Do not administer until 48 hours following cessation of TAMIFLU.

Do not administer TAMIFLU until two weeks following administration of the LAIV, unless medically indicated.

Adverse Reactions:

Most common adverse reactions (>1% and more common than with placebo):

Treatment studies – Nausea, vomiting, bronchitis, insomnia, vertigo.

Prophylaxis studies – Nausea, vomiting, diarrhea, abdominal pain.

Peramivir (Rapivab)

Warnings and Precautions:

Serious skin/hypersensitivity reactions such as Stevens-Johnson Syndrome and erythema multiforme have occurred with RAPIVAB.

Neuropsychiatric events: Patients with influenza may be at an increased risk of hallucinations, delirium, and abnormal behavior early in their illness. Monitor for signs of abnormal behavior.

Drug Interactions:

LAIV, intranasal: Avoid use of LAIV within 2 weeks before or 48 hours after administration of RAPIVAB, unless medically indicated.

Adverse Reactions:

Most common adverse reaction (incidence >2%) is diarrhea.

This study is only enrolling subjects with confirmed influenza who are recommended to receive antiviral treatment according to current CDC guidelines, and treating them with appropriate

antiviral drugs which have been FDA approved to treat patients with influenza. The most commonly used antiviral treatment for influenza is oseltamivir, which is recommended by the CDC antiviral treatment guidelines. Oseltamivir has a low side effect profile, and has been shown to reduce the duration of symptoms in randomized control trials with outpatients and is approved by the FDA for treatment of uncomplicated influenza within 48 hours of symptom onset. Observational studies have shown that oseltamivir reduces mortality, hospital length of stay, and influenza-related complications in various high-risk groups. Peramivir, which is in the same neuraminidase inhibitor class as oseltamivir but is delivered in an intravenous (IV) formulation, has likewise been approved by the FDA for treatment of uncomplicated influenza within 48 hours of symptom onset. Peramivir also has a low side effect profile. There are insufficient studies to date, regarding the use of peramivir for hospitalized patients with influenza.

1.2.2. Potential Benefits

All of the study interventions are standard of care for patients with influenza, and both of the drugs under study are currently FDA approved and used for the treatment of acute uncomplicated influenza.

Subjects will receive study drugs free of charge. Additionally, subjects will have more intensive follow-up than would be routinely provided for ED patients in these facilities, and therefore, any potential complications or treatment failure will be addressed more promptly than standard of care might otherwise allow. Further, an independent, on-call infectious diseases specialist will be made available as part of the study procedures to provide real time consultation to clinicians caring for subjects participating in the study, which may provide additional benefit to subjects participating in the study. Finally, participation in this study will help inform future studies of influenza treatment, which could help in developing improved treatment for future patients with influenza.

2. Objectives

2.1. Study Objectives

Primary Objective: To prospectively enroll high-risk subjects with laboratory-confirmed influenza into a randomized, open-label study of oral versus IV influenza therapeutic to include symptom evaluation and outcome assessments.

Secondary Objective 1: To identify influenza-positive patients utilizing a previously established triage-based assessment and rapid testing algorithm for suspected influenza infection.

Secondary Objective 2: To retrospectively evaluate all potentially eligible patients for potential enrollment biases.

Secondary Objective 3: To create a repository of residual nasopharyngeal (NP) samples collected from ED patients with suspected influenza illness.

2.2. Study Outcome Measures

Primary Objective: To prospectively enroll high-risk subjects with laboratory-confirmed influenza into a randomized, open-label study of oral versus IV influenza therapeutic to include symptom evaluation and outcome assessments.

Outcomes: The number of subjects successfully enrolled; the proportion of subjects who complete treatment with IV or oral study drug in the ED; the proportion of subjects who complete follow-up.

In addition, the following clinical measures will be evaluated for planning future clinical trial endpoints:

- For all subjects:
    - Reported symptoms (including FLU-PRO Symptom Questionnaire);
    - Daily functional assessment;
    - Patient Global Impression of Change (PGIC) on Day 7 and Day 28;
    - Patient Global Impression of Severity (PGIS) at enrollment, and on Day 7 and Day 28;
    - Number of subsequent medical visits or hospitalizations within 28 days of enrollment; and
    - Influenza-related complications including pneumonia, myocardial infarction, and stroke.
- For subjects initially admitted to the hospital from the ED:
    - Severity of disease based on Intensive Care Unit (ICU) admission, mechanical ventilation, or oxygen supplementation; and
    - Ordinal scale up to 14 days:
        - Death;
        - Receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
        - In ICU (without mechanical ventilation or ECMO);
        - Non-ICU hospitalization, requiring supplemental oxygen;
        - Non-ICU hospitalization, not requiring supplemental oxygen;
        - Not hospitalized, but unable to resume normal activities; and
        - Not hospitalized with full resumption of normal activities.

Secondary Objective 1: To identify influenza-positive patients utilizing a previously established triage-based assessment and rapid testing algorithm for suspected influenza infection.

Outcomes: The proportion of ED patients who were screened for influenza; the proportion of screened patients who met testing criteria; the proportion of patients who met testing criteria who were tested for influenza; the proportion of patients tested for influenza who were positive for influenza.

Secondary Objective 2: To retrospectively evaluate all potentially eligible patients for potential enrollment biases.

Outcome: The proportion of eligible patients who were enrolled; comparison of demographic characteristics between those who were prospectively enrolled versus not enrolled.

Secondary Objective 3: To create a repository of residual NP samples collected from ED patients with suspected influenza illness.

Outcome: The creation of a robust repository using all remnant samples of patients tested using the triage-based assessment and testing algorithm from November 2015 through April 2017.

3. Systematic Influenza Testing in the Emergency Department

3.1. Clinical Decision Guideline/Electronic Decision Support System Implementation

Prior to the initiation of the study, a previously derived Clinical Decision Guideline (CDG) for ordering influenza testing was fully integrated into the site's electronic medical record (EMR) utilizing an Electronic Decision Support System (EDSS). This EDSS has now been integrated into the EMR at the Johns Hopkins Hospital (JHH) and at the Maricopa Medical Center (MMC) to inform clinician practice. This systematic influenza screening and testing program is part of the standard ED practice for recognition and management of patients with suspected influenza.

3.1.1. Clinical Decision Guideline

The previously derived and validated CDG will guide influenza testing in ED patients as follows:

A patient will be indicated for influenza testing with Xpert Flu if he/she has a symptom score of 3 or greater. The symptom score is based on the following:

- Within the past 7 days, new or worsening cough (2 points)
- Within the past 7 days, new headache (1 point)
- Within the past 7 days, new subjective fever (1 point)
- Documented temperature at triage of 38°C (100.4°F) or greater (1 point)

3.1.2. Electronic Decision Support System

Working collaboratively with a locally determined team (e.g., physicians, nursing, and information technology (IT) staff), the clinical pathway using an EDSS with the CDG has been integrated into the clinical flow and EMR to prompt influenza testing at initial triage. The overall flow of the EDSS is depicted in Figure 1. The EDSS will begin functioning in October of each influenza season.

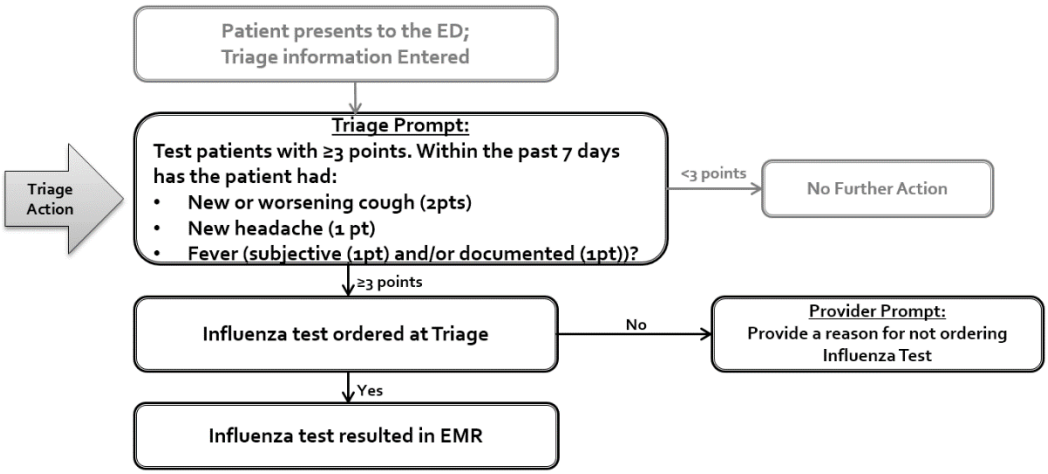


Figure 1: EDSS flow for influenza testing

The EDSS will evaluate if the patient should receive influenza testing by screening for the criteria of the CDG. To determine if the patient is indicated for Xpert Flu testing, a triage nurse will be prompted (at triage) to complete the brief series of questions outlined above. If the testing is not indicated by the CDG (i.e., a score of less than 3), then there is no further action related to this EDSS. If the patient is indicated for influenza testing according to the CDG (i.e., a score of 3 or greater), then the EDSS will automatically generate a prompt stating that the Xpert Flu test is indicated for this patient. If the triage nurse orders the Xpert Flu test, an NP swab will be performed, and the specimen will be sent to the laboratory for processing. Alternatively, if the influenza test is not ordered, the triage nurse will be prompted to enter one of the following reasons for not testing: “Patient refused”; “Patient diagnosed with influenza within previous 48 hours”; or “Other, (insert text).”

For any patient receiving an Xpert Flu test through the EDSS, the result of the test will be recorded in the EMR when complete. Turnaround time (TAT) from placing the order to result received in the EMR will be tracked and it is anticipated that the laboratory will achieve TATs of less than 120 minutes (based on historical experience). However, while this is the expectation, if it is not met it does not constitute a protocol violation, as the influenza testing is part of routine care.

Providers may choose to treat or not treat patients as is clinically indicated.

3.1.3. Run-In Period

Beginning in October and running through April 30 of each influenza season or later, at the co-principal investigators' (Co-PIs') discretion, based on influenza prevalence, all ED patients who are assessed at triage will be evaluated by the CDG and EDSS to determine if they meet the testing criteria of the CDG. To evaluate whether or not the CDG and EDSS are being properly implemented, there will be a run-in period during October of each influenza season. The purpose of this run-in period is to identify and correct any potential problems with implementation of the CDG and EDSS. Principal investigators (PIs) and research staff will closely monitor the implementation of the CDG and EDSS through a standardized monitoring and continuous quality improvement (CQI) process.

During the run-in period, research staff will monitor implementation of the CDG and EDSS to ensure that registered ED patients are screened, and if they meet testing criteria, ensure that the order is placed and the test occurs. Research staff may be on site to act as a resource or to troubleshoot if any problems arise.

Ongoing monitoring will occur throughout the study period (November 1 – April 30 of each influenza season, or later, at the Co-PIs' discretion, based on influenza prevalence). Additionally, the Biomedical Advanced Research and Development Authority (BARDA) personnel will periodically conduct an independent audit to provide relevant feedback which will be informative for guiding future clinical trials.

3.2. Biological Specimens

3.2.1. Safety Precautions

All safety guidelines of the local safety committee and/or institutional policies for handling biological specimens must be followed. Universal precautions guidelines are to be observed.

3.2.2. Sample Collection

From each patient who is indicated for Xpert Flu testing by the CDG through the EDSS, an NP sample will be collected by clinical staff according to standard of care practice, using a flocked swab and universal viral transport media, as is standard clinical practice. All staff collecting NP swabs must undergo appropriate training as required by the medical institution. Once collected, specimens will be transported to the hospital clinical virology laboratory and expeditiously processed according to institutional laboratory protocols.

3.2.3. Sample Processing and Labeling

Between November 1 and April 30 of each influenza season, following sample collection, one aliquot will be removed for immediate rapid testing using Xpert Flu. A sterile pipette, will be used to aliquot the remaining specimen into approximately five 0.5 mL aliquots. Each aliquot will be placed in a separate microtube and labeled with a Waste Specimen identification number and date of collection. These aliquots will be immediately stored in a -80^{0}C freezer until shipment (a log sheet will be maintained on the freezer or in another specified area in the laboratory to

indicate waste sample number, collection date/time, storage time). Freezer boxes will be labeled with "BARDA ED FLU PILOT RCT," the collection site, and the lowest waste specimen identification number included in that freezer box. If samples go outside of range minus -20^{0}C, the samples will be considered compromised and the Coordinating Center must be notified immediately.

3.2.4. Clinical Use of Waste Specimens

Leftover samples will be batched, shipped to, and stored at the central study laboratory at JHH for future analysis (see Appendix 2). These de-identified samples and results will not be available for clinical care.

4. Screening, Enrollment, and Follow-Up of Study Subjects

This section describes the screening, enrollment and follow-up procedures for the:

1. Retrospective Chart Review; and the
2. Randomized Controlled Trial of Influenza Antivirals.

During the 2015-2016 influenza season, this study was implemented only at JHH. During the 2016-2017 influenza season, this study will operate at both JHH and MMC.

4.1. Retrospective Chart Review

In order to evaluate the full potential ED population who might have met criteria for enrollment, all potentially eligible patients will be evaluated via a retrospective chart review. Basic demographic characteristics of patients who were not approached for enrollment, and those who were approached but not enrolled, will be compared (in a de-identified manner) with those who were enrolled into the Randomized Controlled Trial of Influenza Antivirals.

4.1.1. Screening

Research staff will identify subjects by retrospectively screening all ED patient records who presented between November and April of each influenza season, or later, at PI discretion, based on influenza prevalence, for patients who meet all eligibility criteria. Basic presenting, demographic, and eligibility information will be recorded on the Screening and Enrollment Log for every patient who is screened for potential enrollment. Patients that do not meet inclusion criteria will be excluded from the Retrospective Chart Review; the reason for exclusion will be recorded.

4.1.2. Eligibility Criteria

<u>Inclusion Criteria</u>

Full ED chart review will be performed on individuals who meet the following inclusion criteria at the time of the ED visit:

1) 18 years of age or older;

2) Adult ED visit between November and April of each influenza season, or later, at the Co-PIs' discretion, based on influenza prevalence; and

3) Positive influenza test associated with the ED visit

Exclusion Criteria

There are no exclusion criteria.

4.1.3. Informed Consent

Under a HIPAA waiver of consent, research staff will review patient charts to screen and confirm enrollment eligibility. This retrospective evaluation utilizes information that is already collected for clinical purposes and all data collected for the retrospective chart abstraction will ultimately be stripped of personal identifiers (see section 4.1.4).

4.1.4. Data Collection

For all eligible patients, research staff will review the ED and hospital records to retrospectively complete a set of structured clinical data forms to collect the following: basic demographic data; symptoms related to the CDG; criteria for CDC antiviral treatment; initial presentation and clinical course at the ED, including antiviral treatment, antibiotic treatment, Xpert Flu test or other influenza test information; and hospital course if subsequently admitted.

In accordance with HIPAA regulations, no subject personal identifiers will be entered into the study database. Personal identifiers such as name and medical record number will be collected and recorded on a separate study identification (ID) sheet for purposes of completing the retrospective chart review. This identifying information will be linked to the remainder of the subject information only through the study ID number, and will ultimately be stripped of identifying information after all necessary data and samples are collected. Personal identifiers will be destroyed upon final completion and verification of the study database.

All study documents will be kept locked in a limited access area. The study ID sheet that links the study ID numbers to the subject personal identifiers will be kept under double lock separate from all research files, accessible only to research staff.

4.2. Methods: Randomized Controlled Trial of Influenza Antivirals

4.2.1. Eligibility Criteria

Inclusion Criteria

To be considered eligible, patients must meet the criteria listed below at the time of screening:

1) 18 years of age or older;

2) Laboratory-confirmed positive influenza test associated with their current ED visit;

3) Presence of at least 1 of the following symptoms of acute respiratory illness for ≤4 days (96 hours):

    a. New or increased cough;

    b. New or increased shortness of breath;

    c. Change in sputum production (for adults 65 years of age or older);

    d. Sinus pain;

    e. Nasal congestion;

    f. Rhinorrhea;

    g. Sore throat;

    h. Subjective fever; or

    i. Documented fever of ≥38°C.

4) Meets at least one of the CDC criteria for antiviral treatment, defined as:

    a. 65 years of age or older;

    b. Pregnant* or less than two weeks postpartum;

    c. American Indian or Alaska Native;

    d. Morbid obesity (body mass index (BMI) ≥40);

    e. Current resident of nursing home or other chronic-care facility;

    f. Diagnosis of chronic pulmonary disease, cardiovascular disease (except hypertension alone), renal disease, hepatic disease, hematologic disease, metabolic disorders, neurologic and neurodevelopment conditions, or immunosuppression (including that caused by medications or by human immunodeficiency virus (HIV) infection);

    g. Admission to inpatient or an observation unit; or

    h. Clinical diagnosis of pneumonia (by the ED provider)

*For the purpose of this study, pregnancy is an exclusion criterion.

Exclusion Criteria

To be considered eligible for enrollment, a patient must not meet any of the criteria listed below at the time of screening:

1) Does not speak or understand English (JHH); or English or Spanish (MMC);

2) Unable or unwilling to provide informed consent;

3) Previously enrolled in the study during the current influenza season;

4) Unable to take oral medication;

5) Unable to comply with all planned study procedures including availability for follow-up and willingness to complete study diary and self-assessment;

6) Use of neuraminidase inhibitors within the past seven days;

7) Known allergic reaction to neuraminidase inhibitors;

8) Pregnant or breastfeeding;

9) End-stage renal disease, defined as:

    a. Currently undergoing dialysis (either hemo or peritoneal); or

    b. Creatinine clearance (CrCl) of <10 mL/min.

10) End-stage liver disease, as determined by the treating ED provider;

11) Glucose-6-phosphate dehydrogenase (G6PD) deficiency by patient report;

12) Immunodeficiency, defined as:

    a. Solid organ transplant patients receiving immunosuppression;

    b. Hematopoietic stem cell transplant patients within 12 months of transplant or with ongoing immunosuppression;

    c. Oncology patients who have had chemotherapy within the past 30 days;

    d. Current treatment with steroids equivalent to 10 mg of prednisone or more per day for greater than two weeks;

    e. Rheumatologic patients receiving immunosuppressive therapy; or

    f. HIV patients who meet one of the following criteria:

        i. Have a CD4 cell count of <200 cells/mm^3 within the past 3 months;

        ii. Not actively receiving highly active antiretroviral therapy (HAART); or

        iii. Have an absolute lymphocyte count <1.0 x 10^3 cells/µL conducted at the current ED visit

4.2.2. Screening

Eligible subjects will be recruited by dedicated research staff 24 hours a day, 7 days a week. Screening and enrollment occur at the same visit.

Under a HIPAA waiver of consent, research staff will review current ED patient charts for adult ED patients who have a positive laboratory-confirmed influenza test during their current ED visit. If a patient appears to be eligible, the research staff will approach the patient's ED provider to inform them that the patient is potentially eligible. Alternatively, providers may also refer potentially eligible patients to research staff. With the provider's approval, research staff will approach the patient, verify that the patient meets eligibility criteria, and determine if he/she would like to participate in the study.

Eligibility information will be recorded for every patient who is approached for potential study enrollment using a Screening and Enrollment Log. Patients who do not meet inclusion criteria or who meet an exclusion criterion will be deemed ineligible; the reason for their exclusion will be recorded. Screened patients who meet all inclusion and no exclusion criteria, i.e., who are eligible, will be approached for informed consent. For those patients who decline participation, the given reason for refusal to participate will be recorded. Screened patients who are eligible and provide written consent to participate in the study, will be randomized to a treatment arm and considered as enrolled in the study.

4.2.3. Informed Consent

Consent forms will be IRB-approved and the patient will be given sufficient time to read and review the document and discuss it with his/her family member, friend, or legal representative. If he/she requires assistance to reach his/her family member, friend, or legal representative, such as the use of a telephone, that will be facilitated. After this, he/she will be specifically asked if he/she has any questions or concerns, which will be addressed, or would like more time to consider his/her participation, which will also be provided. The investigator or research staff will explain the research study to the patient and answer any questions that may arise. The patient will sign the ICF prior to any procedures being done specifically for the study. The subject may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent will be given to the subject for his/her records; another copy will be included in the patient's chart, and the original will be filed in a study binder. The rights and welfare of the subject will be protected by emphasizing to all potential study subjects that they will still be able to receive medical care at the facility if they decline to participate in this study. The site PI or designee will also sign the consent form indicating that the subject understands the risks and benefits of the study.

5. Study Visit Evaluations: Randomized Controlled Trial of Influenza Antivirals

5.1. Screening/Enrollment

Following written informed consent, the research staff will complete an eligibility checklist and assign a study ID number. The following information and evaluations will be performed:

5.1.1. Chart Review

Research staff will gather the following information:

- Basic laboratory studies:
    - Complete blood count (CBC);
    - Complete or basic metabolic panel; and
    - Serum (or urine) beta-hcg (for women of childbearing potential*).
- Calculate CrCl using the Cockcroft Gault equation (see Manual of Operating Procedures (MOP)); and
- Baseline chest x-ray.

*For the purposes of this study, women will be considered of non-childbearing potential if they are greater than age 54 and have had no menses in the previous 12 months or if they are surgically sterile (e.g., hysterectomy with or without oophorectomy; fallopian tube ligation; endometrial ablation).

In the majority of cases the above mentioned tests will be obtained for clinical purposes (at the time of enrollment or within the previous 24 hours). In cases where any of those tests have not been obtained, research staff will complete those tests as part of study procedures; results of these laboratory and/or imaging results will be given to the treating ED provider to include in his/her medical assessment of the patient. Patients with a CrCl <10 mL/min (or on hemodialysis), a positive beta-hcg, or those who did not have the appropriate laboratory studies performed, will be ineligible for enrollment and will not be randomized to receive antiviral treatment through this study.

5.1.2. Clinical Evaluations

Demographics and clinical data (medical and health history) will be collected using brief structured data forms and will include:

- Basic demographic data;
- Vaccination history;
- Co-morbid illness;
- History of present illness;
- Baseline PGIS; and the
- First day of the validated Daily *FLU-PRO Symptom Questionnaire* (*F10)* and the *Functional Assessment (F12)* form.

5.1.3. Treatment Assignment Procedures

All eligible subjects will be randomized to receive one of two treatment groups using a computerized randomization system in the ratio of 1:1. Subjects will be randomized to receive either oral or IV antiviral treatment. Randomization will be performed by research staff after informed consent, laboratory results, and verification of all eligibility criteria have been performed (see MOP).

5.1.4. Treatment Administration

Subjects will begin their treatment regimen in the ED as described below:

Oseltamivir

Subjects randomized to the oral treatment arm will receive oral oseltamivir. Oseltamivir will be dosed based on CrCl results, as described below.

CrCl Result	Dosage of Oral Oseltamivir	Frequency/Duration
>60 mL/min	75 mg	Twice daily (every 12 hours) for 5 days
>30 – 60 mL/min	30 mg	Twice daily (every 12 hours) for 5 days
>10 – 30 mL/min	30 mg	Once daily (every 24 hours) for 5 days

The first dose will be administered in the ED following randomization. The remaining doses will be taken on the subsequent four days, whether they are inpatient or outpatient, based on the screening CrCl results. If a dose is missed, subjects will be instructed to take the missed dose as soon as they remember, unless it is two hours or less before the next scheduled dose; in this case, subjects will be instructed to discard the missed dose, and continue to take the next dose at the usual time. Subjects will be instructed not to take two doses at a time to make up for a missed dose.

Peramivir

Subjects randomized to the IV treatment group will receive IV peramivir. Peramivir will be dosed based on CrCl results, as described below.

CrCl Result	Dosage of IV Peramivir	Frequency/Duration
≥50 mL/min	600 mg	One time
30 – 49 mL/min	200 mg	One time
10 – 29 mL/min	100 mg	One time

Subjects in the IV treatment arm will receive a single dose of IV peramivir in the ED following randomization. If the subject does not have an IV line, one will be placed by the clinical staff. If the clinical team's plan is for the subject to be discharged home from the ED, he/she will receive no further study drug. If the clinical team's plan is for the subject to be admitted to the hospital, the subject's influenza treatment after leaving the ED will be up to the discretion of the inpatient treating provider. The inpatient treating provider will be informed of the subject's participation in the study and will be provided with the option to continue the use of IV peramivir at the same dose (based on CrCl result) for each subsequent day for up to four days. Treatment will stop upon discharge from the hospital. Should a subject remain in the hospital after five days of treatment, and the subject is symptomatically better, treatment will stop. If the subject remains hospitalized after five days of treatment and has not improved, the treating provider will have the option to continue the use of IV peramivir daily for another five-day course.

Study treatment, either oral or IV, may be stopped at the discretion of the treating provider should the provider believe that it is in the subject's best medical interest.

Treating providers of subjects who are admitted to the hospital will be provided with 24 hours a day/7 days per week access to an infectious diseases specialist, who will be available to consult on the use of peramivir and oseltamivir in admitted subjects.

5.1.5. Enrollment Completion

At the completion of all enrollment processes, subjects will be reminded that they need to complete a daily diary (to assess daily symptom severity, safety data, study drug adherence, as applicable, and provide a functional assessment) for 14 days between 3:00 PM – 11:59 PM local time. Subjects will be encouraged to complete the daily diary at the same time each day. Subjects will be reminded that research staff will be contacting them regarding daily diary entries and self-assessments, and at Days 3, 7, and 28 to collect follow-up information.

Subjects will also be asked to sign an authorization for release of health information which will allow research staff to obtain information on the subject's visits to other hospitals, should there be any subsequent medical encounters in the following 28 days.

Subjects who are discharged from the ED will be instructed to follow the ED standard discharge procedures.

5.2. Follow-Up

After enrollment (Day 1), subjects will be expected to complete a daily diary each day for 14 days, and complete "check-ins" on Days 3 and 7, and a follow-up assessment on Day 28. Research staff will also review the subject's medical records on Day 7 and Day 28.

5.2.1. Daily Diary

Beginning with the day of enrollment, for 14 consecutive days, subjects will be asked to complete a daily diary. The daily diary is expected to take approximately 10 minutes per day to complete, and will consist of the following 3 sections: 1) FLU-PRO Symptom Questionnaire

("Symptom Diary"); 2) medication adherence, side effect profile (including skin reactions and rash, neuropsychiatric events, nausea, vomiting, and diarrhea), and hospitalization history; and 3) a functional assessment.

Research staff will provide subjects with access to the web-based daily diary. The diary may be completed either by the subject via a secure web-based system that can be accessed from a personal web-enabled device, such as a laptop, personal computer, or tablet; or by personal contact (in-person or telephone) with trained research staff who will ask the questions and complete the web-based survey on behalf of the subject. If the subject is in the hospital, research staff will visit the subject daily to complete the diary.

Each day following enrollment, the research staff will review the subject's previous day's diary to verify whether or not the diary entry was completed. Missed diary entries cannot be made up. If a diary entry is missed, the research staff will call to remind the subject to complete the next diary entry as well as all remaining entries. Research staff may also offer to continue to contact the subject daily to assist the subject in completing the daily diary. If at any point the subject reports a skin reaction, rash, confusion, or hallucinations, research staff will immediately call to instruct the subject to return to the ED for evaluation (see section 7.2).

5.2.2. Day 3 and Day 7 Subject "Check-In"

Research staff will call all subjects on Days 3 and 7 to assess tolerability of the study drug, any potential AEs, and hospitalization history. Additionally, on Day 7, subjects will be asked to complete the PGIC and PGIS. If the subject is in the hospital on Days 3 and/or 7, research staff will visit the subject in person to complete the "check-in," and collect an NP swab to assess the duration and magnitude of virus shedding. If research staff are unable to reach subjects on Days 3 and 7, those "check-in" visits will be considered missed visits. Research staff must document each attempt made to reach the subject in the research record.

5.2.3. Day 28 Subject Follow-Up

Twenty-eight days from the date of enrollment, research staff will call the subject by telephone to complete the *Follow-Up Assessment (F13)* form, PGIC, and PGIS. Contact will be attempted on four consecutive days (unless requested otherwise by the subject) with at least one of the calls occurring during non-working hours (i.e., evenings or weekends). Subjects may be categorized as "unavailable for follow-up" if: 1) there is a minimum of four failed contact attempts; 2) the provided contact numbers are non-functional; or 3) the subject requests no further contact from the study.

If the subject remains in the hospital, he/she will undergo an in-person interview to complete the required evaluations.

5.2.4. Medical Record Review

Research staff will review subjects' medical records on Day 7 and Day 28. The following records will be reviewed:

- Day 7: Medical records from the subject's enrollment ED visit.
- Day 28: Medical records from subsequent ED visits, outpatient visits, and hospitalizations that occurred since the ED enrollment visit through Day 28. If the subject reports visits to other medical facilities at the "check-in" visits, the Day 28 follow-up visit, or at any other time, those records will be obtained and included in the medical record review.

6. Study Drug Management

6.1. Study Drug Supply

Two types of study drug will be used in the Randomized Controlled Trial of Influenza Antivirals. Subjects will be randomized to one of the following treatments:

- Oseltamivir (oral); or
- Peramivir (IV).

JHH and MMC will purchase oseltamivir.

BioCryst Pharmaceuticals, Inc. will provide peramivir to JHH for this study. JHH will distribute peramivir to MMC with permission from BioCryst Pharmaceuticals, Inc.

6.2. Study Drug Formulation and Storage

Oseltamivir (Tamiflu)

For this study oseltamivir capsules of 30 mg and 75 mg doses will be used.

- 30 mg capsules (30 mg free base equivalent of the phosphate salt): light yellow hard gelatin capsules. "ROCHE" is printed in blue ink on the light yellow body and "30 mg" is printed in blue ink on the light yellow cap.
- 75 mg capsules (75 mg free base equivalent of the phosphate salt): grey/light yellow hard gelatin capsules. "ROCHE" is printed in blue ink on the grey body and "75 mg" is printed in blue ink on the light yellow cap.

Oseltamivir capsules should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Peramivir (Rapivab)

Peramivir injection is a clear, colorless sterile, isotonic solution. Each single-use vial contains 200 mg per 20 mL (10 mg/mL) of peramivir in a clear glass vial. Peramivir injection is supplied in cartons containing three single-use vials.

Vials of peramivir injection should be stored in original cartons at 20° to 25°C (68° to 77°F). Excursions are permitted to 15° to 30°C (59° to 86°F).

6.3. Study Drug Dispensing and Administration

Oseltamivir will be prescribed and dispensed based on the subject's CrCl result obtained at screening. The first dose of oseltamivir will be administered in the ED. The remaining doses will be dispensed and given to the subject before being discharged from the ED (see section 5.1.4).

Peramivir will be prescribed and dispensed based on the subject's CrCl result obtained at screening. Peramivir is prescribed as a onetime dose to be administered in the ED. If the subject is admitted to the hospital from the ED, the inpatient treating provider may choose to continue administering IV peramivir (see section 5.1.4). Refer to the peramivir package insert for instructions on preparing peramivir for IV infusion.

6.4. Study Drug Labeling

The Pharmacist of Record (PoR) is responsible for ensuring that each container of study drug, dispensed to subjects, is labeled in accordance with federal, local, and institutional labeling requirements. The label must bear the statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use" per 21 CFR 312.6 (a).

6.5. Study Drug Accountability

The PoR at each site is responsible for ordering, receiving, storing, and dispensing study drug and will be required to maintain study drug accountability records. Study drug supply must be stored separately from other clinical drug supplies and/or hospital stock. At study end all unused and expired oseltamivir will be destroyed according to institutional policies; peramivir will be returned to JHH. Subjects will not return unused study drug (see the MOP).

6.6. Monitoring Subject Compliance to Study Drug

To assess subject adherence to oseltamivir, research staff will review the subject's daily diary each day. Subjects will report whether or not study drug for the previous day was taken. This information will be abstracted and entered on the *Medication Form (F24)*.

7. Adverse Event Management

The 21 CFR 312.32 (a) defines an AE (also referred to as an adverse experience) as any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. The occurrence of an AE may come to the attention of research staff during or after the study procedures and interviews.

7.1. General Management of Adverse Events

Acute management of any AE will be according to best clinical practices and the judgment of the site investigator. The relationship between the AE and the study intervention will be presumed related, unless a clearly recognized alternate etiology is identified. Alternative explanations for clinical or laboratory abnormalities must be sought prior to study drug discontinuation.

The following requirements for managing AEs during study participation should be followed, unless otherwise specified in section 7.2:

- Grades 1-4 AEs (not related to study drug):
  Subjects may continue taking study drug per the discretion of the site investigator. The site investigator will monitor all AEs unrelated to study drug according to best clinical practices. Report the event as an AE, following instructions in section 8.1.1.

- Grades 1 and 2 AEs (related to study drug):
  Subjects may continue taking study drug without alteration of the dosage or frequency, with the exceptions noted in section 7.2. The site investigator will monitor subjects according to best clinical practices. If the site investigator deems that the AE warrants study drug discontinuation, this should be communicated to the protocol team, prior to discontinuing the subject from study drug. Report the event as an AE, following instructions in section 8.1.1.

- Grades 3 and 4 AEs (related to study drug):
  The site investigator will determine whether or not subjects may continue taking study drug based on his/her clinical judgment. The site investigator will closely monitor subjects according to best clinical practices until the AE resolves or stabilizes. If the site investigator deems that the AE warrants temporary or permanent study drug discontinuation, this should be communicated to the protocol team as soon as possible and preferably, prior to discontinuing the subject from study drug. Report the event as an AE, following instructions in section 8.1.1; and as an SAE if criteria are met, following instructions in section 8.1.2.

7.2. Protocol-Specific Adverse Event Management

7.2.1. Allergy/Hypersensitivity Reaction to Study Drug

If an allergic reaction occurs, instruct the subject to hold the next study drug dose and go to the ED immediately.

- Grades 1 and 2: Discontinue study drug immediately. The site investigator will closely monitor the subject according to best clinical practices until the AE resolves or stabilizes. Report the event as an AE, following instructions in section 8.1.1.

- Grades 3 and 4: Discontinue study drug immediately. The site investigator will closely monitor the subject according to best clinical practices until the AE resolves or stabilizes. Report the event as an AE and SAE, following instructions in sections 8.1.1 and 8.1.2.

7.2.2. Rash or Skin Reaction

If a rash or skin reaction occurs, instruct the subject to hold the next study drug dose and go to the ED immediately. Any rash or skin reaction that is assessed to be possibly, probably, or definitely related to study drug will be considered an allergy/hypersensitivity reaction to study drug.

- Grades 1 - 4 (not related): Subjects may continue taking study drug per the discretion of the site investigator. The site investigator will monitor all AEs unrelated to study drug according to best clinical practices. Report the event as an AE, following instructions in section 8.1.1.

- Grades 1 and 2 (related): Refer to section 7.2.1 for AE management instructions.

- Grades 3 and 4 (related): Refer to section 7.2.1 for AE management instructions.

7.2.3. Altered Mental Status

If a change in behavior occurs, such as confusion or hallucinations, instruct the subject to hold the next study drug dose and go to the ED immediately. Refer to section 7.1 for AE management instructions.

8. Safety Reporting

8.1. Documenting, Recording, and Reporting Adverse Events

At each follow-up contact with the subject (i.e., phone call follow-up for outpatient and in-person follow-up for inpatients), information regarding AEs and unanticipated problems will be elicited by appropriate questioning and will be documented and reported as outlined below.

8.1.1. Adverse Event

All AEs including local and systemic reactions not meeting the criteria for an SAE will be captured on the *Adverse Events (F20)* form. All AEs occurring while on study will be documented appropriately regardless of relationship.

Any medical condition that was present at the time that the subject was screened/enrolled will be considered a baseline event. It will not be considered an AE. However, if the event worsens at any time after study drug administration through completion of the study period (Day 28), the event will be reported as an AE.

All AEs will be graded for severity and a relationship to the study drug will be assigned.

Severity of all AEs will be assessed by a site investigator using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.0, November 2014). The grading scale is as follows:

Mild (Grade 1): Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated

Moderate (Grade 2): Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated

Severe (Grade 3): Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated

Potentially Life-Threatening (Grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Death (Grade 5): Events resulting in death

Relationship to study drug or causality (likelihood that the event is related to the study drug) will be assessed for all AEs by the site investigator and the ISM. For the purposes of investigational new drug (IND) safety reporting, 'reasonable possibility' of relationship means there is evidence to suggest a causal relationship between the study drug and the AE. Such evidence includes temporal relationship between study drug administration and event, a known or suspected response pattern based on similar agents, and the likelihood (or lack thereof) of an alternative etiology. If a site investigator assesses an AE to be definitely, probably, or possibly related to study drug, the AE will be reported as related. If an AE can be clearly explained by another cause not related to the study drug, then the AE will be reported as not related and an alternative etiology will be documented.

Note: Causality assessment is based on available information at the time of the assessment of the event. The investigator and/or the ISM may revise the causality assessment as additional information becomes available.

8.1.2. Serious Adverse Event

An SAE is an AE that results in one or more of the following outcomes (International Conference on Harmonization (ICH) E6):

- Death during the period of protocol-defined surveillance.
- Events that are life-threatening (i.e., an immediate threat to life).
- Events requiring hospitalization or prolongation of hospitalization.
- Events resulting in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital abnormalities/birth defects.
- Other important medical events that may jeopardize the subject and may require intervention to prevent one of the outcomes listed above.

All SAEs will be recorded on the *SAE Report Form (F21)*, signed by the PI, and followed until satisfactory resolution, or until the event is deemed chronic or the subject is stable.

Many of the subjects enrolled in this study will have significant influenza-related illness, and it is expected that approximately 40% of enrolled subjects will be hospitalized during their enrollment ED visit due to severe influenza at baseline. If the subject is hospitalized due to their baseline illness, the event will not be reported as an SAE. However if the subject's condition worsens after study drug administration and requires prolongation of the hospitalization, the event will be reported as an SAE. Subsequent events that result in hospitalization after the initial ED enrollment visit will be reported as SAEs (see MOP).

Site PIs will report all deaths and immediately life-threatening events to the IRB within 24 hours of awareness. All remaining SAEs will be reported to the IRB within 7 days of awareness, or per institutional policy.

An ISM will be appointed to provide an independent safety review for SAEs immediately after they occur. The ISM will be a clinician with relevant expertise who is not otherwise associated with the study.

A Safety Monitoring Committee (SMC), consisting of the IND sponsor, JHH Co-PIs, Johns Hopkins University Research Program Manager, BARDA Medical Officer, the ISM, and the study biostatistician will review and monitor the safety and compliance data as well as the overall study progress on a regular basis.

Site PIs will report all SAEs to Westat Regulatory Affairs via fax within one business day of the site's awareness of the event. Westat Regulatory Affairs will notify the ISM and copy the SMC within one business day of the *SAE Report Form (F21)* receipt. The ISM will assess the relationship of the SAE to the study drug and the expectedness of the event to determine the reporting status to the FDA. The ISM will return his assessment to Westat and the SMC within 24 hours. Westat will report the SAE to the FDA per the ISM's recommendation. SAEs will also be reported to BARDA and BioCryst Pharmaceuticals, Inc. (if the subject is in the peramivir arm) within the same timeframe as required by the FDA.

9. Statistical Considerations

9.1. Study Objectives

Primary Objective: To prospectively enroll high-risk subjects with laboratory-confirmed influenza into a randomized, open-label study of oral versus IV influenza therapeutic to include symptom evaluation and outcome assessments.

Secondary Objective 1: To identify influenza-positive patients utilizing a previously established triage-based assessment and rapid testing algorithm for suspected influenza infection.

Secondary Objective 2: To retrospectively evaluate all potentially eligible patients for potential enrollment biases.

Secondary Objective 3: To create a repository of residual NP samples collected from ED patients with suspected influenza illness.

9.2. Sample Size Considerations

The proposed sample size is at least 50 subjects per site, per influenza season. This sample size was determined, in collaboration with ASPR/BARDA, to be adequate for this pilot effort which is being conducted specifically to examine the feasibility of achieving higher recruitment rates than has historically been achieved in other clinical venues, and the ability to reliably collect useful therapeutic endpoint data from an ED enrollment site. Estimates are based on data from the JHH ED 2014-2015 influenza season using the aforementioned testing algorithm, where 1604 patients were tested for influenza between November 2014 and April 2015, and 311 influenza-positive patients were identified. Of those 311 patients, approximately 75% met CDC criteria for influenza treatment (i.e., potential enrollment in the study) and 40% were admitted to the hospital. As 2014-2015 was a robust influenza season, it is estimated that a routine influenza season would have approximately 25% fewer influenza-positive patients. Based on similar previous ED based therapeutic clinical trials conducted at the JHH ED, it is anticipated that 56% of eligible patients will agree to participate in the study. Therefore, assuming a routine influenza season, there will be an estimated 174 eligible patients, of whom 97 will be enrolled (58 discharged, 39 admitted). Based on these estimates, at least 50 (conservatively) and up to 225 subjects could be enrolled and followed for 28 days.

9.3. Final Analysis Plan

As this is an exploratory study, data analysis will be principally descriptive. Rates of discreet events, as well as mean values for numerical data will be calculated. Statistical comparisons between groups (e.g., Secondary Objective 2) will be completed using t-test or chi squared as appropriate. This study is designed to be pilot in nature, and the anticipated sample size (225 subjects) is not sufficient for comparison of outcomes between the two treatment groups. Hence, potential clinical endpoints will be described using descriptive statistics for the purposes of future trial planning, and no statistical comparisons between the oral and PO antiviral arms will be made.

10. Clinical Management Issues

The following clinical management guidelines apply to both treatment groups.

10.1. Early Discontinuation of Study Treatment

Subjects will be discontinued from study drug for any of the following reasons:

- Completion of protocol-defined study drug administration period;
- Any allergic reaction to study drug;
- Site investigator or treating provider clinical decision to discontinue study drug; or

- Request by subject.

CRFs will be used to capture both the intended total dosage of study treatment as well as the dosage actually received. Reasons for early termination of study treatment will be recorded.

10.2. Study Withdrawal

A subject may be withdrawn from the study for the following reasons:

- Development of relevant exclusion criteria;
- Subject withdraws consent to participate in the study; or
- The study is discontinued.

All subjects should otherwise be followed according to the protocol. Subjects may withdraw from the study at any time at their request. Even if a subject does not receive all or any of the assigned study treatment, or some required data or specimens cannot be collected, every effort should be made to follow subjects for clinical outcomes until the end of the 28-day study period.

11. Protection of Human Subjects & Other Ethical Considerations

11.1. Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version (2013); the requirements of 21 CFR Parts 11, 50, 54, 56, and 312; ICH GCP Guidelines; Human Subjects Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); and to the local law and regulations, whichever affords greater protection of human subjects.

11.2. Institutional Review Board

Prior to the initiation of the study, the protocol, ICF, and any subject information materials will be submitted to and approved by the JHH and MMC IRBs. Any future amendments to the study protocol, consent materials, and subject information materials will be approved before they are placed into use.

11.3. Informed Consent of Study Subjects

Informed consent must be obtained as described previously for enrollment into the Randomized Controlled Trial of Influenza Antivirals.

11.4. Confidentiality of Study Subjects

In accordance with HIPAA regulations, no subject personal identifiers will be entered into the study database. Personal identifiers such as name, contact phone number, and medical record number will be collected and recorded on a separate study ID sheet. This identifying information

will be linked to the remainder of the subject information only through the study ID number, and will ultimately be stripped after all necessary data is collected. The study database, which will be accessible to research staff and PIs as well as key study personnel at Westat, will only contain study ID numbers and will not contain any personal identifiers. Personal identifiers will be destroyed upon final completion and verification of the study database.

Subject confidentiality will be held strictly in trust by the investigators and research staff. This confidentiality will be extended to cover testing of biological specimens and genetic tests in addition to the clinical information relating to subjects. The clinical study sites will permit access to all documents and records that may require inspection by the sponsor or its authorized representatives, IRB, or regulatory agency representatives, including but not limited to, medical records (e.g., office, clinic or hospital) and pharmacy records for the subjects in this study.

Data obtained in this study will be maintained in a 21 CFR Part 11-compliant, secure encrypted remote data capture (RDC) system. Access to the RDC system is limited to approved individuals; the PIs and Westat will set the level of access for individuals to the database. Information that can be used to identify specific subjects will not be entered in RDC and will only be available to the PIs, other research staff directly involved in the study and that interact with the subjects, and site monitors.

12. Data Management

12.1. Data Management Responsibilities

The site investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All CRFs and/or source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Blue or black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change.

Research staff will complete a web-based training for entering study data into the Oracle Clinical (OC)-RDC database. Westat will provide training on CRF completion before the start of the study. Ongoing in-service trainings may be conducted periodically throughout the study, as necessary. Verification of training will be documented and maintained in each site's study regulatory binder. Data collection is the responsibility of the research staff at the sites under the supervision of the site investigators. During the study, the site investigators must maintain complete and accurate documentation for the study. Data analysis will be the responsibility of the Johns Hopkins University Protocol Co-PIs, under the direction of the protocol biostatistician.

Each subject will be assigned a unique study ID number for use on CRFs and in the database. Names or any other personal identifiers will not be entered on any CRF or the study database. Forms that contain the subjects' name, date of birth, or contact information will be kept on-site and filed in a secured cabinet. A study ID sheet, the key linking each subject to his/her unique study ID number, will be created and kept secured by the site investigators under double lock separate from all research files, accessible only to research staff.

All CRFs must be reviewed by the research staff for accuracy, clarity, and completion, and by the data entry staff for completion. Study related laboratory reports will be reviewed and signed by a site investigator. AEs must be assessed for severity and relationship to study drug, and reviewed by the site investigators or designee. Data reported on the CRF that are derived from source documents or chart review should be consistent with the source documents or the discrepancies should be explained in the subject's research record. The subject will not be contacted for CRF data validation.

12.2. Data Capture Methods

Data will be captured using paper CRFs in blue or black ink with all text printed neatly and legibly (i.e., do not use cursive writing except when writing a signature), and with all fields completed except when left blank as specified by a skip pattern. Once completed, CRFs will be promptly entered into a 21 CFR Part 11-compliant, secure, password-protected electronic database by trained research staff. Data capture will be ongoing throughout the period of the study.

Daily diary data will be entered into a 21 CFR Part 11 compliant database that will be developed by Westat. Subjects may access the web-based daily diary system with a user ID and password from any personal computer, laptop, or tablet; or they may complete the daily diary as an interview (phone or in-person) with a research staff member, who will enter the data into the database for the subject (see MOP).

12.3. Data Submission

Sites must follow the guidelines for CRF completion and data entry that are specified in the MOP. Once the study database is developed and validated, the RDC screens will be available for data entry to research staff who have completed protocol training as well as OC-RDC training. Research staff at each site will be responsible for ensuring that CRF data are entered into RDC, as specified in the MOP.

12.4. Quality Control

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. All CRFs must have corresponding source documentation on file at the clinical sites to substantiate all submitted data, unless the CRF serves as the source document. For this study, many of the CRFs will be used as source documentation. However, it should be noted that additional source documents may be required, such as laboratory reports, hospital records, and clinical memoranda, to describe or clarify data reported on the CRFs.

The CRFs that will serve as source documents are listed in the MOP.

Data Accuracy Check: Data edits through range checks and field inconsistencies will be built into the RDC database to enable real time correction of key entries and CRF completion errors. In addition, all data that is entered into OC-RDC will be checked against the CRF shortly after

data entry by a different research staff member. For a randomly selected 10% of the subjects, all data forms and data entry will be checked by a different research staff member to ensure appropriate data collection. Any corrections will be noted, initialed, and resolved by consensus between the two research staff. Corrected data will be entered into OC-RDC as appropriate. Research staff will generate a report of the data accuracy check.

If it is determined that the original data recorded on a CRF is incorrect, both the hard copy CRF and the electronic database must be updated to reflect the change. The procedure for performing data updates is as follows:

- Using blue or black ink, strike a single horizontal line through the incorrect data value on the CRF, taking care not to obliterate the original entry. Do not erase or use white out;
- Record the correct data value adjacent to the original value;
- Record your initials and the current date next to the updated information;
- Make the necessary modifications in OC-RDC.

Data Completion Check: All data entered into OC-RDC will be evaluated monthly by Westat data management staff for CRF completion. If at the time of the data completion check there are CRFs that have not been entered in OC-RDC, Westat will send site research staff a missing forms report by email. Site Research staff will have 10 business days from receipt of a missing forms report to enter the data in OC-RDC or respond to the sender with a dispute such as a subject's missed visit or early termination or request an extension during times of high enrollment. These timelines for review and resolution of missing data may be shortened if necessary prior to an interim analysis and at the end of the study in an effort to receive the necessary data prior to the analysis. .

12.5. Protocol Deviations

A protocol deviation is any non-compliance with the study protocol, GCP, or protocol-specific MOP requirements. The noncompliance may be either on the part of the subject, the site investigator, or other study personnel. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, section 5.1.1

5.20 Noncompliance, sections 5.20.1, and 5.20.2

All protocol deviations, as defined above, must be addressed on the *Protocol Deviation (F22)* form. A completed copy of the *Protocol Deviation form* must be maintained in the regulatory file as well as in the subject's chart.

It is the responsibility of the site PIs and other study personnel to use continuous vigilance to identify and report protocol deviations. The site PIs and other study personnel are responsible for knowing and adhering to their IRB requirements. Only protocol deviations that are related to subject safety and/or eligibility will be reported to the local IRB per its guidelines.

12.6. Source Documents and Access to Source Data/Documents

ASPR/BARDA will assist the Co-PIs in creating source documents for the study prior to subject enrollment, including source documents to record information on screening (i.e., meeting inclusion and exclusion criteria), enrollment (demographics, patient history, pre-existing conditions, etc.), laboratory and medical record data, AEs, and all information entered on the CRFs.

The study sites will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of the confidentiality of subjects. Each site will permit authorized representatives of BARDA, its designees, site monitors, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance (QA) reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

12.7. Clinical Site Monitoring

Site monitors will visit sites to review selected portions of the individual subject records, including consent forms, CRFs, and supporting source documentation to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. Regulatory files, as required, will also be inspected to ensure that regulatory requirements are being followed.

Site monitors will also visit sites' investigational pharmacies to review the overall study product management system, including receipt, storage, disposition and accountability of study agents. Regulatory files kept within the pharmacy will also be inspected to ensure that regulatory requirements are being followed.

Appendix 1: Schedule of Evaluations

Evaluation/Test	Screening	Enrollment	Day 3	Day 7	Day 14	Day 28
Obtain informed consent	x					
Demographics	x					
Medical History	x					
Medical Assessment	x					
CBC[a]	x					
Complete or Basic Metabolic Panel[a, b]	x					
Beta-hcg (serum or urine) for women of child-bearing potential[a, c]	x					
Chest X-Ray[a]		x				
NP swab for storage		x				
NP Swab: duration and magnitude of virus shedding[f]			x	x		
Study Drug Administration[d]		x				
Subject Check-In[e]			x	x		
Medical Chart Review				x		x
Follow-Up Assessment						x
PGIS		x		x		x
PGIC				x		x
Daily Diary[g] (*FLU-PRO Symptom Questionnaire (F10)* and *Functional Assessment (F12)* form		x				
Obtain authorization for release of health information		x				

[a] If conducted as part of clinical care at enrollment or within the previous 24 hours, data may be extracted from the medical record.

[b] Calculate CrCl using the Cockcroft Gault equation to determine eligibility.

[c] Women will be considered of non-childbearing potential if they are greater than age 54 and have had no menses in the previous 12 months, or if they are surgically sterile (e.g., hysterectomy with or without oophorectomy; fallopian tube ligation; endometrial ablation).

[d] First dose of oral oseltamivir will be administered in the ED; the one time dose of IV peramivir will be administered in the ED.

[e] Conduct “check-ins” via phone. If the subject is in the hospital, complete the “check-in,” in person in the hospital.

[f] Collect NP swabs if the subject is hospitalized for the “check-in” visits.

[g] The Daily Diary *FLU-PRO Symptom Questionnaire (F10)* and *Functional Assessment (F12)* form will be completed in the ED. The subject will complete the daily diary for 14 days via the internet or by personal contact with trained research staff. Research staff will review subjects’ daily diaries each day.

Appendix 2: Shipping of Nasopharyngeal Specimens for Storage

Shipping Instructions

Frozen aliquots will be batch shipped monthly to the central study laboratory at Johns Hopkins University Division of Virology and stored for future analysis. These de-identified samples and results will not be available for clinical care.

All shipments will be made in accordance with institutional environmental safety regulations regarding shipment of hazardous materials. Frozen samples will be shipped by properly trained staff in an insulated container with dry ice and next day delivery to ensure samples remain frozen in accordance with International Air Transport Association (IATA) regulations. The laboratory is not open on the weekends or holidays; shipments must be received Monday – Friday only (excluding holidays).

Shipping address and contact info:

ATTN: Michael Forman
Johns Hopkins Hospital
600 North Wolfe St
Pathology B136
Baltimore, MD 21287
Phone: (410) 955-2642
Fax: (410) 614-8087
Email: mformaa@jhmi.edu

When shipping the specimens, create a “notice of shipment” (Appendix 2a: Notice of Shipment) that includes the sender’s name, phone and fax numbers, the study IDs, the shipping information and fax it to the above fax number, ATTN: Michael Forman. Upon receipt of the specimens, someone at the receiving laboratory will sign and fax back the notice, indicating receipt of shipment and specimens.

Appendix 2a: Notice of Shipment

NOTICE OF SHIPMENT
BARDA: Influenza Therapeutic Trial Study

Shipping address and contact info:

ATTN: Michael Forman
Johns Hopkins Hospital
600 North Wolfe St
Pathology B136
Baltimore, MD 21287
Phone: 410-955-2642
Fax: 410-614-8087
Email: mformaa@jhmi.edu

Part I: To be completed by Sender at time of shipment:

Senders Name:	
Senders Phone Number:	
Senders Fax Number:	
Study IDs of included specimens:	
Shipping Information:	

Part II: To be completed by Michael Forman's Research Staff upon receipt of shipment and faxed back to Sender:

Name:	
Signature:	