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WRAIR# 2725 IND# 17022
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Walter Reed Army Institute of Research
Consent for Research Participation

Title: A Phase 2a, Randomized, Double-Blind Study To Evaluate The Safety And Immunogenicity Of A Hantaan Virus DNA Vaccine and a Puumala Virus DNA Vaccine For The Prevention Of Hemorrhagic Fever With Renal Syndrome, Administered To Healthy Adult Volunteers Using The PharmaJet Stratis® Needle-Free Jet Injection Delivery Device

Sponsor: Office of the Surgeon General (OTSG), Department of the Army

Funder: Military Infectious Diseases Research Program

Principal Investigator (PI): Trevor Wellington, MD, MAJ MC, US Army, WRAIR

Contact Info: 301-319-9660 (office)
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IND Number: **17022**

You are being asked to take part in a research study. This study is supported by the United States Department of Defense. The WRAIR Scientific Review Board and Institutional Review Board (WRAIR IRB) have reviewed and approved this study.

The box below tells you important things you should think about before deciding to join the study. We will provide more detailed information below the box. Please ask questions about any of the information before you decide whether to participate. You may also wish to talk to others (for example, your family, friends, or your doctor) about this study, before agreeing to join.

Please contact one of the below if you have any questions concerning the study or if you have any other questions or concerns.

Trevor Wellington, MD, MD MAJ, US Army (301) 319-3095

WRAIR Clinical Trials Center * **(301) 319-9660**

*Open 6:00AM-2:30PM Monday-Friday

Key Information for You to Consider

Purpose

- This clinical trial is meant to study the safety and effectiveness of two vaccines for Hantaan and Puumala virus.
- Hantaan and Puumula viruses are from a family of viruses called hantaviruses. These viruses are found everywhere in the world and spread to humans from small animals, primarily from rodents, through bites, open skin (i.e., cuts), or exposure to an infected animal's urine, feces, saliva; or breathing dust from their droppings.
- Infected people may have no symptoms, have mild flu-like symptoms, or have a severe and/or life-threatening illness.
- These vaccines have been tested before in humans (in a Phase 1 study) to examine initial safety and reactions in humans and were found to be safe.
- Enrolling up to 132 participants to verify the safety and immune responses.

Voluntary Consent

- Your participation is up to you whether you choose to participate or not; this research study is voluntary.
- After you join, you can decide you no longer want to participate. There are no penalties, costs or obligations.
- If you decide to leave the study early, we want to ensure your safety by asking you to complete follow-up visits and blood work.

Duration, Procedures and Activities (See Visits and Compensation Schedule for detail)

- Participation is approximately 15 months including today's screening visit.
- A series of four (4) vaccine injections will be given with follow-up appointments in between. You will be asked questions about how you feel and given physical exams.
- Visits range in time from thirty (30) minutes to two (2) hours. During this study we will use an FDA approved, needle-free injection device called the PharmaJet Stratis® to place four doses of the experimental Hantavirus' vaccine on the uppermost part of each arm. After the placement of the vaccines, we will monitor your safety and your immune responses.

Risks

This is an investigational vaccine, and not all of the side effects are known. From previous studies, common side effects are usually short-term and resolve on their own. These may include one or more of the following symptoms:

- Pain, tenderness, swelling, warmth, or redness at the injection site,
- Fever, muscle aches, joint pains, headache, abdominal pain, diarrhea, vomiting and nausea.

- Severe allergic reactions are less likely, have not been observed with these vaccines, and are described in more detail later in this informed consent document.

Benefits

- There is no direct benefit to you for participating in this study. Future benefit from the information learned from the study may help in the development of a successful vaccine to reduce significant illness and death caused by Hantaviruses.

Alternatives

There are currently no known medical alternatives to immunizing against Hantaan and Puumala virus.

Why Are We Doing This Research?

Clinical trials are conducted in Phases (Phase 1, 2, etc.). Each “Phase” seeks to learn things like medication dosage and delivery safety, how well people tolerate the medication (side effects), and how well the investigational medications work compared to other treatments (if available).

You are invited to participate in this Phase 2a clinical trial of an experimental Hantaan Virus (HTNV) DNA vaccine and Puumala Virus (PUUV) vaccine. These are two different vaccines, for two closely related viruses both from the hantavirus family. The main purpose of this study continues to assess the vaccines’ safety and ability to stimulate the body’s immune system to protect against Hantaan and Puumala viral infection. Since you won’t actually have the virus, we will test if this experimental vaccine helps the body to makes antibodies that might protect against the Hantaan and Puumala viruses. Antibodies are made by our body’s immune system as part of our defense against foreign “invaders” like a virus.

Antibodies are made by your immune system when your immune system sees a germ (such as a virus or bacteria for example) for the first time. The next time your immune system sees the same germ it "remembers" and releases the previously-made antibodies that protect against the germ. Vaccines expose our bodies to germs to produce immunity, with the goals of lessening the risk of a disease causing serious illness, becoming widespread and or causing other health problems or death.

Vaccines work to help the body make antibodies without the person actually having the disease. They send a message to the immune system to make the antibodies to a specific germ- in this study the germ(s) are the Hantaan and Puumala virus. If a vaccinated individual is then exposed to the actual germ, the protective antibodies are released into the blood and prevent the disease. We will measure antibodies by running tests on blood samples.

What Is A DNA Vaccine?

This DNA vaccine was produced in the lab to “look” like the natural viral DNA of either the Hantaan or the Puumala virus. The vaccine CANNOT give you the viral infection.

What Are Hantaan And Puumala Viruses?

The Hantaan and Puumala viruses are found everywhere in the world. Human exposure to Hantaviruses come from infected rodent urine, feces, and saliva. Humans can get the virus through bites from infected animals, breathing in dust from infected animal droppings, or coming in contact with feces through nose, mouth, or broken skin. Infected people may have no symptoms, have mild flu-like symptoms, or have a severe and possibly life-threatening illness. These vaccines are being studied as a possible way to protect against infection from Hantaan and Puumala viruses.

Currently, there is no approved treatment or cure for these infections and no vaccines are commercially licensed by the US Food and Drug Administration (FDA) to help prevent hantavirus infections.

A vaccine to prevent the Hantaan and Puumala viral infections would be helpful to the global communities where these viruses are found including those serving in or beside US military personnel. Scientists at WRAIR and throughout the world are working to develop potential new drugs and vaccines to combat this infection.

Previous Clinical Human Research of HTNV and PUUV Vaccines

Although these experimental vaccines have not been approved by the FDA for commercial use, the FDA has allowed them to be used in human research. WRAIR has performed multiple HTNV and PUUV vaccine clinical trials safely and successfully in humans.

Participants in previous studies referred to as Phase 1, received the vaccines both separately and combined using various injection devices.

In a previous Phase 1 vaccine trial, which used these same vaccines and the same PharmaJet injector device used in this study, 27 volunteers received four immunizations and then were followed over time to see that they were safe and that their immune systems were making protective antibodies. The vaccines were safe and well tolerated, with no serious side-effects, and there was good production of protective antibodies. This Phase 1 trial used the exact same ingredients as our vaccine, but we are testing it again to be sure of the safety data in a larger number of volunteers and to see if the half-dose of the vaccine can also work to produce a similar level of protective antibodies. It is important to note that these vaccines are still considered experimental for prevention of these hantaviruses.

What Are The Risks If I Participate In This Research?

If you decide to participate in this study, you should carefully consider the risks, which are described below. While participating in this study, you are not allowed to participate in any other clinical trial. We will share information about new risks with you as the study continues.

Known and Unknown Risks of the Vaccine and Vaccination

Not all of the side effects of this vaccine are known.

This study is for research purposes only and is not intended to treat any medical condition. After you receive this investigational vaccine, you should not expect the vaccine to protect you from becoming ill with the virus if you travel to a part of the world where the viruses are present.

If you are at risk of being exposed to rodent urine, feces, and saliva, bites from infected animals, breathing in dust from infected animal droppings, coming in contact with feces through nose, mouth, or broken skin or traveling; **take proper personal protection and or travel precautions, as prescribed by your doctor.**

Frequent side effects from previous studies include:

- Mild to moderate injection site pain, redness, or bruising lasting 24 to 72 hours (but sometimes up to 7 days).
- Side effects similar to common commercially approved vaccinations such as pain in the area of the armpit, swollen "glands" (i.e., lymph nodes), fever, headache, fast breathing, fatigue, and muscle soreness.

The vaccine itself will not cause an infection with hantavirus because it has been modified in the lab to prevent active infection. As with many vaccines, you may experience one or more of the following: pain, tenderness, swelling, itching, warmth, or redness at the injection site.

Other common body wide side effects include generally feeling unwell or tired, fever, chills, muscle aches, headache, dizziness, rash rapid breathing, and nausea. These reactions, if present, are usually short term and often do not require treatment.

These are investigational products and there is the potential risk of a serious, or even life-threatening, allergic reaction to one or more components of the vaccine to be used in this study. To decrease this risk, **any person with a history of severe allergic reaction of any kind, or significant allergic reaction to a known component of the vaccine, will not be allowed to participate in this study**. **All vaccinated subjects will be observed for 30 minutes after vaccination to ensure that there are no immediate effects prior to being released.**

In the event of a severe allergic reaction (such as with trouble breathing and swallowing), the WRAIR Clinical Trials Center (CTC) is staffed with trained medical personnel and stocked with appropriate medical emergency equipment to provide immediate care. If needed, a formal emergency medical response service (fire department), capable of treating and transferring any life-threatening injuries to a higher level of medical care, is available and is very close to the CTC.

Guillain–Barré Syndrome: Guillain-Barré syndrome (GBS) is a rare disorder occurring in roughly 1 person out of 100,000 people and has been known to occur on rare instances after vaccinations. The first symptoms of this disorder include varying degrees of weakness or tingling sensations in the legs. Symptoms can increase in intensity until certain muscles cannot be used at all (paralysis). Most individuals recover from even the most severe cases of GBS, although some continue to have a certain degree of weakness (National Institutes of Health 2018).

This is a DNA vaccine. The HTNV DNA and PUUV DNA vaccines do not contain live virus and, therefore, are not expected to cause infection with these viruses.

However, use of DNA vaccines have theoretical risks that include infection and incorporation (insertion) of the vaccine DNA into your DNA. Animal studies using other similar DNA vaccines have shown no incorporation (insertion) of the vaccine DNA into the DNA of the animals. In other DNA vaccine studies, people have been tested after receiving viral DNA vaccines to see whether their bodies made any harmful antibodies against human DNA. This has not happened in the past.

Long-term effects of DNA vaccines have not been studied. Possible long-term effects include having a stronger localized or whole body reaction if you are exposed to a similar disease in the future, than a non-vaccinated person. These effects have been seen with other vaccines but not with DNA vaccines to date.

Risks Related To Delivery of the Vaccine with the PharmaJet Stratis Device

The low risk of a skin infection with bacteria found on your skin at the site of injection is minimized by cleaning the skin of the upper arm well prior to vaccination.

The PharmaJet Stratis device injects a liquid jet very fast that penetrates the skin and enters into the muscle tissue to deliver the vaccine. There are no reports of major side effects from use of this device filed with the FDA.

The side effects observed in prior trials with this device are similar to those of normal vaccinations (i.e., with a needle and syringe) and occurred only at the injection site. The most common side effects reported for the PharmaJet Stratis device include mild bruising, small amount of bleeding, redness, itching, and pain/discomfort.

Risks of Drawing Blood

Blood will be drawn from a vein in your arm using a needle. Blood draws are performed by trained and experienced technicians which will help prevent (but not eliminate) the risk of pain and bruising at the needle insertion site. Blood is always collected using standard aseptic techniques to prevent infection. The low risk of a skin infection from bacteria found on your skin is minimized by cleaning the area of skin at the blood draw site prior to taking blood.

Sometimes people may feel lightheaded or faint when blood is being drawn. These symptoms can be stopped by laying down and/or by stopping the blood draw. Physician investigators are always on site to provide supportive care in the event of an adverse reaction.

There is also a risk of getting anemia from the repeated blood draws. To decrease this risk, the total amount of blood drawn throughout this entire study is less than 30 tablespoons (450 mL) of blood. There will be several times throughout the study where safety lab work is done to check for anemia.

Risks during pregnancy

Pregnant and/or lactating women cannot participate in this study. You should not get pregnant or breastfeed while taking part in this study. The female partners of men participating in this study should not become pregnant during the study.

If you are a female who is able to become pregnant and you want to take part in this study, you must agree to consistently use acceptable birth control (defined below) at least 30 days before enrollment and through 90 days (3 months) after the last study vaccination.

Acceptable birth control methods include: progestin-releasing subdermal implants and intrauterine devices (IUD), prescription oral contraceptives, contraceptive injections, combined pill, progestin-only pill, hormone-releasing transdermal patch or vaginal ring, and depot medroxyprogesterone acetate injection (Depo-Provera), having one male sex partner who has had a vasectomy ≥3 months prior, and/or a male partner with barrier protection plus the use of vaginal spermicide, and abstinence. Non-childbearing potential is defined as surgically sterilized.

A urine pregnancy test will be given today and prior to each vaccination. If these tests are positive, you will not be allowed to participate in this study.

If you become pregnant during the study or suspect you might be pregnant, contact the Principal Investigator of this study listed in the Contact Information section at the top of this document. You will be referred to a health care provider for further evaluation and care. **If you are pregnant at any time during the study, you will be followed for safety purposes throughout the study until birth, and will not receive any further vaccinations.**

Unknown or Unanticipated Risks

There may be risks that are not known at this time or that have not been reported yet. If any new risk is reported, the study doctors will let you know as soon as possible.

Participating in this hantavirus vaccine study will not protect you from getting hantavirus in the future. After you complete the study, you should take normal steps to prevent hantavirus as recommended by your doctors.

Privacy and Data Confidentiality Risks and Protections

We will take measures to protect your privacy and maintain confidentiality. *Privacy* is your ability to control how other people see, touch, or obtain information about you. Confidentiality refers to your private information and how this information will be kept safe.

We will try our best to protect your privacy and confidentiality by doing the following:

- Your name and any identifiable information (for example, your address or social security number) will be removed from study files and your lab samples and be replaced with an identification code that consists of numbers and letters. Different codes may be used for you during the course of the study. Only the study investigators, study coordinators, research monitor and representatives from certain agencies (described below) will be allowed to know which codes belong to you, and to have access to your study information.
- Your study files will be kept in a safe, secure storage area at the WRAIR Clinical Trials Center for the duration of the study.
- The collection of sensitive information will be limited to the minimum amount necessary to achieve the aims of the research.

How Will Data be Protected

Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. Computer-based files will be encrypted and only made available to personnel involved in the study through the use of secure access privileges and passwords. Whenever possible, identifiers will be removed from study-related information.

What Happens to The Information and Specimens Collected For This Research?

Information and data collected from you for this research will be used to help us determine whether a new hantavirus vaccine is safe and protects against infection.

The blood samples you provide during the study will be used for laboratory tests to assess your safety. Some blood samples may be pooled for future analysis. We say that **samples** are pooled when they are equally mixed or processed together in such a way that the individual samples can no longer be determined, but rather any results reflect all samples tested together. Any blood left over after pool creation will be stored for up to 20 years, with your permission, for future use in hantavirus research.

Any information discovered from your data or samples during this trial that may negatively impact your health (for example, if we discover you have high blood pressure or hepatitis) will be shared with you, and if appropriate you will be counselled by a study investigator and referred to a health care provider for further evaluation and care.

Your data and samples will not have your name or other identifying information about you. Your data and samples will be labeled by a code (such as a number) and may be sent to investigators at WRAIR or other research scientists throughout the country who work with us, without asking for your permission.

No whole genome sequencing will be conducted on your samples in this study. Whole genome sequencing involves the analysis and description of your entire genetic code, or DNA.

Your stored samples will be used for research only and will not be sold. Research using your blood samples may help develop new products in the future that have the potential for commercial profit**,** but you will not receive payment for such products.

You will not be informed regarding when these future studies occur on blood samples or what results come from it, but it is your choice as to whether we can use your blood samples for this future research.

Once the study is complete, your records will be kept in secure storage at WRAIR for a period of at least 2 years. Records will be maintained until it has been deemed no longer necessary to retain them by the study Sponsor (US Army Surgeon General), and

then destroyed as per applicable regulations. Any remaining blood specimens will be kept at WRAIR. Storage and destruction of these samples will be as per the applicable facility Standard Operating Procedures (SOPs). These samples, either individually, or in pool form, will be stored for a maximum of 20 years (counting from when the last subject performed the last study visit), unless regulations or guidelines arise in the interim which require different timeframes or different procedures.

Any future research using your data will require a research protocol and approval by an Institutional Review Board (IRB) (a committee responsible for protecting research participants) or other authorized official responsible for protecting human subjects in research studies. For instance, an IRB reviewed and approved this current study that you are taking part in. The data protections for privacy and confidentiality described in this document will apply to any future use of your stored data and samples.

After the study is complete, you may request to find out the overall study results from the study investigators.

Required Disclosures

We may report medical information and lab results to authorities, to prevent serious harm to yourself or others.

- We are required to report information regarding certain infectious diseases (like HIV or AIDS and viral hepatitis) to the local health department. If your blood tests show that you have one of these infections, we will report this information to the health department, and they may need to interview you to get more information. This may cause you some distress, and could affect your personal and professional relationships. We will provide trained counselors to discuss test results and refer you for further care as required.
- For volunteers who are in the military, information bearing on your health may be required to be reported to appropriate medical or command authorities. This may include information bearing on your safety, the safety of others, or your ability to perform your duties.
- Representatives from the following agencies may have access to review research records as part of their responsibility to protect humans in research and oversee the quality of the research efforts. As government agencies, they must also maintain confidentiality of your records within the limits of the law.
  - The Study Sponsor, US Army Surgeon General
  - The WRAIR Institutional Review Board (IRB)
  - US Army Medical Research and Development Command (USAMRDC)
  - The US Food and Drug Administration

Even though we have strategies in place, there are always risks to breaches of confidentiality and privacy.

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

What Is The Volunteer Registry Data Sheet?

It is the policy of the US Army Medical Research and Development Command (USAMRDC) that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential database includes your name, address, Social Security number, study name and dates.

The intent of the data base is two-fold:

1. To readily answer questions concerning an individual's participation in research sponsored by USAMRDC; and
2. To ensure that the USAMRDC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRDC for a minimum of 75 years. The Volunteer Registry Data Base is a separate form and not linked to this protocol database.

Are There Disclosures Of Financial Interests Or Other Personal Arrangements From The Research Team?

The Principal Investigator and members of the research team have no financial interests or personal arrangements related to this trial to disclose at this time.

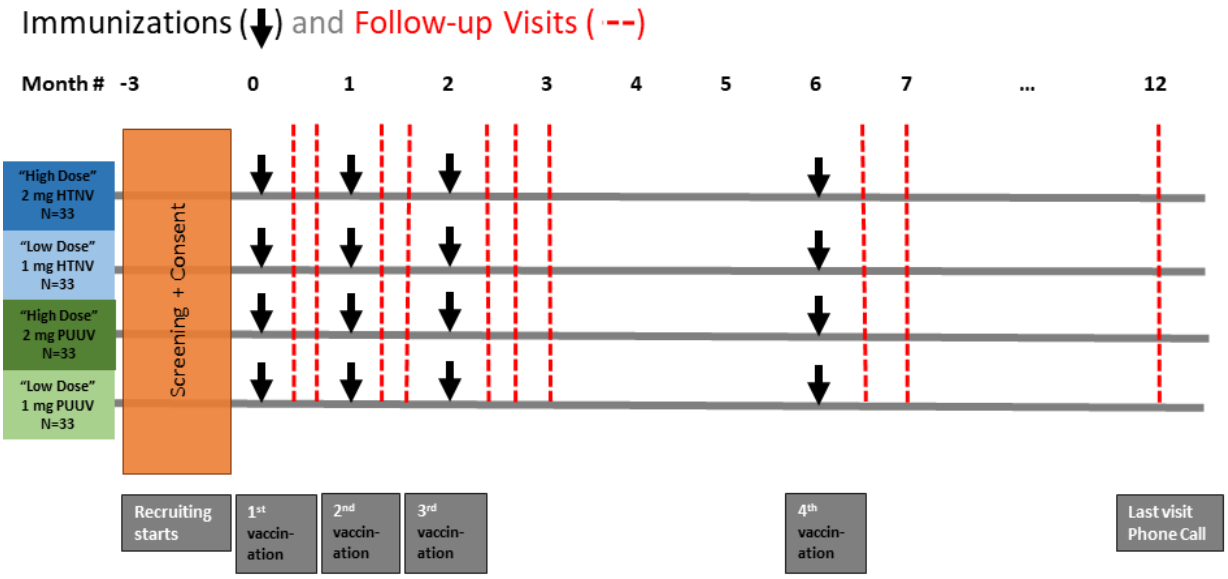
Who Will Be Participating in this Clinical Trial?

We are looking for 132 people to take part in this study at WRAIR for approximately 15 months. Figure 1 provides an overview of the clinical trial plan.

- There are four (4) different groups in total. You will be randomly assigned to one of the groups if you choose to participate in this study.
- Two of the four groups are using the same dose and immunization schedule as the Phase 1 study.
- Two additional groups have been added, that will test the half dose of the HTNV and PUUV vaccines (low dose groups).

Random assignment is like the flip of a coin, in this case to 1 of 4 groups. It is called a "double blind" study because you will not know which group you are assigned to, and neither will the study investigators. Only a few assigned staff members at WRAIR will know which vaccine you are getting.

Figure 1:



How Long Will I Be in This Research Study?

A Visits and Compensation Table will be provided along with this form that lists the study activities, compensation amounts for each visit and gives the approximate length of time for each study visit for the next 15 months.

Where Will This Study Take Place?

The screening visits, vaccinations and follow ups will take place at the Walter Reed Army Institute of Research (WRAIR) Clinical Trials Center in Silver Spring, Maryland.

Compensation

You will receive compensation for your time and efforts. Compensation for your participation is outlined in the ‘’Visits and Compensation Table’ found at the end of this document. The table applies to non-federal employees as well as off-duty Federal Employees(Federal Civilians and active military members).Compensation includes:

- $50.00 at screening to $200.00 for vaccination day visits.

Federal employees, both civilian and active duty, who are on-duty during study visits will receive $50.00 compensation for visits that consist of blood draws. **On-duty Federal employees will not be compensated for visits that do not have blood draws associated with them.**

- The total amount of compensation may vary depending on if you are a federal employee presenting for visits while on-duty or if you are found to require extra visits for blood draws for any reason during the protocol.

- If you need to return to clinic for any additional unplanned visits the compensation will be $100.00 per visit (non-federal employees only).

- If you complete the study, the total compensation is a maximum of $1980.00 ($550.00 for on-duty federal employees) if you make all scheduled visits.

- For all volunteers receiving more than $600.00, an IRS form 1099 will be issued.

Federal and military regulations place limits how much and for what federal civilian employees and active duty research volunteers may be compensated, if participating while on duty hours.

In order to participate on- or off-duty, active duty military volunteers will require approval from their supervisor through branch director using the Statement of Supervisor's Approval, which will be provided to you.

- Other than medical care that may be provided and any other payment specifically stated in this informed consent, there is no other compensation available for your participation in this research study; however, you should also understand that this is not a waiver or release of your legal rights.

The maximum possible compensation for a volunteer who attends all study visits amounts to approximately $1980.00. The maximum possible compensation for an **on-duty** federal employee amounts to approximately $550.00. Please note that we will not provide extra money to pay for costs you may have from being in this study, such as the cost of transportation to and from the study site or child care costs.

If you choose to leave or are removed from the study by the Principal Investigator prior to its completion, you will still be eligible for the compensation related to all study visits and procedures that you have successfully completed up until that point.

Other than medical care that may be provided and any other payment specifically stated in this informed consent, there is no other compensation available for your participation in this research study; however, you should also understand that this is not a waiver or release of your legal rights.

Are there costs for participating in the research?

There is no cost to you to participate in the study. You will not have to pay for medical visits, physical examinations, blood tests, medical procedures, or hospitalizations that occur as a result of this study. However, **we will not pay for any transportation or childcare costs.**

What Will Happen If I Decide to Be in This Research Study?
If you agree to be in this research, you will be expected to complete the number of visits and procedures outlined in the Visits and Compensation Table, beginning with today's screening visit. A basic outline of these activities is as follows:

Screening Phase (up to 3 months before immunizations start)

- If you decide today that you would like to participate, we can complete your screening visit today. You will be asked questions to determine if you are eligible to participate in this study. You will not be able to take part in this study if you have a medical condition that could get worse if you get the vaccine.

- In addition to going over this form together, we will deliver a presentation that goes over the details of this clinical trial and the information presented in this form. A small test called the 'Assessment of Understanding' will be given to you. We require at least 80%, or 8 out of 10 answers correct. If you do not score 80% on your first try, we will review the study information with you, and you will be able to take the test again. If you get less than 80% the second try, you will not be able to be in the study
- If you meet all the participant study requirements in the Screening process, and still agree to be in this study, you will be asked to sign this consent form. There are two other consent forms to go over:

    Permission to photograph the injection sites (where we inject the vaccine) and;

    A State of Maryland HIV test consent form.

After your consents are signed, a study physician will obtain your medical history and perform a physical examination. Your height, weight and vital signs (blood pressure, temperature, and heart rate) will be documented. If you are a female of childbearing potential, a urine pregnancy test will be performed. If your pregnancy test is positive, you will not be able to be in the study.

Initial blood samples, less than 2 tablespoons (approximately 20 mL) will be drawn for the screening process laboratory tests. Blood collection occurs by placing a small needle in a vein in your arm.

These initial blood tests will establish your baseline:

- Complete blood count (CBC)
- Liver and kidney function tests
- Glucose (a type of sugar in your blood) and;
- Tests for HIV, hepatitis B and hepatitis C

These clinical tests are done to ensure you are in good health and able to safely participate in this study. The results will be discussed with you. Upon request we will give you the results of our medical history, physical exam, and lab tests so that you can give them to your regular doctor.

Blood is drawn for lab tests throughout the study to monitor your health and safety. It is possible that the physician may order additional lab testing either for safety or to clarify your clinical condition. These lab tests would be discussed with you throughout the process.

If any of your clinical test results are abnormal, you will be informed about the test result and referred to a health care provider for further evaluation and care. At your request, we will provide you a copy of your clinical laboratory test results. State regulations require that if any of your tests show that you have HIV, hepatitis B, or hepatitis C infection, we must report the information to the Maryland Department of Health. If you are a military service member, this information will also be reported to the military preventive medicine service.

If you meet all study requirements and wish to continue in the study, you will then be assigned to a vaccination group. You will randomly be assigned to one of 4 groups.

Vaccination Phase:
There are 4 intramuscular vaccinations for each of the four (4) vaccination groups. At each vaccination we will inject the vaccine into uppermost portion of both arms. All groups will be vaccinated using the PharmaJet Stratis injector device. This is a needle – free device, and instead uses a liquid jet stream to inject the vaccine into your upper arm area.

Each group will receive their vaccinations at 0, 1, 2 and 6 months after your enrollment into the study. The safety of each vaccine dose will be closely monitored. At any point after the administration of the vaccine, it is determined that continuation would be too risky to your health, you will not continue to get any more of these vaccinations.

Doses of the vaccine will differ in concentration between the four (4) groups.

- Group 1 receives all four doses of the 2 milligram high dose of HTNV vaccine. This will be the higher concentration of the vaccine that we are evaluating, which has been tested before in a Phase 1 study.
- Group 2 receives all four doses at the 1 milligram low dose of HTNV vaccine. This is the lower concentration of the vaccine that we are evaluating.
- Group 3 receives all four doses of the 2 milligram high dose of PUUV vaccine. This will be the higher concentration of the vaccine that we are evaluating, which has been tested before in a Phase 1 study.
- Group 4 receives all four doses at the 1 milligram low dose of PUUV vaccine. This is the lower concentration of the vaccine that we are evaluating.

Before any dose of the vaccines, you will see the study doctor to review your medical history since your previous visit and have a brief physical exam. New medications will be recorded along with your vital signs. We will review eligibility and elimination criteria.

If you are still qualified to participate, you will be asked for another blood draw for laboratory tests prior to receiving the vaccination on the same day. For all four vaccinations, on each vaccination visit, we will collect less than 2 tablespoons (approximately 20 mL) of blood.

- If you are female, you will have a urine pregnancy test prior to each vaccination. Volunteers with a positive pregnancy test will not be allowed to continue participation in the study, however, you will be followed for safety if you have received a vaccination in the study until the birth of your baby.

- The vaccine will be given by trained staff in the upper, outer part of the arm, for both arms at each vaccination visit.

- After receiving the vaccine, you will be observed in the WRAIR Clinical Trials Center (CTC) for about 30 minutes. You will be given a memory aid to keep track of any symptoms you may have at home. You will also be given a thermometer and a ruler to take your temperature at home and measure any redness or swelling at the injection site. You will also be given an emergency contact card after the first vaccination, in the event that you have any medical issues once you have left the CTC.

Follow up will occur after each vaccination:

- 3 days after vaccinations 1-3, you will return to the CTC. At this visit you will have vital signs taken, review your medical history since your last visit, review medications you are taking, undergo a short physical exam, and address any problems or symptoms you might be experiencing with a study physician.

- 2 weeks after every vaccination, you will return to the CTC. For these visits you will have vital signs taken, review your medical history since your last visit, review medications you are taking and your memory aid, undergo a short physical exam, address any problems or symptoms you might be experiencing with a study physician, and we will collect less than 1 tablespoon (10mL) of blood.

- Approximately 1 month following the third vaccination, you will return to the CTC. At this visit you will: have vital signs taken, review your medical history since your last visit, review medications you are taking, and any symptoms you might be experiencing, and we will collect approximately 6 tablespoons (approximately 80 mL) of blood.

- Approximately 1 month following the fourth vaccination, you will return to the CTC. On this visit we will review medications or any symptoms and collect approximately 6 tablespoons (90 mL) of blood.

- The Final visit will occur by phone call approximately 6 months after your fourth vaccination. On this visit we will ask about any symptoms you have had or any problems since the last visit that required a visit at the doctor's or hospitalization.

What Requirements Do I Have To Meet In Order To Participate In This Study?
You may be allowed to participate in the study if you meet the following requirements:

- You are between the ages of 18 and 49 years old.
- You have a valid state or government-issued photo ID (e.g. driver's license, military ID, or U.S. passport) & be able to pass a background check in order to gain access to the base & participate in a study with us.
- You are willing and able to participate in all planned study visits for the duration of the study.
- You are in good general health based on your medical history, physical examination, and screening laboratories.
- You are able to understand and sign this informed consent.
- You pass the written test called the 'Assessment of Understanding' with a score of at least 80% (8 out of 10 questions correct) in one out of two attempts.
- If you are a female, you must either have had a surgical procedure that resulted in the inability to have children or must agree to consistently use acceptable birth control (defined below) at least 30 days before enrollment (the day of your first vaccination) and through 90 days (3 months) after the last study vaccination. Females have to agree not to donate their eggs from screening until 90 days after the last study vaccination.
    - *Acceptable methods of contraception include: progestin-releasing subdermal implants and intrauterine devices (IUD), prescription oral contraceptives, contraceptive injections, combined pill, progestin-only pill, hormone-releasing transdermal patch or vaginal ring, depot medroxyprogesterone acetate injection (Depo-Provera), having one male sex partner who has had a vasectomy ≥3 months prior, and/or a male partner with barrier protection plus the use of vaginal spermicide, and abstinence.*
- If you are male, you must agree not to father a child or donate sperm from screening until 90 days after the last vaccination.
- If you are a military employee, you must have approval from your supervisory chain to participate. The appropriate approval form will be provided to you.

- You must not have a fever in order to receive the study vaccine.
- Women must agree to not donate eggs (ova, oocytes) and male subject agrees not to donate sperm from the start of screening onwards until at least 90 days after the last vaccination.
- You must agree not to participate in another clinical trial during the study.
- You must agree not to donate blood to a blood bank for 3 months after receiving the last study vaccine.

You are not allowed to participate in this study if any of the following criteria apply to you:

- Any history of previous hantavirus vaccine.
- Any serious medical illness or condition involving the heart, liver, lungs, or kidneys.
- A history of severe allergic reactions.
- If you have received licensed vaccines within 7 days before or after immunization (30 days for live vaccines)
- Any history of neurologic disease (including migraines or seizures).
- If you lack the ability to observe possible local reactions at the injection sites (upper arm region) or if the injection areas are obscured due to a physical condition or permanent body art (tattoo).
- If you have donated blood for human use (eg, American Red Cross or other similar blood drives) within the 56 days prior to study entry or if you plan to during the study period.
- If you have had an acute illness (as determined by the study doctors), within 72 hours prior to study vaccination.
- Any past or current infection with HIV, Hepatitis C, or Hepatitis B.
- Any use of investigational drugs or vaccines within 30 days before starting the study.
- You must not be pregnant or nursing or have any plans to become pregnant or breastfeed during the period from now through the end of the study.
- Any chronic use of steroids or other medications that affect the immune system within 6 months of study entry and during the study period.
- You plan to have major surgery that in the opinion of the investigator, could impact your safety or interpretation of adverse events between enrollment and the end of the study.
- Any active alcohol or drug abuse that in the opinion of the investigator could impact safety, interpretation of adverse events, or ability to follow-up.

- History of active/recent cancer still within treatment or active surveillance follow-up (except basal cell carcinoma of the skin and cervical carcinoma in situ). Treated/resolved cancers with no likelihood of recurrence may be deemed acceptable at Principal investigator discretion.
- Concurrent participation in another clinical research study.
- Receipt of antibodies or blood products within four (4) months before enrollment.
- History of Diabetes mellitus (type I or II), with the exception of gestational diabetes.
- You have any other physical or psychologic condition or laboratory abnormality that the study doctor thinks may increase your risk of having side effects or compromise the results of the study.
- If you are unwilling to allow storage and use of blood for future hantavirus-related research

What Are My Responsibilities as A Participant in This Research Study?

If you agree to participate in this study, you will be expected to keep all of your study visit appointments. If you cannot make your scheduled appointment, call the WRAIR CTC at 301-319-9660 during operating hours (Monday to Friday 06:00AM to 2:30PM).

What Happens If I Am Injured as A Result of This Research?

Any participant injured because of participation in this research, is entitled to medical care for injury(ies) at a DoD medical facility.

If you are injured because of your participation in this research and you are a Department of Defense (DoD) healthcare beneficiary (e.g. active duty in the military, military spouse or dependent, retiree), you are entitled to medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary. This care includes but is not limited to free medical

Medical care charges for care at a DoD medical facility will be waived for research-related injury for all participants. Participants are entitled to seek care for injury(ies) at other non-Army DoD hospitals, but such care may be time-limited, and you or your insurance may be billed and responsible for medical expenses.

If you incur medical expenses to treat research-related injuries, reimbursement is not available. We will not provide additional compensation for research-related injuries. You are not waiving any legal rights.

If you believe that you have sustained a research-related injury, please contact the Principal Investigator, , or the WRAIR Clinical Trials Center, whose contact information is given at the top of this document. In addition, an emergency contact card will be provided to you with numbers to contact at any time.

What happens if I withdraw from this research?

PARTICIPATION IN THIS STUDY IS VOLUNTARY. You may decide not to take part in this study or withdraw from (leave) the study at any time and for any reason. There is no penalty or loss of benefits to which you are otherwise entitled- there is no expectation that any compensation received up to your time of withdrawal will be returned. The quality of the medical care you receive will not be affected by your decision to withdraw from the study. We do ask, for your safety, to continue to monitor or provide any treatment that is necessary for your treatment.

If you decide to leave the study, we ask you to contact a study investigator or the CTC staff. The information you provided prior to withdrawal will be stored and treated in the same way as for other volunteers. Any data and specimens collected prior to your withdrawal will be still be kept and used by the study, in the same ways as for other volunteers. This is because by agreeing to participate in this study, you agreed to allow future use of your samples taken during the study. No more payments will be made to you after the final blood work.

The principal investigator may decide not to allow you to continue participating in this study under the following conditions:

- If you develop a medical condition that would make it unsafe for you or others if you were to continue participating, or that would interfere with the study results.
- If other situations or conditions arise that would make participation harmful to your own health.
- If you fail to comply with the procedures as outlined in this form.
- If the study ends for any reason.
- If the investigator believes that it is in your best interest.

You should also know that the WRAIR Institutional Review Board (IRB), the DoD Research Monitor, and the US Army Medical Research and Development Command (USAMRDC) can end this study at any time. If the study ends, or your participation ends, you may be asked to complete follow-up visits and/or medication for your safety.

If we discover any significant or new information during the study that may affect your health and willingness to continue participation we will inform you and seek your new consent to continue with the study.

Who can I contact if I have questions about my rights as a research participant?

If you have questions about your rights as a research volunteer in this study, you may contact:

Walter Reed Army Institute of Research
Human Subjects Protection Branch
503 Robert Grant Avenue

Silver Spring, MD 20910
Phone number 301-319-9940

usarmy.detrick.medcom-wrair.mbx.hspb@health.mil.

Consent for Future Research

Samples received for this project may also be subject to future testing in Hantaan and Puumala Virus research. Future testing on your blood samples may include hantavirus related tests or tests to look at your immune system response to the vaccine and/or hantavirus infection.

The results of these tests will not be made available to you. They will be used exclusively for these specified research purposes.

The test results will not be linked to your name or other personally identifying information and the test results will be coded by the study number.

Consent

If there is any portion of this document that you do not understand, ask the investigator before signing the form. Signing this form means that you understand the information we have provided to you about the study and your signature indicates that you consent to participate in this research, at this time.

A signed and dated copy of this document will be given to you.

Please initial the sentences that reflect your choices, and then sign below:

_____ *(initials)* I acknowledge that by participating in this study, I authorize the storage of my biological specimens for use in future hantavirus research studies.

_____ *(initials)* I authorize the use of my individually identifiable data for future hantavirus research studies.

SIGNATURE OF PARTICIPANT

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Permanent Address of Participant

SIGNATURE OF INDIVIDUAL ADMINISTERING CONSENT
(Can only be signed by an investigator or staff approved to administer consent)

_____
Printed Name of Administering Individual

_____ _____
Signature of Administering Individual Date

DEPARTMENT OF THE ARMY
WALTER REED ARMY INSTITUTE OF RESEARCH
503 ROBERT GRANT AVENUE
SILVER SPRING, MD 20910-7500

Visits and Compensation Table:

Purpose of the Visit	Study Day	Time Needed (Approximate)	Activity	Compensation* Non-military/ Non-federal Employee	Compensation Military/Civilian Employee Seen While On Duty
Screening visit	7 to 90 days before the 1st vaccination	2 hours	Explanation about the study, informed consent, medical history, review of concomitant medications, demographic information, physical exam including, pregnancy test for women, blood draw for lab work	$50	$50
First vaccine	Day 1	1 to 1.5 hours	Medical history since last visit including medications taken, physical, blood draw, pregnancy test for women, Review elimination criteria and eligibility Criteria, **vaccination #1**, 30 minute evaluation, memory aid and emergency contact card issued.	$200	$50
Follow-up	Day 4 (Day 3 post 1st Dose)	30 minutes	Medical history since last visit including medications taken, physical, review memory aid, evaluate injection site, monitor AEs/SAEs	$100	n/a
Follow-up	Day 15 (Day 14 post 1st Dose)	30 minutes	Medical history since last visit including medications taken, physical, review memory aid, evaluate injection site, monitor AEs/SAEs, blood draw	$130	$50
Second vaccine	Day 29	1 to 1.5 hours	Medical history since last visit including medications taken, physical, blood draw, pregnancy test for women, Review elimination criteria and eligibility Criteria, **vaccination #2**, 30 minute evaluation, memory aid issued	$200	$50
Follow-up	Day 32 (Day 3 post 2nd Dose)	30 minutes	Medical history since last visit including medications taken, physical, review memory aid, evaluate injection site, monitor AEs/SAEs	$100	n/a

Follow-up	Day 43 (Day 14 post 2nd Dose)	30 minutes	Medical history since last visit including medications taken, physical, review memory aid, evaluate injection site, monitor AEs/SAEs, blood draw	$130	$50
Third vaccine	Day 57	1 to 1.5 hours	Medical history since last visit including medications taken, physical, blood draw, pregnancy test for women, Review elimination criteria and eligibility Criteria, **vaccination #3**, 30 minute evaluation, memory aid issued	$200	$50
Follow-up	Day 60 (Day 3 post 3rd Dose)	30 minutes	Medical history since last visit including medications taken, physical, review memory aid, evaluate injection site, monitor AEs/SAEs	$100	n/a
Follow-up	Day 71 (Day 14 post 3rd Dose)	30 minutes	Medical history since last visit including medications taken, physical, review memory aid, evaluate injection site, monitor AEs/SAEs, blood draw	$130	$50
Follow-up	Day 85 (Day 1 month post 3rd Dose)	30 minutes	Medical history since last visit including medications taken, physical, evaluate injection site, monitor AEs/SAEs, blood draw	$130	$50
Fourth vaccine	Day 169	1 to 1.5 hours	Medical history since last visit including medications taken, physical, blood draw, pregnancy test for women, Review elimination criteria and eligibility Criteria, **vaccination #4**, 30 minute evaluation, memory aid issued	$200	$50
Follow-up	Day 183 (Day 14 post 4th Dose)	30 minutes	Medical history since last visit including medications taken, physical, review memory aid, evaluate injection site, monitor AEs/SAEs, blood draw	$130	$50
Follow-up	Day 197 (1 month post 4th Dose)	30 minutes	Medical history since last visit including medications taken, physical, evaluate injection site, monitor AEs/SAEs, blood draw	$130	$50
Final Visit Phone Call	Day 337 (6 months post 4th Dose)	10-30 minutes	Phone call to record serious adverse events (SAE) and medically attended adverse events (MAAEs)	$50	n/a

*Compensation applies to non-military/non-federal personnel. Active duty/federal employee will be compensated ($50) for visits in which a blood draw occurs unless the visit occur during off-duty or leave hours. If the visits occur during off-duty or leave hours, active duty/federal employee will be compensated the same as non-military/non-federal employee personnel.