UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

# RESEARCH CONSENT FORM

V6.0; 02 September 2021

**Protocol Title: A Phase 1, Randomized Trial to Assess the Safety, Reactogenicity, and Immunogenicity of a Combination HTNV and PUUV DNA Vaccine Candidate Administered by Electroporation**

**Study No.:** HP-00081472

**Principal Investigator:**

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**Sponsor:** The Surgeon General, Department of the Army

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This is a research study. This research study will include only people who volunteer to take part. Before you decide whether to take part, it is important for you to know why the research is being done, what it will involve, and what will be the possible risks to you. Ask us if there is anything that is not clear or if you would like more information. Please take your time to make your decision. Feel free to ask any questions before you agree to take part in the study and at any time.

## HANTAVIRUS BACKGROUND

Hantaviruses are distributed worldwide among various rodent host populations. Humans are infected with Hantaviruses by breathing in dry rodent urine or feces that contain the virus, or being bitten by an infected animal. Infection with Hantaviruses can result in a range of clinical presentations from asymptomatic to life threatening. Four of the Hantaviruses, Hantaan virus (HTNV), Dobrava virus, Seoul virus, and Puumala virus (PUUV) can cause possibly life-threatening hemorrhagic fever with renal syndrome (HFRS). People who get HFRS can have fever, low platelets, low blood pressure, and acute kidney damage. Up to 15% of people with HFRS can die from these infections, and full recovery in those who survive may take weeks to months. HTNV is found on the Korean peninsula. PUUV is located in Scandinavia. Neither of these Hantaviruses is circulating in the United States, but other viruses of the Hantavirus family can be found in areas like the Southwestern United States. The main treatment for Hantaviruses is supportive care (e.g., intravenous (IV) fluids, medications for low blood pressure, blood products) and medicines to reduce fever.

There is no treatment for these viruses and there are no approved vaccines against this family of viruses in the United States. The US military has interest in creating a vaccine against these

viruses. During the Korean War, up to 1,000 soldiers developed HFRS and 5%-10% of those died. From 2000 to 2009, US forces in Korea had 8 hospitalizations and 72 outpatient visits for Hantavirus infections. The risk posed by Hantaviruses to soldiers has prompted the US Army Medical Research and Development Command (USAMRDC) to develop a vaccine against several of the viruses that cause HFRS. In this study, we are examining a vaccine against the HTNV and PUUV in the Hantavirus family.

**HOW DOES A VACCINE WORK?**

Your body can fight off most germs (e.g., viruses and bacteria). Often it takes a while to be able to fight germs after you have been in contact with them. During that time, the germs can make you sick. A vaccine tricks your body into thinking that it has seen the germ already so your body is prepared to fight the germ if it is exposed to it.

**PURPOSE OF STUDY**

The purpose of this research study is to test an experimental Hantavirus vaccine at different doses and with different injection devices to see which group has the most volunteers that make antibodies (used by the body's immune system to identify and fight bacteria and viruses). We will also see how long antibodies last and get more information about the safety of the vaccine. The information may help us to make a Hantavirus vaccine that protects people from HTNV and PUUV. After each vaccination, we will look at how the immune system responds.

You are being asked to participate in this study because you are a healthy adult (18-49 years old) who has not had hantavirus in the past or participated in a different hantavirus-related clinical trial, although we will confirm this using laboratory tests for hantavirus antibodies in your blood.

The US Food and Drug Administration (FDA) have not approved this experimental vaccine for sale. However, the FDA is permitting its use for human research. Independent institutional review boards (IRBs) (special committees to protect the rights of people who are in research studies) approve the research study. This vaccine has been given to US citizens before at different doses.

This study will take place at the University of Maryland, Baltimore. Approximately 216 volunteers will be enrolled in this study. Of those 216 volunteers, approximately 82 volunteers will be eligible for vaccination and continued participation in this research study. You will be randomly assigned (like flipping a coin) to one of six groups depending on the time you are qualified for enrollment. You will be randomly assigned to the early pilot groups (2 and 4), the second pilot groups (5 and 6), or the remaining enrollment groups (1-6). Each group will have a vaccine to HTNV, PUUV, or both and at different doses. We are also interested in whether it is better to inject the experimental vaccine in the muscle (like a typical vaccine) or in the skin (like a tuberculosis test). The study will be about 8 months long. The experimental vaccine will be injected in your arm 3 times over a two (2) month period, and alternating arms will be used each time you visit. During your study participation, we will perform various follow-up visits, tests, and sample collection. Some of these samples will be used for studying immunity to Hantaviruses and some will be stored for future research.

**WHAT ARE THE INVESTIGATIONAL VACCINES AND HOW WILL THEY BE GIVEN?**

These experimental HTNV and PUUV vaccines were manufactured by Ajinomoto Althea, Inc., San Diego, California. They are DNA (deoxyribonucleic acid) vaccines. The object of DNA vaccination is to deliver DNA directly into your cells, which can then present parts of the virus to your immune system. Your immune system will develop a response to the virus that will protect you from getting the infection. However, we do not know the proper dose or whether it is best to give the vaccine in the skin or muscle in order to get the best immune response. These experimental vaccines do not contain live virus. You cannot get a Hantavirus infection from these experimental vaccines, but like with an injection site, it is possible to get an infection due to a break in the skin.

The HTNV and PUUV DNA vaccines will be administered using an investigational device called the TriGrid™ Delivery System supplied by Ichor Medical Systems, Inc. The device can deliver the vaccine within your muscle (intramuscular or IM) and it can deliver the vaccine within the skin (intradermally or ID). We will study the best device to decide how to design future vaccines. The device is manufactured by Ichor Medical Systems, Inc, San Diego, California.

**HOW AND WHEN WILL THE INVESTIGATIONAL VACCINES BE GIVEN?**

You will be randomly assigned to one of six study groups with 12 volunteers in each group. This means that the group you are in will be based on chance. There is no evidence that any study group is better than the other study groups at this time. Each group will receive three vaccinations.

- Group 1 will get 3 doses of HTNV vaccine at dose 0.6 mg within the skin (ID)
- Group 2* will get 3 doses of HTNV vaccine at dose 3.0 mg within the muscle (IM)
- Group 3 will get 3 doses of PUUV vaccine at dose 0.6 mg ID
- Group 4* will get 3 doses of PUUV vaccine at dose 3.0 mg IM
- Group 5* will get 3 doses of a combination of HTNV/PUUV vaccine at 0.6 mg of each for a total of 1.2 mg ID
- Group 6* will get 3 doses of a combination of HTNV/PUUV vaccine at 3.0 mg of each for a total of 6.0 mg IM

The experimental vaccine will be given as a shot in the upper arm muscle or skin.

*Groups 2, 4, 5 & 6 will each have a pilot group (2 volunteers in each) who will receive the first vaccination followed by a 48-hour observation period. This is the first time this precise combination has been given to humans although similar vaccinations have been given to humans before. If the shot is tolerated without any concerning safety problems, the remainder of the

group will proceed to vaccination. You will be allowed to volunteer to be part of the pilot group and will not be assigned into the pilot group without permission.

**WHAT ARE THE REQUIREMENTS TO BE IN THE STUDY?**

Investigators plan to include 82 healthy men and women in the study. If you would like to be in this study, we will examine the results of your blood sample tests, a physical exam, and answers to questions at the screening visit to determine if you qualify to participate.

To be in the study you must give your written informed consent (permission) before any exam or study procedure can be performed. You must be:

- Willing and able to complete the requirements of the protocol, such as filling out the memory aids and returning for follow-up visits
- Willing to sign the informed consent before screening
- Able to score at least 80% correct on a short multiple-choice quiz to show that you understand the study.
- Between 18 and 49 years of age (you have had your 18th birthday and have not had your 50th birthday) at the time of consent
- Healthy when you start the study
- Sexually active men* and women of childbearing potential** must be using an effective method of contraception from 30 days before the first study vaccination until 6 months after the last study vaccination.

  * A sexually active man is defined as one whose partner is a woman of childbearing potential (see definition below) and has not had a vasectomy performed > 1 year prior to screening. You must agree not to father a child until 6 months after the last vaccination. You must agree to use a barrier method of birth control (e.g., either condom with spermicidal foam/gel/film/cream or partner usage of occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository).

  **Women of childbearing potential are defined as those who have not been sterilized (e.g., tubal ligation, bilateral oophorectomy, bilateral salpingectomy, hysterectomy, or successful Essure® placement [permanent, non-surgical, non-hormonal sterilization]) with history of documented radiological confirmation test at least 90 days after the procedure and are still menstruating or less than 1 year of the last menses if perimenopausal. For this study, an effective contraceptive method is defined as one that results in a failure rate of less than 1% per year when it is used consistently and correctly.
- Women must be willing to agree not to donate eggs and men must agree to not donate sperm from the date of screening until at least 6 months after the last vaccination

- Negative hantavirus PsVNA test result at screening

If anything in the list below applies to you, you will not be able to be in the study:

- Have any history of HTNV or PUUV or Andes virus infection or vaccination in the past (we will screen your antibody results before starting)
- Have traveled to or plans to travel to an area with native Hantavirus within in 30 days of screening or at any time during the study
- Have history of severe reactions to vaccination or a history of severe allergic reactions. This includes a known allergy to an aminoglycoside (e.g., gentamicin, tobramycin, neomycin, and streptomycin).
- Currently participating in or plans to participate in another study involving any investigational item (including vaccines) or requires blood drawing, and/or anything invasive. A procedure requiring anesthesia or intravenous dyes or removal of tissue would exclude you from the study. This includes any scope of your lungs, esophagus, colon or stomach or administration of IV contrast.
- Receipt or planned receipt of any live vaccination, experimental or otherwise, within the period 30 days prior to or after each vaccination and receipt or planned receipt of an inactivated vaccination, experimental or otherwise, within the period of 14 days prior to or after each vaccination
- Have a skinfold measurement in the upper arms (deltoid area) larger than 40 mm or have too little muscle mass to safely receive the 1 inch/25 mm injection.
- Individuals who have a physical condition or barrier (like tattoos) that make it difficult to observe reactions to the injection in the upper arm (deltoid area).
- Have any abnormal blood counts, kidney tests, or liver tests
- Have any condition that the investigator thinks would make you unable to be in the study. This can include any chronic illnesses; autoimmune diseases; kidney, liver or heart diseases; psychiatric diagnoses (schizophrenia or bipolar disease) or any other condition in which the investigator thinks it's unsafe to participate
- Have an implanted device, such as cardiac demand pacemakers, automatic implantable cardiac defibrillator, nerve stimulators, or deep brain stimulators.
- Excessive drinking or the use of drugs within the past 5 years.
- Hospitalization for psychiatric illness, history of suicide attempt, or other confinement for danger to self or others within the past 10 years.
- Use of any drug that can lower your immune system defenses (the study doctor will ask you what drugs you are taking). This includes use of chemotherapy or radiation therapy for cancer in the past 3 years.

- Receipt of a blood transfusion or blood products 120 days prior to screening or planned during the study period
- Have donated blood to a blood bank within 56 days prior to screening and at any time during the study.
- Taking chronic (defined as more than 14 days) immunosuppressants or other immune-modifying drugs medicines that lower your immune system within 6 months of screening. For corticosteroids, this will mean prednisone, or similar steroids, greater than or equal to 5 mg/day. Intranasal, inhaled (less than 800 beclomethasone mcg/day), and topical steroids are allowed.
- Positive for hepatitis B, hepatitis C, or HIV
- Have had any neurological disorders (including Guillain-Barré syndrome), seizures, or epilepsy (excluding a single seizure caused by fever as a child)
- Any history of fainting spells in the past year
- Pregnant or lactating female, or plan to father a child or become pregnant during the study
- Any bleeding condition that prolongs bleeding time
- Any history of abnormal heart rhythms (like atrial fibrillation) or palpitations
- Any presence of surgical or metal implants at the site of injection
- Any history of diabetes type 1 or 2
- A current employee or staff paid by the contract for this study, or staff who are supervised by the study doctors
- In the opinion of the investigator is not likely to comply with the visits

Some temporary reasons to delay vaccination include

- Evidence of a fever or illness within 48 hours of the study vaccination
- Use of any antibiotics within 24 hours of vaccination or use of any antiviral medication within 72 hours of vaccination
- Use of allergy shot treatments within 30 days of the first vaccination

Throughout the study, you should make sure to look at this list above and do not do or take anything that would affect your ability to stay in the study to the best of your ability.

You should not take any medicines without first telling the study staff. Some drugs may interfere with the study. Examples of medications that may interfere are prednisone (oral steroid medication), allergy shots, or certain arthritis medications (like methotrexate). Your study doctor can help determine if that drug is OK to use or can suggest an alternative medicine if one is available. However, if your family doctor feels a medicine is needed urgently, you should not

delay your treatment, but you must let the study doctor or nurse know what you are taking as soon as possible. Acetaminophen (Tylenol) can be taken for headaches or fevers if necessary, but you should record the medication on your memory aid and tell your study doctor that you took this at your next visit.

## WHAT PROCEDURES OCCUR DURING THE STUDY?

Here is a summary of the activities that will happen during the study and the amount of time these activities will take.

- **Screening Visit(s)** (Approximately 2 hours, can occur over 2 visits)
    - Review and sign the informed consent form.
    - **10-question Quiz** – An 80% or higher score is required to participate in the study. If you do not score high enough, we will review the study with you, and you will be offered to take the same quiz a second time. If you do not score 80% or higher on the second attempt, you will not be eligible for the study.
    - **Review of Inclusion/Exclusion Criteria** – A review of the inclusion/exclusion criteria will be performed prior to study procedures to determine if you are eligible to participate in the study.
    - **Medical History** – We will ask you questions about any past or present illnesses, previous allergic reactions, travel history, history of spleen removal, etc. We will take additional information to see if you have any risk factors for heart disease.
    - **Blood Draw** – About 7 teaspoons (33 mL) of your blood will be collected from a vein in your arm to measure your blood counts, liver and kidney function, hepatitis, and HIV infection. You will be asked to sign a separate consent form for the HIV blood test. If a positive test for HIV, hepatitis or Hantavirus is found, you will not be able to be in the study and the information will be reported to the Public Health Department as is required by the State of Maryland. We will alert you of any abnormalities and we will also help you find a doctor if you do not already have a provider. If your screening laboratories are normal, we will then collect about 2 teaspoons (10 mL) of your blood to see if you had prior exposure to Hantavirus. If your first experimental vaccination occurs more than 56 days after your first set of screening labs, we may repeat them by drawing about 5 teaspoons (24.5 mL) of your blood to re-evaluate your blood counts, liver and kidney function.
    - **Pregnancy Test** – If you are a woman able to have children, your blood will be collected for a pregnancy test at screening. A sample of your urine will be tested on the days of vaccination. If you are pregnant, you will not be able to take part in the study.
    - **Physical Exam** – We will measure your vital signs including temperature, heart rate, breathing rate, blood pressure, and weight. You will have a brief physical exam to make sure you are healthy. A skinfold measurement of your upper arm will be done to determine potential injection sites.

- **Electrocardiogram** – You will have an electrocardiogram (ECG) to determine any irregular heart conditions. An ECG is a tracing of your heart's electrical activity used to look at the pattern of your heartbeat, and it can detect things that may not be normal with your heart. You will have small wires attached to your body (using small sticky patches in several places). This procedure takes about 15 minutes to complete.

- **Vaccination Visits** (three visits, approximately 1-2 hours each)

  After screening, if you are able to be in the study, you will come to the study site for three vaccination visits, eight follow-up visits and one final visit, for a total of 11 on-study visits over a 5-month period (See Table 1).

  - **Cheek Swab** – a swab to the inner part of your cheek will be collected to help us learn how a volunteer's genes affect how they make antibodies after getting vaccine. This is only done once, at the first experimental vaccine-dosing visit.

  All volunteers in each group will receive a total of 3 shots of the experimental vaccine in the upper arm muscle or skin depending on the group you are assigned: one shot will be given at each of these study time points, alternating arms for the time points: Day 0 (first day), Month 1 (Visit 4), and Month 2 (Visit 7). Study visits involving injections are expected to take 2 hours. Other on-study visits will take approximately 30 minutes.

  - **Interim Health Assessment** – We will check that you are healthy on the days you receive the experimental vaccine, and ask about any changes since the last visit. We will ask about any medications including antibiotics. We will measure your vital signs including temperature, heart rate, breathing rate, blood pressure before and after injections. A doctor may do a targeted physical examination if needed. Your weight and a skinfold measurement of the potential injection sites will be taken.
  - **Review of Inclusion/Exclusion Criteria** – A review of the inclusion/exclusion criteria will be performed prior to study procedures to determine if you are still eligible to participate in the study.
  - **Blood Collection** – About 5 teaspoons (22.5 mL) of your blood will be collected on the day of the injection. We will use your blood to measure your blood counts, liver, and kidney function for safety of the experimental vaccine and to test if you are responding to the vaccine.
  - **Pregnancy Test** – If you are woman able to have children, a sample of your urine will be collected for a pregnancy test. If you are pregnant, you will not be able to participate in this study.
  - **Memory Aid** – You will be given a memory aid (printed card) and asked to write down your temperature once a day and any symptoms you have for 2 weeks following the experimental vaccination. You will be asked to write down any signs or symptoms (possible side effects) that you see for the first time during the

study or, if a disease or condition you had before the study appears to worsen during the study. You should also write down any medicines, including over-the-counter drugs, herbals, vitamins or supplements, you take during this time. The study staff will explain the memory aid to you in detail on your first vaccination. You will be provided a thermometer for taking your temperature and ruler for measuring site reactions

- **Additional Reminders** – If at any time during the study, you experience any signs or symptoms you think could be serious, you should call the study center for the study doctor and seek immediate medical attention.

- **Post-vaccination Follow-up Visits** (six visits, approximately 15-30 minutes each)

  Six post-vaccination visits occur 2 and 14 days after each vaccination (Visits 2, 3, 5, 6, 8, and 9) as seen in Table 1.

  - **Interim Health Assessment, Physical Exam, and Memory Aid Review** – We will review your health and medication history since your most recent study visit. Vital signs will be performed at each visit. We will review your memory aid for temperature, signs and symptoms experienced following vaccination. A targeted physical exam may be performed if you have any signs or symptoms that have occurred since your last visit.
  - **Review of Inclusion/Exclusion Criteria**
  - **Blood Draw** – Your blood samples will be collected on Visits 3, 6, and 9 to test for safety of the experimental vaccine and to test if you are responding to the vaccine. The amount of your blood collected at each visit will be about 3 teaspoons (12.5 mL).
  - **Symptoms** – Following administration of the experimental vaccine and completion of the memory aid, we will continue to ask you for any signs or symptoms that have occurred since your last visit.

**Table 1. Schedule of Events**

| **Visit # Study Procedure** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Day 0 vaccine given** | **Day 2 after shot** | **Day 14 after shot** | **Day 28 vaccine given** | **Day 2 after shot** | **Day 14 after shot** | **Day 56 vaccine given** | **Day 2 after shot** | **Day 14 after shot** | **Day 84** | **Day 140** | **Day 220 Phone call** |
| **History, I/E*, and Physical Exam (as needed)** | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| **Pregnancy Test as Needed** | ● | | | ● | | | ● | | | | ● | |
| **Blood Sample** | ● ~5 tsp. | | ● ~3 tsp. | ● ~5 tsp. | | ● ~3 tsp. | ● ~5 tsp. | | ● ~3 tsp. | ● ~14 tsp | ● ~4 tsp | |
| **Buccal Swab -HLA** | ● | | | | | | | | | | | |
| **Shot** | 1 | | | 2 | | | 3 | | | | | |
| **Review Memory Aid Information** | | ● | ● | | ● | ● | | ● | ● | | | |
| **Collect 14-day Memory Aid Information** | | | ● | | | ● | | | ● | | | |

*I/E – Inclusion/Exclusion Criteria

- **Follow-up Visit/Conclusion Visit** (two visits, approximately 15-30 minutes)
  Visit will occur at Month 1 (Visit 10) and Month 3Visit 11 following the last vaccination (3).
    - **Interim Health Assessment and Physical Exam** – We will review your health and medication history since the last visit. Vital signs will be performed daily and a targeted physical exam may be performed if you have any signs or symptoms that have occurred since your last visit.
    - **Review of Inclusion/Exclusion Criteria**

      **Blood Draw** – Month 3 (Visit 10) after the final vaccination (3) to test for vaccine safety, how well the vaccine is working and collect blood for future research. The amount of blood collected from you at this visit will be approximately 14 teaspoons (72.5 mL). At Month 5 (Visit 11), about 4 teaspoons (23.5mL) will be collected for safety and to determine how well the vaccine is working.
    - **Electrocardiogram** – An ECG will be performed to determine any irregular heart conditions.
    - **Pregnancy Test** – If you are a woman able to have children, a blood sample will be collected for a pregnancy test.
- **Final Telephone Contact Visit** (one telephone call). Visit will occur at Month 6 Visit 12 following the last vaccination.
    - **Final Health Assessment** -We will review your health and medication history since the last visit.
- **Unscheduled Events**
    - If it is not an emergency, call a study nurse or doctor (contact information on page 1) before starting any new medications or getting any vaccines or shots of any type, including those recommended by your doctor, while in this study.

## GENETIC TESTING

Some of your blood and the cheek swab may be used for genetic research tests to help us understand how this experimental vaccine works. Genetic tests done in a research laboratory from your stored samples are not used for health care purposes. The samples will not be labeled with your name or other personal identifying information when sent to the research laboratory. The results will not be in your medical record.

HLA type is a genetic test of markers in the immune system that is sometimes used in medical practice, such as to match organ transplants. In this study, any HLA test will be done in research laboratories only. The HLA test from this study will not be used for health care purposes and will not be put into your medical record.



Genetics is a fast moving field where the technology is evolving. If we proceed with detailed genetic analysis, we will look for genes associated with responses to the experimental vaccine. If your genome (all of your genes) is sequenced, "misspellings" (gene variants) may be found. These are called "incidental" findings. We will not routinely tell you about the incidental findings from genetics tests.

You should not expect the genetic research tests to give you any health information or to be part of your standard medical care. In rare cases, if an incidental finding from a genetic test is clearly important to your health based on well-established and valid criteria, the study clinician will attempt to contact you. This type of finding is very uncommon. Since the research may be done after the study is complete, you should let the study team know how to contact you in the future.

Any genetic information collected will be confidential. Researchers with access to your genetic information will take measures to maintain the confidentiality of your genetic information.

Genetic test results will not be released to you or anyone else (such as family members, primary care doctors, insurers, or employers), unless we are required to do so by law.

In addition, you should know that a new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.

- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

- All health insurance companies and group health plans and all employers with 15 or more employees must follow this law.

**Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.**

## WHAT WILL YOU DO WITH MY BLOOD SAMPLES AT THE END OF THE STUDY?

After tests are done on your blood, we would like your permission to keep any remaining blood indefinitely to use in possible future research studies. These studies may test for antibodies against Hantaviruses and/or other infectious diseases. Specimens will not be used to generate a cell line for genetic testing. The samples will not be sold or used directly for the reproduction of commercial products.

The risks of storing your samples for use in possible future research studies or having them used in future research studies are those associated with possible loss of confidentiality. Your samples will be labeled only by a code—your study volunteer number—and will not be labeled with your

name or other personal identifying information. The samples will be stored at a repository at the United States Army Medical Research Institute of Infectious Disease and may be shared with investigators at this institution and with other investigators at other institutions. Electronic files associated with these coded samples will be password protected. Only people who are involved in the conduct, oversight, or auditing of this study will be allowed access.

If these stored samples are tested in the future, the results may be published. Such publication will not contain any information about you that would enable someone to determine your identity. The results of any future testing will be kept confidential in the same way as the results of testing done for this study. Results from this future research would not be reported to you or your doctor or placed in your medical record.

Although the results from this future research, including your donated samples, may be patentable or have commercial value, you will have no legal or financial interest in any commercial development resulting from the research.

Storing your samples for use in possible future research studies or having them used in future research studies may not benefit you directly.

Below, please initial your decision about permission for future research with your samples:

_____YES. Date _____ You may store my unused, encoded, de-identified samples for an indefinite period of time for future research as described above.

_____NO, Date _____ You may NOT store my unused, encoded, de-identified samples for an indefinite period of time for future research as described above.

**WHAT ARE MY RESPONSIBILITIES IF I TAKE PART IN THIS RESEARCH?**

If you take part in this research, you will be responsible for doing the following:

- Come to all of your study visits as scheduled
- Complete a memory aid by recording any reactions you experience after you receive each experimental vaccine.
- Contact the study staff or doctor if you have severe symptoms (not feeling well), or are hospitalized, or feel concerned about symptoms, or if you start new medications or receive any vaccines recommended by your physician
- If you are sexually active and able to have children (i.e., not sterilized, post-menopausal, or in same sex relationship), you must avoid pregnancy by agreeing to use an effective means of birth control during the entire study. Refer to the section Potential Risks/Discomforts, Pregnancy in this consent form.

- Avoid breastfeeding
- Avoid participating in another clinical trial with an investigational agent until study completion.



**POTENTIAL RISKS/DISCOMFORTS**

If you decide to participate in this study, you should carefully consider the risks. We will share any information about new risks that arise during the course of the study.

- **Risks of Blood Drawing**

Blood will be drawn from a vein in your arm using a needle. Blood drawing may cause pain and bruising and, rarely, infection at the place where the blood is taken. Sometimes drawing blood causes people to feel lightheaded or even faint. It is possible to get an infection from having blood taken. This is not very likely. To reduce the risk of infection, the area where the blood will be drawn will be cleaned using aseptic technique. Sterile equipment will be used.

- **ECG**

You will have an ECG performed to evaluate for cardiac problems. If you have an allergy to adhesive, you may experience mild redness and irritation. In order to achieve a good reading, it may be necessary to shave a small portion of your skin to allow the adhesive to stick.

- **Local Reactions**

Local reactions in previous studies have included pain, stinging, itching, bruising, redness and scab formation at the injection site.

In the study that used the Ichor injection device, brief, but intense, muscle contractions and associated local pain/discomfort during the period of vaccine administration were observed. Additional symptoms associated with the vaccination included minor bleeding at the sites of electrode and needle site, and mild to moderate injection site soreness/bruising lasting for 24 to 72 hours, but in some instances, up to 7 days post administration.

- **Systemic Reactions**

The systemic reactions that have been reported in previous studies using the experimental vaccines or injection devices included fever, fatigue, headache, muscle aches, enlarged lymph nodes, underarm pain, fast breathing and light headedness/dizziness. Fainting, with a duration of 30-60 seconds has been observed in three subjects. Monitoring for these and other systemic symptoms commonly seen in investigational vaccine studies (e.g., fever, chills, rash, nausea, and allergic reaction) will be performed throughout the study.

Two other potential risks from the use of DNA vaccines in this study include infection and integration of the vaccine DNA into that of the test volunteer. The HTNV and PUUV DNA vaccines do not contain live virus and are, therefore, not able to cause infection by these Hantaviruses. The FDA reviewed safety information with similar DNA designs and decided that there was very little risk that your immune system would produce antibodies to the DNA portion of the vaccine itself.



- **Pregnancy**

Risks to unborn babies are unknown at this time; pregnant females will be excluded from this study. All female volunteers of childbearing potential must be abstinent or utilize adequate contraceptive precautions (e.g., intrauterine contraceptive device, oral contraceptives, diaphragm, or condom in combination with contraceptive jelly, cream, or foam; Norplant® or Depo-Provera®) from 30 days prior to the first study vaccination through 6 months after the last injection to minimize any potential risk. Non-childbearing potential is defined as either surgically sterilized or 1 year post-menopausal (defined as 12 consecutive months without menses). Study volunteers (or their female partners) should not become pregnant for at least 6 months after the last study vaccination. Similarly, any pregnancies in the partners of male volunteers should be avoided. In the unlikely event that you (or your partner) do become pregnant, we will halt future experimental vaccinations (if you are pregnant) and will follow you (or your partner) for safety for the duration of the pregnancy until 30 days after delivery to assess any potential harm to the fetus. Any evidence of harm to the fetus will be reported.

Risks to nursing infants are unknown at this time; breastfeeding females will be excluded from this study. Lactating females will be excluded from the study and for 6 months after the last dose of study vaccination.

- **Allergic Reaction**

As with any experimental product and no matter what precautions are taken, there is always the risk of a serious, or even life-threatening, allergic reaction. To reduce this risk, if you have a history of severe allergic reaction of any kind, or significant allergic reaction DNA vaccines or normal saline you should not participate in this study. There are no egg-based parts to this vaccine. The University of Maryland Center for Vaccine Development has equipment to handle an emergency. Allergic emergencies include swelling of the throat, wheezing, and difficulty breathing.

- **Guillain-Barré Syndrome**

Guillain-Barré syndrome (GBS) is an illness in which your body's immune system attacks your nerves. It afflicts only about one person in 100,000, and vaccinations very rarely increase the risk of GBS. The first symptoms of this illness include weakness or tingling sensations in the legs. These symptoms can worsen until certain muscles cannot be used at all. Most individuals recover from even the most severe cases of GBS, although some continue to have some weakness (refer to National Institutes of Health, National Institute of Neurological Disorders and Stroke. Guillain-Barré Syndrome Fact Sheet: http://www.ninds.nih.gov/disorders/gbs/detail_gbs.htm). To reduce this risk, anyone with a history of GBS, other neurologic diseases per the physician investigator's discretion, or other significant reaction to vaccination should not participate in this study.

- **Risks Associated with the Device**

**TDS-ID Administration Device:** In previous clinical evaluation, the use of the TDS-ID administration device has been associated with acute pain/discomfort at the site of electric field application in most volunteers. Minor cutaneous bleeding at the sites of electrode or injection needle penetration has been frequently observed following device removal. Injection site reactions including redness, swelling, bruising, localized skin color changes, dark scab or localized soreness at the injection site lasting for 24-72 hours after administration is common. Dizziness/lightheadedness and, in rare cases, syncope, have been reported in volunteers receiving intramuscular injections with the TDS technology and may be observed following TDS-ID procedure administration.

**TDS-IM V1.0 Administration Device:** Over 1100 people have received vaccinations by the TDS-IM device. In previous clinical evaluation, the use of the TDS-IM administration device has been associated with discomfort or pain at the time of electroporation application, which feels like a "punch" or "cramp" in the muscle lasting for less than a second. Rarely, volunteers have reported a mild tingling sensation or numbness immediately after injection in the injected arm or fingers lasting for a few seconds up to several minutes after administration. Bleeding at the sites of the four electrodes has been found to be similar to that of a normal (needle and syringe) injection and resolved quickly. Occasionally a small hematoma (blood collection) remains. Mild to moderate bruising and/or the formation of small scabs or small amounts of swelling is possible. Itching, redness, and muscle soreness related to use of the device has been rated "mild" to "moderate" and may last for 24-72 hours, but has been observed for up to 7 days. Sometimes volunteers have reported tingling and numbness in the arm hand or fingers where the IM device was used. This may be difficult to distinguish between that caused by the vaccine product or device use. On rare occasions, volunteers have become dizzy or lightheaded after administration. In three cases, this caused the volunteer to become faint for ~30 seconds. In two of the three cases where the subjects became faint, the subjects also had seizure like muscle movements which are known to be associated with fainting spells. . In all cases the volunteers recovered with no residual effects. If the injection depth for the device is set too deeply, it is possible that the needle or



electrodes could contact the volunteer's bone, which could result in pain at the injection site and/or deformation of the electrodes and/or injection needle with increased difficulty in device withdrawal. On one occasion during vaccination in the early phase of this study, it was noted that the needle came in contact with the volunteer's outer bone, which made it difficult when the vaccinator attempted to withdraw the device. No vaccine was delivered. This was believed to be due to an improper calculation of the thickness of the skin. Every effort will be made to proper calculate your skin thickness (see also Risks Associated with the Device, below).

The TDS-IM device also carries a theoretical risk that excessive energy could be delivered to the local tissues of the volunteer, resulting in more pronounced local site reactions than have been observed to date. However, the TDS-IM Pulse Stimulator incorporates multiple redundant mitigations to prevent this hazard, including performance of a pre-pulse safety check, the use of multiple circuits that monitor total energy delivered, and which will terminate energy delivery. There have been no occurrences of excessive energy delivery in any of the nonclinical and clinical studies conducted with the pulse stimulator to date.

- **Unknown Risks**

Furthermore, as with all research there is the rare possibility of risks that are unknown or that cannot be foreseen based on available information. The long-term effects on EP delivery of DNA is not known.

## POTENTIAL BENEFITS

You will not benefit directly from your participation in this study. We will closely monitor you and provide medical care for study-related issues during the active follow-up surveillance period. Medical issues not related to the study will be referred to your Primary Care Provider.

## ALTERNATIVES TO PARTICIPATION

This is not a treatment study. Your alternative is to not take part. If you choose not to take part, your health care at University of Maryland, Baltimore will not be affected. If you choose to exit the study early, we will follow up to analyze your safety.

## COSTS TO VOLUNTEERS

It will not cost you anything to take part in this study. You are responsible for transportation to and from the University of Maryland Center for Vaccine Development for all study visits. We will also provide you with parking vouchers or bus tokens, if appropriate. You will not have to pay for study visits, physical examinations, blood tests, or study-related procedures.

## PAYMENT TO VOLUNTEERS

Payment will be provided to compensate you for your time and inconvenience in the form of checks, as described in Table 2. Transportation reimbursement will also be provided. You will be responsible for reporting this income to the Internal Revenue Service (IRS).

**Table 2. Payment Schedule**

| | Reimbursement per visit | Number of Visits | Specific Study Days |
|---|---|---|---|
| Screening visit | $75 | 2 | |
| Vaccination visit | $150 | 3 | Days 0, 28, 56 |
| Follow-up visit | $75 | 8 | Days 2, 14, 30, 42, 58, 70, 84,140 |
| Return of Memory Aid | $50 | 3 | Days 14, 42, 70 |
| Final Telephone visit | $10 | 1 | Day 220 |
| Completion Bonus | $200 | 1 | Day 220 |

| | | |
|---|---|---|
| Screening Visit(s): | $75 | (2: Screening visits) |
| Vaccination(s): | $150 | (3: Days 0, 28, 56) |
| Follow-up Visits: | $75 | (8: Days 2, 14, 30, 42, 58, 70, 84 and 140) |
| Return of Memory Aid: | $50 | (3: Days 14, 42, 70) |
| Final Telephone visit | $10 | (1: Day 220) |
| Completion Bonus: | $200 | (1: Day 220) |

If every visit is completed, then the compensation for the different schedules is $1360. In addition, if you fulfill all study duties, you will receive a $200 bonus for a total compensation of $1560.

If you are injured because of research study participation, you will receive emergency medical care if needed and you will receive assistance in getting other medical care as needed. You or your insurance carrier will be billed for the cost of the care, just as you would be billed for any other medical care. If you incur uninsured medical costs, they are your responsibility. The research staff can give you more information about this if you have a study injury. In general, the NIH or the Federal Government will provide no long-term medical care or financial compensation for research-related injuries.

## CONFIDENTIALITY AND ACCESS TO RECORDS

It is very important to us that your personal and medical information stay confidential and secure. We will protect your information in accordance with the law. There are some instances where we cannot guarantee complete confidentiality, because information about your health may need to be reported to medical authorities to ensure your safety during the study.

We are required to report information regarding certain infectious diseases (like HIV and 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 state health department, and they may need to interview you to get more information.

When you sign this consent form you agree that we can use your personal and medical information as described in this form.

Efforts will be made to limit your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the National Institutes of Health (the study funder); The Geneva Foundation (the study contractor); USAMRDC (the study sponsor); the University of Maryland Baltimore Human Research

Protections Office; the University of Maryland CVD study staff; and regulatory authorities, such as the FDA, to make sure that the study is being run properly and to ensure your protection throughout the study.

Researchers at this study site can use information that identifies you (such as name and address) only for the purpose of the study.

Study information will be labeled with a code number (for example, 1234). It will not include your name or address. Only certain members of the study team have the link between your name and the code number. The sponsor may use this coded study information and:

- keep it electronically, and analyze it by computer to find out what the study is telling us,
- share it with regulatory agencies that approve new vaccines and medicines,
- share it with people who check that the study is done properly (such as the independent ethics committee or review boards),
- combine it with results from other studies to learn more about the vaccine and Hantavirus. This may help us to assess the risks and benefits of other vaccines or medicines, or to improve disease understanding,
- publish study results in medical journals, for meetings, and on the internet for other researchers to use.
- share coded information with other companies, organizations or universities to carry out research.
- use it to improve the quality and efficiency in conducting clinical research trials in general. Create a dataset in which the link between you and your information is removed (anonymized). This anonymized data may be used by independent researchers (such as other companies, organizations, or universities) to understand other (non-study) medicines/vaccines and other conditions/diseases.

Volunteer Registry Data Sheet: The USAMRDC requires that data sheets (Volunteer Registry Data Sheet, Form 60-R) be completed for entry into this Command's Volunteer Registry Data Base for all individuals participating in this research trial. This information includes the volunteer's name, address, Social Security Number, study identity, and dates of participation. The intent of this database is twofold: first, to readily answer questions about an individual's participation in research sponsored by the USAMRDC; and second, to ensure that USAMRDC can exercise its obligation to ensure that all research study volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. This information will be stored at USAMRDC for a minimum of 75 years and is kept confidential. The Volunteer Registry Data Base is a separate form and is not linked to the study database.



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.

Data from the study may be published. However, you will not be identified by name. People designated from the institutions where the study is being conducted and people from the sponsor will be allowed to inspect sections of your medical and research records related to the study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law.

In some circumstances, you may not be able to access your study information while the study is ongoing. However, the study doctor will share any important medical information if it is relevant to your health during the course of the study.

If you withdraw your consent for us to use your personal information, you will no longer be able to continue in the study. At any time, you may ask to see your personal information and correct it if necessary.

## CERTIFICATE OF CONFIDENTIALITY

To help us protect your privacy, we have received a Certificate of Confidentiality from the NIH. The certificate says that the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this certificate cannot be disclosed to anyone else who is not connected with the research unless:

- There is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);
- You have consented to the disclosure, including for your medical treatment; or
- The research information is used for other scientific research, as allowed by federal regulations protecting research volunteers.

As noted above, disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the FDA.

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

## RIGHT TO STOP VACCINATIONS OR WITHDRAW

Your participation in this study is voluntary. You do not have to take part in this research. You are free to withdraw your consent or stop your experimental vaccinations at any time. Refusal



to take part or to stop taking part in the study will involve no penalty or loss of benefits to which you are otherwise entitled. If you decide to stop taking part, or if you have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the investigator Kirsten E. Lyke, M.D., or the CVD Recruiting office (Telephone: 410-706-6156 Day; 202-236-2948 evenings).

If you stop your vaccinations or withdraw from this research, there will be no adverse consequences (physical, social, economic, legal, or psychological). If you wish to withdraw from this research, you may do so in writing to Dr. Kirsten E. Lyke.

If you stop your experimental vaccinations or withdraw from this study, already collected data may not be removed from the study database. You will be asked whether the investigator can collect data from your routine medical care. If you agree, these data will be handled the same as research data.

You will be told of any significant new findings that develop during the study that may affect your willingness to participate in the study.

If you are an employee or student, your employment status or academic standing at UMB will not be affected by your participation or non-participation in this study.

**CAN I BE REMOVED FROM THE RESEARCH?**

The study doctor or the sponsor can remove you from the research study without your approval. Possible reasons for removal include if the study doctor thinks your health has changed and the research is no longer safe, or because you do not follow the directions of the research staff. The sponsor can also end the research study early. The study doctor will tell you about this and you will have the chance to ask questions if this were to happen. In addition, the study safety monitors and study review boards at the University of Maryland or NIH, or the Food and Drug Administration may stop the study at any time.

**UNIVERSITY STATEMENT CONCERNING RESEARCH RISKS**

The University of Maryland, Baltimore (UMB) is committed to providing volunteers in its research the rights due them under state and federal law. You give up none of your legal rights by signing this consent form or by participating in the research project. This research has been reviewed and approved by the Institutional Review Board (IRB). Please call the IRB if you have questions about your rights as a research subject.

Participating in research may result in an injury, as explained above. If you suffer an injury directly related to your participation in this project, UMB and/or one of its affiliated institutions or health care groups will help you obtain medical treatment for the specific injury and provide referrals to other health care facilities, as appropriate. UMB and/or its affiliated institutions or health care groups will not provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury. The institution or group providing medical treatment will charge your insurance carrier, you, or any other party responsible for your treatment costs. If you incur



uninsured medical costs, they are your responsibility. The study staff can give you more information about this if you have a study injury.

By signing this Consent Form, you are not giving up any legal rights. If this research project is conducted in a negligent manner and you are injured as a direct result, you may be able to recover the costs of care and other damages from the individuals or organizations responsible for your injury.

If you have questions, concerns, complaints, or believe you have been harmed through participation in this research study as a result of researcher negligence, you can contact members of the IRB or the Human Research Protections Office (HRPO) to ask questions, discuss problems or concerns, obtain information, or offer input about your rights as a research participant. The contact information for the IRB and the HRPO is:

University of Maryland Baltimore
Human Research Protections Office
620 W. Lexington Street, Second Floor
Baltimore, MD 21201; Telephone 410-706-5037

Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

If you agree to participate in this study, please sign your name below.

| | |
|---|---|
| _____ | __HTNV-_____ |
| Participant's Printed Name | Participant's Volunteer ID # |
| _____ | _____ |
| Participant's Signature | Date |
| _____ | _____ _____:_____ |
| Investigator or Designee Obtaining Consent Signature | Date Time (24 hr) |