Title: Immunogenicity of a Two vs Three dose, Intradermal (ID) vs Intramuscular (IM) Administration of a Licensed Rabies Vaccine for Pre-Exposure Vaccination

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SUNY Upstate Medical University

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Consent / Authorization Form

Background/Purpose:

You are being asked to participate in a research study to help evaluate an investigational dosing schedule and route of administration for a Rabies vaccine, called RabAvert®, because you are a healthy individual between 18 and 60 years of age. This research study is being funded by the US Department of Defense, Walter Reed Army Institute for Research.

Research studies include only those subjects who choose to take part. Please take your time to make your decision. Please ask the study doctor or the study staff to explain any words or information that you do not understand. You may also want to discuss it with your friends and family.

The RabAvert® rabies vaccine is approved by the US Food and Drug Administration (FDA). The standard (approved) way to give this vaccine for the prevention of rabies is 3 doses given as an injection into the muscle. In this study we will use the FDA approved vaccine; however, we are testing a different dosing schedule and different route of administration; which is considered investigational.

We will compare two things:

1) A two dose schedule (investigational) versus a three dose schedule (standard) of vaccine.
2) Injection of the vaccine just under the skin (investigational) compared to injection of the vaccine into a muscle (standard).

We plan to enroll 60 subjects in the study. Subjects will be randomly assigned by chance to one of the six study groups shown below. You will be told to which group you have been assigned.

Vaccine Group	Day				Number of subjects per Group
	0	7	21	365	
1	IM	IM	IM	IM	12
2	ID	ID	ID	IM	12
3	IM	IM		IM	12
4	ID	ID		IM	12
5 (control)	IM				6
6 (control)	ID				6

IM = intramuscular ID = Intradermal

Study Procedures:

The study will last for 13 months and will include 3-12 visits to the Clinical Research Unit (located on the Upstate campus) depending on what group you are in.

At the first visit you will be evaluated by the study team to see if you are eligible for the study. This is called the screening visit and will include a medical evaluation. To be eligible you must:

- Be at least 18 years old and no more than 60 years old
- Be in good health, as determined by medical history, and physical examination.
- If you are a female of child-bearing potential, you must have a negative urine pregnancy test result and be willing to use oral, implantable, transdermal or injectable contraceptives or another reliable method of contraception, approved by the study doctor, for the duration of the study and for 30 days after your last vaccination.
    - The study doctor or study staff will tell you if the pregnancy test results are positive.
    - The results of pregnancy testing must be negative in order for you to be in the study
- Be able to give your informed consent
- Come to the study center for all visits with the study doctor

If you are eligible and want to continue to participate in the study, you will be randomly assigned to one of the six study groups. Your chance of being assigned to any group is two times higher for groups 1 to 4 then groups 5 or 6. The six study groups are:

- Group 1 which will receive **four doses of vaccine on day 0, day 7, 21 and day 365**. The vaccine will be administered **intramuscularly (into the muscle) by needle and syringe**. There will be 12 subjects in this group.
- Group 2 which will receive **four doses of vaccine on day 0, day 7, 21 and day 365.** The vaccine will be administered **intradermaly (under the skin) by needle and syringe on days**

0, 7 and 21. The dose on day 365 will be administered intramuscularly by needle and syringe. There will be 12 subjects in this group.

- Group 3 will receive **three doses of vaccine, on day 0, 7 and day 365.** They will be administered **intramuscularly by needle and syringe**. There will be 12 subjects in this group.
- Group 4 will receive **three doses of vaccine on day 0, 7 and day 365**. They will be administered **intradermaly by needle and syringe on days 0 and 7. The dose on day 365 will be administered intramuscularly by needle and syringe.** There will be 12 subjects in this group.
- Group 5 will receive **one dose of human serum albumin on day 0**. It will be administered **intramuscularly by needle and syringe on day 0.** There will be 6 subjects in this group.
- Group 6 will receive **one dose of human serum albumin on day 0**. It will be administered **intradermaly by needle and syringe on day 0.** There will be 6 subjects in this group.

You will need to stay at the study site for about 30 minutes after vaccination; these visits will be about one hour.

You will be asked to come back at regular intervals for follow up visits and blood draws. Most of these follow up visits will take 30 minutes. You will be provided with a schedule of the remaining visits at your Day 0 vaccination.

Follow up blood draws will be between 3ml and 98 mls of blood (max amount: about 6 1/2 tablespoons).

A further description of the tests/procedures that will be done while in the study (after screening) is explained below:

- Physical examination based on your signs and symptoms of any illness,
- Vital signs (temperature, heart rate, pulse and respiratory rate),
- Urine test for pregnancy at each vaccination visit (females of child bearing potential only),
- Blood test for presence of vaccine components,
- Blood test for the presence of innate immune responses. Innate immune responses are the first defense to fight infections caused by pathogens. Innate immune responses provide an immediate but non-specific response. Innate immunity occurs naturally as a result of a person's genetic constitution or physiology, and does not require previous exposure to the pathogen or vaccination,
- Blood test for the presence of cellular immune responses.

- Cell-mediated immunity is an immune response that does not involve antibodies but rather involves the activation of specific cells in response to a foreign antigen. These cells will recognize and kill infected cells, thereby providing protection from spread of infection,
- Assessment of any adverse experiences (side effects) and changes in medications you are taking.

The total volume of blood drawn for the entire study will be approximately 9-604 mls, depending on your assigned group. For comparison, when people volunteer to donate blood, the volume is about 250-450 ml at one time. Most of your samples will be used for tests described above. We will also be looking at how differences in each person's immune system may affect their response to the vaccine. To do this we will be looking at your HLA type. HLA means human leukocyte antigen. Your HLA type is defined by a group of genes that are important elements for immune function. This is considered a type of genetic testing.

While this testing will reveal genetic information about you, the only genetic information we are looking for is the genetic information that affects your immune response to the vaccine. You may have heard of genetic testing that is used in determining biologic parents or a person's ability to get or keep medical and/or life insurance. We will not be collecting or storing this type of genetic information and since the significance of these tests is not known for you, we will not release the results of any genetic testing. There will be no other genetic testing done, other than HLA typing.

Saving Leftover Samples for Future Research (OPTIONAL):

Any blood sample left over may be used for future research studies, such as additional analysis. These samples will be stored (possibly indefinitely) at a designated facility and provided to scientists performing research. Your stored sample will be coded with a unique number for this study and your identity will only be known by the study site. Saving these leftover blood samples for future research is OPTIONAL and you may choose to allow us to save your samples or not to save your samples. Your decision about whether or not to allow your samples to be saved for future research will have no affect on your participation in the rest of the study. No genetic testing of any kind will be done on your leftover samples.

Please let us know whether you allow us to save your samples to perform such studies by responding the following:

☐ I **agree** to allow my blood samples collected in this study to be saved for future related research.

☐ I **do not agree** to allow my blood samples collected in this study to be saved for future related research.

Are there things you should not do while participating in the study?

There are some restrictions if you decide to participate in this study. You should not receive any other vaccines in the 4 weeks before the first vaccination is given and in the 4 weeks after the last vaccination. If you participate in this study, you should not be involved in other vaccine studies or other clinical studies (involving drugs or other agents, or medical devices) until one month after the last visit of this study.

Risks/Discomforts:

Overall, the vaccine is well tolerated. Reactions to the current rabies vaccines are mild with local pain, redness, and swelling at the injection site. Some general reactions occurring less frequently are headache and fatigue.

Rabies vaccine is the first vaccine to have been developed by Louis Pasteur as a rabbit spinal cord vaccine. The rabies vaccine is currently available in the U.S. as a human diploid cell vaccine (HDCV) or as a purified chick embryo cell vaccine (PCECV). The vaccine being used for this study, RabAvert® is a PCECV, and is used for pre and post exposure. It is made by Novartis Pharmaceuticals.

Human serum albumin is a liquid diluent that has a similar composition of your body's blood make-up. This diluent is used as a form of blood component replacement for people in the hospital. It is made by Greer Labs, Inc.

Could you have an allergic reaction?

Sometimes people have allergic reactions to vaccines. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:

- a rash
- having a hard time breathing
- wheezing
- a sudden drop in blood pressure (making you feel dizzy or lightheaded)
- swelling around the mouth, throat, or eyes
- a fast pulse
- sweating

You should get medical help right away and contact the study doctor or study staff if you have any of these or any other side effects during the study.

For female participants of child bearing potential:

All women of child bearing potential participating in the study will be asked to have a pregnancy test before each vaccination. You should also not participate in this study if you are nursing a child. The effects of the vaccine on nursing children are not known at this time.

Any woman who finds that she has become pregnant while taking part in the study should immediately inform the study doctor.

The person will not receive further vaccinations and they will be followed-up to determine the outcome of the pregnancy.

There are some known risks involved with participating in this study:

- Vaccinations:
    - Subjects may have discomfort associated with intradermal or intramuscular injection of the vaccine. The injections will be in the forearm for ID and in the deltoid for IM.
    - Subjects may develop a flu-like illness with fever and body aches after vaccination. This is similar to other vaccines for viruses.

- Blood draws: Subjects may have pain and/or bruising at the location on your arm where the blood was taken. On rare occasions, it may cause lightheadedness or fainting or infection.

Benefits:

You may or may not benefit from participating in this study. We do not know if giving the rabies vaccine in this way will allow your body to develop protective antibodies to the rabies virus. Participation in this study does not mean you are protected against Rabies virus and any possible exposure to Rabies virus should be treated with the standard (FDA approved) post exposure treatment regimen. The information obtained from this study may help confirm a new effective dosing and route administration of the rabies vaccine to help protect a greater population in the future.

Voluntary Participation/ Study Withdrawal:

Your participation in this study is entirely voluntary and you may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which you would normally be entitled. Your decision about whether or not to participate in the study will not affect your relationship with SUNY Upstate Medical University.

The Study Doctor can take you off the study without your consent if:

- He or she feels it is for your benefit and/or safety, for example if a side effect or medical condition develops during the study.
- You are unable to follow the study procedures.
- It is discovered that you do not meet the study requirements.
- If the study is stopped by the Study Doctors or other oversight committees before the end of the study

If there are significant new findings or information that might change your mind about participating in the study, we will give you the information and allow you to reconsider whether or not to continue.

If you decide to stop taking part in this study, you should tell the study doctor. If you stop being in the study early, the study doctor or study staff may ask you some questions about being in the study. To help you leave the study safely, the study doctor may ask you to participate in more tests.

If the study is stopped early or if you choose to stop participating in the study, you are encouraged to return to the study site for these assessments:

- Physical examination
- Injection site assessment (if you leave the study within 14 days of vaccination)
- Blood test for presence of study vaccine components (if you leave the study within 14 days of study vaccination)

Alternatives:

You can receive the standard rabies vaccine outside this research study. If you feel you should be treated with the rabies vaccine, you should discuss this with your regular doctor. If you decide not to participate in this research study, you may still enroll in other research studies.

Costs/Payments:

There are no costs to you or your insurance carrier for participating in this study. All costs for the required study visits, examinations, laboratory procedures and study vaccine will be paid by the study.

You will be paid for each visit to cover your expenses. You will be paid $50 per visit for every visit you complete beyond the screening visit. Total payment for the study will be between $150 and $600 dollars depending on which vaccination group you are assigned. In the event that your participation in the study is discontinued early, you will only be paid for the visits completed.

In addition, by accepting payment for participating in this study, certain identifying information about you may be made available to professional auditors to satisfy audit and Federal reporting requirements, but confidentiality will be preserved. Please note that if you earn $600 or over in a calendar year as a research subject, you may have to pay taxes on these earnings.

Questions:

If you have any questions about the research, or in the event of a research-related injury, please contact Dr. Mark E. Polhemus at (315) 464-9493. If you have any questions about your rights as a research subject, please contact the SUNY Upstate Medical University Institutional Review Board Office at (315) 464-4317.

In Case Of Injury:

In the event of illness or physical injury resulting from taking part in this research study, medical treatment will be provided at University Hospital. You will be responsible for any costs not paid by your insurance company. No other compensation is offered by SUNY Upstate Medical University. SUNY Upstate Medical University has no plans to give you money if you are injured. You have not waived any of your legal rights by signing this form.

Confidentiality of Records and Authorization to Use/Share Protected Health Information for Research:

If you agree to participate in this research, identifiable health information about you will be used and shared with others involved in this research. For you to be in this research we need your permission to collect and share this information. Federal law protects your right to privacy concerning this information.

When you sign this consent form at the end, it means that you have read this section and authorize the use and/or sharing of your protected health information as explained below. Your signature also means you have received a copy of Upstate's Notice of Privacy Practices.

Individually identifiable health information under the federal privacy law is considered to be any information from your medical record, or obtained from this study, that can be associated with you, and relates to your past, present, or future physical or mental health or condition. This is referred to as protected health information.

Your protected health information will be kept confidential. Your identity will not be revealed in any publication or presentation of the results of this research.

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.

Why is it necessary to use/share your protected health information with others?

The main reason to use and share your health information is to conduct the research as described in this consent form. Your information may also be shared with people and organizations that make sure the research is being done correctly, and to report unexpected or bad side effects you may have.

In addition, we may be required by law to release protected health information about you; for example, if a judge requires such release in a lawsuit, or if you tell us of your intent to harm yourself or others.

What protected health information about you will be used or shared with others as part of this research?

We may use and share the results of tests, questionnaires, and interviews. We may also use and share information from your medical and research records. We will only collect information that is needed for the research.

Who will be authorized to use and/or share your protected health information?

The researchers, their staff and the staff of Upstate Medical University participating in the research will use your protected health information for this research study. In addition, the Upstate Institutional Review Board (IRB), a committee responsible for protecting the rights of research subjects, and other Upstate Medical University or University Hospital staff who supervise the way the research is done may have access to your protected health information.

The researchers and their staff will determine if your protected health information will be used or shared with others outside of Upstate Medical University for purposes directly related to the conduct of the research.

With whom would the protected health information be shared?

Your protected health information may be shared with:

- Representatives from the US Department of Defense, funders of this research;
- Collaborators at the Walter Reed Army Institute of Research;
- Kansas State University Rabies Laboratories;
- Frontier Science, database management group
- The research monitor;
- Federal agencies that supervise the way the research is conducted, such as the Department of Health and Human Services' Office for Human Research Protections, the Food and Drug Administration (FDA) or other governmental offices as required by law.

All reasonable efforts will be used to protect the confidentiality of your protected health information. However, not all individuals or groups have to comply with the Federal privacy law. Therefore, once your protected health information is disclosed (leaves Upstate Medical University), the Federal privacy law may not protect it.

For how long will your protected health information be used or shared with others?

There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be used and analyzed for many years and it is not possible to determine when this will be complete.

Can you withdraw your authorization to collect/use/share your protected health information?

You always have the right to withdraw your permission (revoke authorization) for us to use and share your health information, by putting your request in writing to the investigator in charge of the study. This means that no further private health information will be collected. Once authorization is revoked, you may no longer participate in this research activity, but standard medical care and any other benefits to which you are entitled will not be affected. Revoking your authorization only affects uses and sharing of information obtained after your written request has been received, but not information obtained prior to that time.

Even after you withdraw your permission, Upstate Medical University may continue to use and share information needed for the integrity of the study; for example, information about an unexpected or bad side effect you experienced related to the study.

Can you have access to your health information?

At the end of the study, you have the right to see and copy health information about you in accordance with the SUNY Upstate Medical University policies; however, your access may be limited while the study is in progress.

Consent To Participate In Research & Authorization To Use And Share Personal Health Information:

I hereby give my consent to participate in this research study and agree that my personal health information can be collected, used and shared by the researchers and staff for the research study described in this form. I will receive a signed copy of this consent form.

_____ _____
Signature of subject Date

_____
Printed name of subject

_____ _____
Signature of Person Obtaining Consent/Authorization Date

_____
Name of Person Obtaining Consent/Authorization