

RESEARCH AND EDUCATION INSTITUTE AT HARBOR-UCLA MEDICAL CENTER
HUMAN SUBJECTS CONSENT FORM

Child's Name: _____

Date: _____.

Title of the Research Study

A Multicenter, Randomized Dose Response Study of the Safety, Clinical and Immune Response of Dryvax[®] Administered to Children 2 to 5 Years of Age (NIH, DMID Protocol 01-650; Version 1.2 dated June 24, 2002)

1. Purpose of the research

The purpose of this research study, sponsored by the UCLA Center for Vaccine Research and the National Institutes of Health (NIH), is to learn more about the safety and immune response (the body's ability to fight infection) to a vaccine that is given to prevent smallpox.

Smallpox is a serious disease that affects only humans and is caused by a virus called variola. In the past, a vaccine against smallpox, called Dryvax[®] (manufactured by Wyeth Laboratories), was given to children and adults. It was found to be very effective if given before exposure to the smallpox virus or within 2 to 3 days after exposure. Due to the success of an international immunization effort, the world was declared free of smallpox in 1980. Routine immunization for smallpox was stopped in the U.S. in 1971 and the last naturally occurring smallpox case in the world was in 1977. Because those born after 1971 did not routinely receive the smallpox vaccine and the immunity from the vaccine does not last for a lifetime, it is estimated that only about 20% of the population is protected against smallpox today.

Dryvax[®] vaccine does not contain the smallpox virus. It is made from the vaccinia virus, a virus related to the smallpox. Because smallpox was thought to be eliminated, the manufacturer stopped producing Dryvax[®] vaccine in 1983, and it is no longer licensed in the United States. Today, there are about -----
-----doses of Dryvax[®] vaccine stored -----

In recent months, there has been a growing concern about the risk of bioterrorism, or the intentional use of germs as weapons to cause widespread illness and harm to others. Although smallpox was eradicated many years ago, there is a possibility that the virus has been obtained and could be used in a bioterrorist attack. Because of these concerns, efforts are being made to figure out the best way to protect the public with the limited vaccine that is available. Recently, two studies have been conducted in adults (with no prior history of Dryvax[®] vaccination) to find out how to increase the number of Dryvax[®] doses that are available while making sure that the vaccine is safe and effective. One of the studies that was completed found that the Dryvax vaccine, when given to adults full strength (one part active vaccine with one part solution) or as a 1:10 diluted vaccine (one part active vaccine to 10 parts solution), can produce a good immune response (the body's ability to fight infection).

The purpose of this study is to test the safety and immune response to the Dryvax vaccine, when given undiluted or at a 1:5 dilution to healthy children 2 to 5 years of age. The results of this study may help scientists and public health officials to develop better recommendations for the most effective use of the current supply of Dryvax vaccine in the event of an emergency. If, for example, the vaccine is found to be effective with only 1/5 of the usual dose, it may be possible to provide 5 times as much Dryvax vaccine in the event of an emergency.

2. **If your child takes part in this research, the following will be done:**

Forty healthy children from 2 U.S. sites will participate in this research study. Each child will participate in the study for 3 years. The first month will be the active part of the study. During this time, you will be asked to bring your child to the clinic for at least 12 visits. The number of visits may be greater (up to 20 visits) and the length of the active part of the study may be longer if needed to monitor the shot site and change the dressing. Once the shot site is scabbed, the remaining part of the study will not require visits to the clinic and will be for safety follow-up only. At one year, two years and three years after the vaccine is given, you will be asked to bring your child to the clinic for a blood test to find out if s/he still has protection against the vaccinia virus that will also protect against smallpox.

All study visits will take place in the outpatient clinic at the General Clinical Research Center at Harbor-UCLA Medical Center. You will be asked to provide the name and address of your child's regular pediatric care provider, so that they can be told of the child's study participation and given the name and telephone number of the study doctor for any questions.

To participate in the study, children should be 2 to 5 years of age, in good health, and without any current illness or fever. **Your child must not attend day care or school for 30 days after s/he receives the Dryvax® vaccine or longer until the scab at the shot site is well formed.** Your child must be up to date with childhood immunizations. Your child will not be able to participate in the study if he/she has any of the following:

- Problems with the immune system (including cancer, HIV infection, or other immune system conditions) or taking medications, such as steroids, that could affect the body's ability to fight illnesses or diseases.
- Certain skin conditions or irritations, including eczema, atopic dermatitis, cuts, burns (larger than 1 inch), or other conditions that the doctor or nurse can discuss with you
- Current illness with fever of 100.4°F or higher (temperature taken under the arm)
- Behavioral or developmental problems that may make it difficult for your child to cooperate with the study procedures.
- There are occupational responsibilities or any medical or psychiatric condition(s) that would prevent you from bringing your child to the clinic for study procedures.

There is a possibility that after receiving the Dryvax vaccine, your child could pass along the vaccinia virus to other adults or children, including those who might be susceptible to serious side effects. Your child will not be able to take part in the study for the following additional reasons:

- A family member or regular contact is pregnant.
- A family member or regular contact has eczema or a history of eczema, atopic dermatitis, cuts, burns, or shingles (varicella zoster).
- Other children in the household are less than 12 months of age.
- Family members or regular contacts have immune system problems, including cancer, HIV/AIDS, or other immune system conditions OR family members or regular contacts are taking medications, including steroids, that may affect the immune system.

There may be other conditions not listed here that could interfere with your child's participation that the doctor or nurse will discuss with you.

Screening Visit

You will receive written and verbal information about the Dryvax® vaccine and the study procedures. You will have an opportunity to discuss the study with study personnel and family, and have all of your questions answered. Before signing the consent form, you may be asked basic questions about the study to make sure you understand the study procedures.

After informed consent is obtained, your child will undergo screening tests to find out if he/she is eligible to participate in the study. A medical history will be obtained, and your child will have a brief physical exam. In addition, between one and two teaspoonsfuls (5-10ml) of blood, will be drawn from a vein in your child's arm by a research nurse or specialist nurse who is experienced in drawing blood from young children. Some of the blood will be used to test your child's kidney function and immune response (ability to fight infection) to the vaccinia virus. Some of the blood sample will be tested for HIV (Human Immunodeficiency Virus). It will take a few days to get the HIV test results, but they will be shared with you. Results of HIV testing will be confidential and will not be shared with anyone who is not a member of the research team. HIV counseling will be made available to you.

Enrollment Visit (within 30 days after the screening visit)

If the child meets the study requirements and the HIV test is negative, you will be asked to return to the clinic for the second study visit. A brief physical assessment that includes taking your child's temperature will be completed. If your child has a temperature of 100.4°F or greater (when taken under the arm), you will be asked to bring your child back to the clinic when he/she does not have a temperature.

After a brief health assessment, your child will be randomly assigned to one of two vaccine groups. Your child's group assignment will be decided by chance (like tossing a coin). Children in group 1 will get the full strength Dryvax® vaccine, and children in the second group will get the vaccine diluted 1:5.

At this visit, your child will be given the Dryvax® vaccine. The standard method of giving the vaccine is to apply some of the vaccine to the surface of the skin (usually on the upper arm), and then use a special needle to make small pricks in the skin in the area where the vaccine was applied.

The vaccine will be given with 5 skin punctures. You will be asked to wait in the clinic for 30 minutes after the vaccine is given so that your child can be checked for any allergic reactions.

During this visit, you will be given the first of two 14-day diary cards and a digital thermometer and asked to record your child's temperature and any complaints for 14 days after vaccination. You will also be asked to record any medications given to your child. In addition to the diary card, you will be asked to keep a record of contacts that your child may have throughout the study. A second 14-day diary card will be given to you after the first 14 diary card has been completed.

A chart that shows the schedule of study visits and activities is included with this consent form.

Care of the shot site

For this study, the shot site and sore will be covered with a dressing to reduce the risk of spreading the vaccinia virus to others. You will be asked to bring the child to the clinic every 2-4 days for dressing changes. You will be instructed to call the study nurse or doctor if the dressing needs to be changed between study visits. You will also be given extra dressing materials and instructions on how to secure your child's dressing if the dressing accidentally comes off or if you are unable to bring your child to the clinic.

The shot site will be covered with a dressing until a scab is formed and the study personnel determine that the child is unlikely to spread the virus to others. Although no absolute restrictions can be made regarding your child's interactions with others, you should follow the guidelines listed below to minimize the risk to others:

1. Your child's bandage should be checked before contact with others
2. Your child should wear a garment with sleeves when he/she is in contact with others
3. Visitors should be restricted, using the same guidelines listed above for family members, that is, persons with eczema, atopy, acute or chronic skin conditions, persons with problems with the immune system, pregnant women, and children less than 12 months of age should not visit with your child.

You will be given a handout to give to possible visitors so that they can be informed of possible risks.

Your child will not be allowed to attend any type of daycare setting or school for 30 days after vaccination, or longer if the sore has not healed. Your child will need to avoid contact with other children or adults who may be at greater risk of becoming sick from vaccinia infection. This will be explained in detail in a handout given to you.

Vaccine "Take"

It is expected that the shot site will turn into a sore, which is also called a "take." This is a sign that your child is responding to the vaccine. About 3 to 5 days after vaccination, a small bump (called a papule) will develop over the shot site. The bump becomes a blister, then fills with pus, and reaches its largest size about 8 to 10 days after vaccination. The pus-filled blister dries and forms a scab as early between 2 weeks and 4 weeks after vaccination. The scab eventually falls off, which may take 3 to 8 weeks. The area where the vaccine was given may be left with a small flat scar about 1/4 inch across.

If your child does not develop a "take" after the first vaccine, your child will be given a second Dryvax vaccine in the opposite arm. The second shot will be the same strength (dilution) and given with the same number of skin pricks as the first shot. You will be given a new 14-day diary card to fill out. You will be asked to wait in the clinic for 30 minutes to check for any immediate reactions.

A photograph of the shot site will be taken, and the site will be swabbed to test for the presence of virus. More photographs of the shot site may be taken during other study visits to record the condition and healing of the site. The photographs will be confidential and will be kept in your child's study file.

Immune Response to the Vaccine

45 to 60 days after the vaccine is given, a blood sample will be taken to test your child's immune response (ability to fight infection) to the vaccine. One to two teaspoonfuls (5 to 10ml) of blood will be taken from a vein in your child's arm. Similar blood samples will be taken at one year, two years and three years after vaccination to check your child's immune response over time.

Follow-up

Your child will continue to come to the clinic to have the shot site checked and have the dressing changed, as needed, until the site is well scabbed. This may take as long as 6 to 8 weeks. You will be asked to report any new illnesses or health problems for your child that require a visit to a medical care provider for 6 months after the first vaccine is given. If your child received a second shot with the Dryvax vaccine, clinic visits and dressing changes will continue until both sites are well scabbed.

Reimbursement

You will receive compensation for the time and effort required for your child's participation. You will receive \$10 for each clinic visit completed. If your child is brought to the clinic for 12 visits, you will receive \$120. In addition, if your child completes the entire study, you will receive a \$40 gift certificate to a children's store. If for any reason your child is unable to complete the study, you will be compensated for the part of the study that is completed

3. **The following treatments and procedures are experimental:**

All of the treatments and procedures listed above are considered experimental.

4. **Your child reasonably expect the following risks and discomforts (including the likely results if the experimental treatment does not work):**

The risks associated with participation in this study are mostly associated with the Dryvax® vaccine. It is common to develop a mild fever between 4 and 14 days after vaccination. About 1 in 5 children develops a fever of 102°F or higher after vaccination. After vaccination, children may also develop chills, rash, muscle aches, diarrhea, nausea, headache, and tiredness. These side effects do not usually last long or require treatment.

As with all vaccines or drugs, there is a rare possibility that your child could develop an allergic reaction after the Dryvax vaccine is given. An allergic reaction may include rash, hives and/or difficulty breathing. Study personnel will ask you to wait in the clinic for 30 minutes after the vaccine is given to check for any immediate allergic reactions.

As with all vaccines, there may be pain, soreness, redness and swelling at the site where the vaccine is given. With Dryvax vaccine, it is expected that a sore or "take" will develop at the vaccine site. This is a sign that the child is developing an immune response to the vaccine. A scab forms as early as 2 weeks (maybe later) after vaccination. The scab eventually falls off, which may take 3 to 8 weeks. The area where the vaccine was given may be left with a scar.

It is common to develop swelling and tenderness of the lymph nodes closest to the shot site, which would be the ones under the arm. Swelling of the lymph nodes may start about 3 to 10 days after vaccination and may last up to 2 to 4 weeks after the vaccine site has healed.

Although less frequent, there may be arm soreness and less movement of the arm for a few days after vaccination.

Results from studies of Dryvax® in over 650 healthy adults between 18 and 32 years of age showed that 1 in 10 had areas of redness around the vaccine site of more than 4 inches, 1 in 5 reported moderate to severe muscle aches, 1 in 3 had enlarged lymph nodes near the vaccination site, and 1 in 3 had moderate to severe pain at the vaccination site.

The risks of drawing blood include pain, swelling, bruising and rarely infection at the needle site. Research staff who are experienced with drawing blood from infants and young children will obtain the blood samples.

Because vaccinia virus is present at the shot site, it is possible that other people could become infected if they come in direct contact with your child's vaccination site sore. Your child can also spread the virus from the vaccination site to another person by touching the sore and then touching another person. Most of the time, passing the virus to another person does not lead to serious illness in the person who is contacted. However, persons who have problems with their immune system (difficulty fighting infection and illness) and persons who have eczema or a break in the skin are at greater risk of developing some of the serious complications listed below. To reduce the risk of passing the virus onto another person, you will need to make sure that the shot site dressing stays in place at all times and practice good handwashing after touching the area around the shot.

It is also possible that your child could spread the virus from the vaccination site to other parts of his/her body such as the eyelid, the face, the mouth, the nose, the rectum or the genitals. The risk of passing the virus to another part of the body can be reduced by keeping the shot site dressing in place, making sure your child does not touch the site, and good handwashing. If your child does infect another part of the body, blisters may develop and they usually heal without treatment. If the virus is transferred into the surface of the eye (the cornea), treatment may be given to prevent scarring of the cornea. For any infection of the eye, your child will be seen by an eye specialist who will decide what type of treatment is needed.

It is possible that other skin problems and complications at shot site could develop. These complications may include:

- 1) A mild rash from the vaccinia virus that develops on other parts of the child's body. This reaction may require hospitalization but usually does not.
- 2) An eczema type of reaction (red, itchy, irritated skin reaction) that may develop on other parts of the child's body.
- 3) Delayed healing of the shot site.
- 4) Bacterial infection at the shot site sore.

More serious reactions may also occur, but they are rare and occur most often in small infants, people with eczema and people who take medicines, such as steroids, or have problems with their immune system. More serious reactions may include signs and symptoms of brain and nervous system infection such as 1) convulsions or seizures, 2) muscle weakness, 3) paralysis, and/or 4) stiff neck.

Because the smallpox vaccine has not been routinely given to the public since 1971, the most recent information about the risks of complications associated with vaccination comes from surveys done in the 1960s. The risk of a generalized rash from the vaccine, or accidental infection of the eye, or bacterial infection of the vaccination site is estimated to be less than 600 for every 1,000,000 first vaccinations. A complication associated with eczema (eczema vaccinatum) was seen in 38 for every 1,000,000 first vaccinations. The risk of nervous system infection or of infection in those who have problems with the immune system is less than 3 for every 1,000,000 first vaccinations. The risk of death from smallpox vaccination for children in this age group was estimated to be 2 for every 1,000,000 first vaccinations. Complications occurred less often in children who received a second vaccine (revaccination).

In rare cases, vaccinia immune globulin (a substance which provides antibodies or substances that fight infection against vaccinia) is needed to prevent or treat complications. If any serious complications develop, vaccinia immune globulin, VIG, a substance made from the blood of people who have previously received vaccinia vaccine, may be obtained from the CDC and given to the child. VIG is generally considered safe and effective to treat eczema-like reactions and most accidental infections of the eye with vaccinia virus. It is usually not given to people with severe reactions at the shot site or other parts of the body unless they are very ill. VIG is an investigational product that is not licensed in the U.S. A separate consent form will be given to you if your child develops a complication that requires treatment with VIG.

If a serious problem develops and treatment with VIG does not appear to be enough to cure it, your child may be treated with another medicine called cidofovir (Vistide®). This drug is licensed in the U.S. and used to treat infections caused by another virus (cytomegalovirus), which can cause serious, life-threatening infections in people who have difficulty fighting infection. Cidofovir is not approved for use in children or for the treatment of vaccinia infections, but it appears to be effective in animals when given to treat infections caused by vaccinia and similar viruses. If there were a complication that required treatment with cidofovir, your child would need to be followed closely in the hospital. A separate consent describing the procedures, risks, benefits and alternatives would be provided to you.

5. **Your child may reasonably expect the following benefits:**

To your child:

Children who participate in this study may benefit by developing protection against the smallpox virus. It is also possible that your child may receive no benefit from participation in this study and that they will not develop a "take" after vaccination.

There will be no costs to you or your child for participation in the study.

Your child will continue to receive routine and sick child care from their regular pediatrician or nurse practitioner.

To humanity:

Participation in this study may provide benefits to society in the search for a method for giving Dryvax vaccine safely and effectively so that the greatest number of individuals may receive protection against smallpox.

These benefits may not happen and unexpected side effects may also develop.

6. **If you choose not to have your child take part in this research, the following alternative procedures might help you:**

Smallpox vaccine is not available to the public at this time. The alternative to participating in this study is for your child to receive no smallpox vaccination and to continue routine health care provided by your child's regular physician or healthcare provider.

Your child's participation in this study is voluntary, and if you choose not to participate this will not lead to any penalty or loss of benefits to which your child is otherwise entitled. You will be told of any significant new findings that develop during the course of the study that may influence your willingness to continue your child's participation in the study.

7. **Retention of specimens and contact for future studies**

After work is finished on blood samples taken from your child for this study, we would like the option of keeping the samples for possible future research studies. The samples will be stored at the UCLA Center for Vaccine Research (located at the Research and Education Institute at Harbor-UCLA Medical Center). The samples will not be sold or used to make products for profit. They will be used for future research only when they may help even out future tests or learn more about smallpox vaccine or other diseases. No human genetic tests will be performed on your child's specimens. Reports about future research done with your specimens will NOT be kept in your child's health records but may be kept with the study records in a secure location.

You can make your mind up if you want your child's leftover samples to be stored for future research. You can change your mind at any time by calling the study doctors or nurses. This will not affect your child being in this study or other studies.

Is it OK for us to store your child's blood samples for future research? Please initial below:

_____ YES, you may store my child's unused identified samples for future smallpox research, forever.

_____ NO, you may not use my child's samples for other future smallpox research. Throw away my unused samples at the close of the study.

Someone may contact you in the future to find out if your child would be willing to be in future studies associated with this vaccination. The human subjects review board (IRB) at the Research and Education Institute at Harbor-UCLA Medical Center will review any future studies.

At this time, you can make up your mind if you want to be contacted. If and when you are contacted, you can decide if you want to be in any of the other studies. This will not affect your child being in this study.

Is it O.K. for us to contact you about being in other studies? Please initial below:

_____ YES, you may contact me about other studies.

_____ NO, you MAY NOT contact me about other studies.

8. The results of this research may be published to inform other physicians and scientists. Your child's laboratory tests, photographs, videotapes and x-rays, if any, may be published. Your child's name or your records will not be given out without your consent, unless required by law.

Your child's records may also be reviewed and/or photocopied by the Food and Drug Administration, the Institutional Review Board (IRB) or it's staff and the sponsor of this study.

By signing below, you will be agreeing to allow the researchers to decide what to do with any surplus tissue (blood, culture of smallpox site, etc.) removed from your child during the research described above. You will be told if the researcher has any current personal interest, such as any economic interest, related to performing the proposed research.

- 9. A committee of medical and non-medical people (IRB) will regularly review and approve this research for scientific and ethical merit. You will be told of any new information that may affect your desire to have your child continue in this research. You/your child may leave this research at any time. If you decide to leave this study, it will not affect your child's future medical care. Your questions will be answered at any time.

- 10. If your child is injured because of this research, emergency medical care will be available. The care will not necessarily be free of charge. Financial compensation for any injury from this research is not available. If your child is injured because of this research, you should first try to contact the principal investigator, who is listed below. If you cannot reach the investigator, you may call the hospital emergency department (adult, 310-222-3514, or pediatrics, 310-222-2317). You can also call the Harbor-UCLA Research and Education Institute Compliance Office, 310-222-3624, for further information on the availability of medical treatment or compensation, your rights as a research subject or if you have questions about the research study.

- 11. Your child has taken part in the research studies listed below within the past three months. (Describe the Studies):

- 12. You and your child's participation in this study is entirely voluntary. Refusal to take part in this study will involve no penalty or loss of benefits to which you/your child are otherwise entitled. You/your child may stop taking part in this study at any time without penalty or loss of benefits to which you are otherwise entitled. You have fully reviewed the contents of this consent form and had them described to you. You have been given a copy of this consent form and the Human Subject's Bill of Rights.

Name of parent or legal guardian- printed

Relationship to child

Signature of parent or legal guardian

Date

Witness to signature of parent/guardian

Date

For the Investigator or Designee:

13. I certify that I have reviewed the contents of this form with the person signing above, who, in my opinion, understood the explanation. I have explained the known side effects and benefits of the research.

Principal Investigator
or Authorized Representative

Telephone Number

Date

14. For all in-patient research studies, to ensure that patients receive coordinated care from the investigator and the primary physician, the primary physician must sign this form indicating s/he has knowledge of the research study. If the patient has no primary physician, the physician treating the patient is considered the primary physician.

Primary Physician

15. I certify that I am the principal investigator and am responsible for this study, for ensuring that the subject is fully informed in accordance with applicable regulations, and for advising the Human Subjects Committee of any adverse reactions that develop from the study.

Principal Investigator

Date

Principal Investigator: Joel Ward, M.D.
Telephone Number: (310) 781-3636