



Use this form for all **NEW**, **RENEWAL**, **REVISED** and **ADDENDUM/AMENDMENT** projects involving human subjects.

FAILURE TO COMPLETE ALL APPLICABLE SECTIONS OF THIS SUBMISSION FORM MAY DELAY PROCESSING THE PROJECT.

GUIDELINES FOR COMPLETING HUMAN SUBJECTS SUBMISSION FORM

Page I Heading.

Provide the requested information on the Principal Investigator, Project Title and Agency/Sponsor. Provide the REI Project Number and contact information. Indicate whether the GCRC is involved.

Type of Project.

Indicate New, Revised or Renewal. If you believe that the project is either expedited or exempt, indicate the appropriate category (Consult attachments 2 and 3 for guidance).

Amendment/Addendum.

Use this space to summarize the nature of the amendment (change to procedures in an existing protocol) or addendum (an entire new experimental protocol added to a current protocol). Discuss changes to patient safety and/or risk:benefit ratio. Use additional pages if necessary.

Investigator's and/or Sponsor's Assurance and Signature.

Sign and date as either Principal Investigator or (if you are sponsoring a student or other non-REI member) as Sponsor. The Sponsor assumes all the responsibilities of a Principal Investigator.

Lay Summary

Use this space to provide a summary of the project, answering the questions listed. The summary should be in sufficient detail to allow a member of the committee to understand what your project involves. The summary should be written at the level of an educated non-medical person. Explain specialized technical terms and acronyms. Even medical members are unlikely to be conversant with the specialized vocabulary of your specific discipline.

Risks and Benefits

Describe previous information regarding risks and benefits, assess risks in terms of seriousness and frequency, describe how you will minimize such risks and evaluate the overall risks in relation to the perceived benefits.

Subject Demographics

Describe the population you wish to study, as indicated. For specially vulnerable populations, indicate what additional steps you will take to ensure that **informed** consent will be freely given. For example, for a non-English speaking subject, you may choose to use a consent form in the person's native language and/or a consentor who is fluent in that language.

Women and Minorities

NIH policy mandates that when a disease has similar prevalence in men and women or across ethnic groups, then women and minorities must form an appropriate proportion of the study population unless it can be demonstrated that there are strong scientific reasons for studying only men, or only one ethnicity.

Children - If children (under 18) are involved, fill in the number of the appropriate category from the "Additional Protection for Children in Research" (Attachment 5); explain the reason and basis for this designation and explain their participation in the study. NIH Policy mandates that when a disease has similar prevalence in adults and children, then children must form an appropriate portion of the study population, unless it can be demonstrated that there are strong scientific reasons for studying only adults.

Logistics

This section seeks information on the logistics of the study, recruitment of subjects, etc.

Consent

This section describes the process by which you will obtain consent. Please note that no one may be involved with human subjects research that has not obtained institutional training in the protection of human study volunteers

PLEASE CALL THE COMPLIANCE OFFICE (EXT. 3624), IF YOU NEED FURTHER INFORMATION OR ASSISTANCE.



JOHN F. WOLF
HUMAN SUBJECTS COMMITTEES
310.222.3624

HUMAN SUBJECTS SUBMISSION FORM

THIS FORM MUST BE TYPED OR WORD-PROCESSED. IT IS AVAILABLE ON THE REI INTRANET

| | | | |
|-------------------------|--|---|--------------------------|
| Principal Investigator: | Joel Ward, M.D. | REI Project No.: | 10410-01 (101) |
| Project Title: | A Multicenter, Randomized Dose Response Study of the Safety, Clinical and Immune Responses of Dryvax Administered to Children 2 to 5 Years of Age | Telephone No./Ext.: | 781-3636 |
| Agency/Sponsor: | | NIH/NIAID/Division of Microbiology and Infectious Diseases (DMID) | GCRC Involved: |
| | | Pager No. (required): | |
| | | E-mail Address (required): | joelward@ucla.edu |

TYPE OF PROJECT

- NEW – FULL COMMITTEE REVIEW
- REVISED – FULL COMMITTEE REVIEW
- RENEWAL (COMPETING CONTINUATION) – FULL COMMITTEE REVIEW
- EXPEDITED – CATEGORY # _____
- EXEMPT – CATEGORY # _____

Before claiming expedited or exempt, please consult Attachments 2 or 3 and select the appropriate category.

If you are claiming this project to be exempt, please sign here _____ and complete page 2.

AMENDMENT/ADDENDUM – Use the space below to submit amendments/addenda to currently approved protocols. Date the amendment and briefly describe the change. Attach supporting documentation.

As the Principal Investigator of this project, I understand that I have the ultimate responsibility for the protection of human subjects. I give my Assurance that emergent problems, unexpected side effects, serious adverse reactions and deaths (whether or not related to the study) and proposed procedural changes which may affect the status of the investigation, will be immediately reported to the Human Subjects Committee. No procedural change will be made without Committee approval except to eliminate apparent immediate hazards.

| | |
|--|-------------|
| Investigator's Signature | Date |
| | |
| Signature of faculty sponsor (for students or off campus researchers) | Date |
| | |

LAY SUMMARY

Write this in **LAY LANGUAGE** for lay members of the committee, house staff and nurses. Please address the following, **but do not exceed the space provided**:

In light of recent terrorist attacks, there has been heightened concern over the use of infectious agents as weapons. Smallpox (variola) is one type of orthopox virus that is thought to be one of the most dangerous biologic agents that could be used for a bioterrorist attack.

The use of vaccinia vaccine (Dryvax) led to the global eradication of smallpox in 1977. It is highly effective in producing immunity to smallpox (variola) if administered before or within 2-3 days after exposure. Routine use of Dryvax in the U.S. was discontinued in 1971, and in 1983, the only active producer of vaccinia vaccine in the U.S. (Wyeth Laboratories) discontinued distribution of vaccinia vaccine for civilians. Immunity conferred by the vaccine is not lifelong, and it is estimated that at least 80% of the U.S. population is now susceptible to smallpox, including individuals 32 years of age or younger.

There is a limited supply of Dryvax vaccine that has been stockpiled at the CDC and has been used for the past 30 years for routine vaccination of susceptible laboratory workers. The vaccine is not longer licensed in the U.S. but is available from CDC under an IND protocol. There are concerns on the part of the federal government and the scientific community that the amount of Dryvax in storage will be not be adequate for those who might be exposed during a bioterrorist attack, and the current focus is on evaluating dilutions of the vaccine to expand the number of available doses. As one of 7 NIH-funded Vaccine Treatment and Evaluation Units (VTEUs), the UCLA CVR has been called upon to assist with Dryvax dilutional studies. Other VTEUs have recently conducted 3 clinical trials of Dryvax dilutions in 830 adults (740 previously unvaccinated, 90 previously vaccinated). The CVR has now been asked to undertake a dilutional study of Dryvax vaccine in children as soon as possible, with strong support from the American Academy of Pediatrics. This study will evaluate the safety and immune response of Dryvax vaccine given full strength compared with a 1:5 dilution in children 2 to 5 years of age.

This study will be conducted 2 VTEU sites: the UCLA CVR and Cincinnati Children's Hospital. A total of 40 healthy children will be enrolled, including 20 from our site. Recruitment will take place primarily at the Kaiser Permanente pediatric clinics (Harbor City and satellite clinics), but children may also be recruited from the community. Education, consent, screening, enrollment and follow-up activities will take place in the Harbor-UCLA outpatient GCRC. This study will require significant parental education and cooperation. The parent will be told that the child will not be able to attend day care/school for at least 30 days after vaccination, or until the vaccination site is completely healed and felt to be no longer infectious. The parent will need to bring the child for frequent dressing changes at the clinic until the site is well healed, and be available for long-term follow-up for up to 3 years. The parent will be given an instruction sheet about contact with friends, family and other caregivers. The child will not be able to participate if they have members of the household or close exposure to individuals who are immunocompromised or pregnant. In addition, the child will be excluded if they have a history of eczema/atopic dermatitis, acute skin conditions (burns, impetigo) or exposure to someone with those conditions.

During the screening visit (within 30 days of vaccination), the parent will have a chance to ask questions, learn more about what to expect during the study, and provide informed consent prior to any study procedures. A screening history and physical will be performed, which will include a blood test for HIV and serum creatinine and a thorough review of inclusion/exclusion criteria for the child and family. If eligible, the child will return to the clinic for the vaccination visit. The child will be randomized (1:1) to the full strength or 1:5 dilution group. A single dose of Dryvax will be administered by scarification technique (5 pricks with a bifurcated needle) in the upper outer arm. The parent will wait with the child in the clinic for at least 30 minutes after vaccination to check for any immediate adverse reactions. The parent will be given a digital thermometer and instructed to take the child's temperature and complete a diary card regarding systemic and site reactions. A semi-occlusive dressing will be applied at the site, and the parent will be asked to have the child wear a short or long sleeve shirt to help prevent scratching or tampering with the dressing. The parent will return with the child to the clinic every 2 to 4 days for site assessment and dressing change. Old dressings will be placed in ziplock bags and disposed of through standard handling of biohazardous waste at the UCLA CVR.

The success of vaccination is called a "take" which consists of small blisters progressing to a pus-filled blister, a cratered sore, and then scabbing. The maximum reaction is expected at 7 to 10 days. If a child does not develop a "take," parents will be offered the option of revaccination. Parents will be given instructions and pictures of the way the site is expected to look. They will be given emergency dressing materials to reinforce (not change) the dressing and the beeper number for the investigator or research nurse. A blood sample will be obtained at 45 to 60 days (5-10ml) and again at 1, 2 and 3 years after vaccination.

The success rate of Dryvax vaccine is high, and children will likely benefit by developing neutralizing antibodies to orthopox viruses, which will provide protection against the smallpox (variola) virus. Dryvax vaccine is associated with known reactions such as fever, lymphadenopathy, muscle aches, chills, malaise and site reactions such as erythema, soreness, pruritis, and induration. Most of these reactions resolve without

intervention. Anaphylaxis after vaccination is very rare. Moderate to serious adverse reactions may occur but are relatively infrequent and are usually observed in individuals who are immune compromised or have pre-existing skin conditions. Documented serious adverse reactions that occur rarely include vaccinia necrosum, inadvertent autoinnoculation, generalized vaccinia, eczema vaccinatum, encephalitis and death, and they are discussed below.

RISKS AND BENEFITS

Describe prior experience in humans or, if none, the results of prior animal studies.

Dryvax (Wyeth Laboratories) is a lyophilized, live virus preparation of vaccinia virus; it does not contain smallpox (variola) virus. The vaccine is prepared from calf lymph with a seed virus derived from the NYC Board of Health Strain of vaccinia virus. Dryvax has been used for more than 20 years to produce immunity to smallpox and closely related orthopox viruses. It has been given to millions of children and adults worldwide leading to the eradication of smallpox infection in 1977.

Currently, there are no licensed vaccinia vaccines in the U.S., including the lots of Dryvax vaccine to be used for research staff and for subjects enrolled in proposed clinical trials. Wyeth did not seek licensure of the product following a change in the vaccine diluent. The previously licensed Dryvax included a diluent that contained brilliant green to enhance visualization during the vaccination process. The current diluent, manufactured by Baxter Laboratories, does not contain brilliant green. The change in formulation is not expected to change the suspension characteristics or interfere with vaccine potency. The vaccine lots to be used in this study may not have completed release testing (e.g. determination of an expiration date), and are therefore only available for use under an IND. Historical data on the potency of this vaccine has been good, in that there has been very little decline in potency over time.

During the past year, a NIH multicenter study to evaluate Dryvax in full strength versus diluted preparations in 680 previously unvaccinated healthy adults (JAMA April 25, 2002, article included in submission packet), was conducted at 4 VTEUs in the U.S. 665 of 680 (97.8%) subjects had a successful vaccine "take" after a single dose (diluted and undiluted vaccine were not significantly different) and an additional 7 subjects developed a take after revaccination, for an overall rate of 98.8%. The vaccination site lesion reached a maximum size at days 13-14. The maximum area of erythema (mean of 51.4mm) and induration (mean of 48.1mm) was observed on days 10-12. Systemic reactions included fever, headache, muscle aches, chills, nausea, fatigue, and rashes at remote sites. Two subjects developed vaccine-related serious adverse events: 1) severe headache and nausea lasting between 5 and 14 days post vaccination, and 2) a large area of erythema (290mm) around the vaccination site that developed on day 8 and resolved on day 15.

In April 2002, a NIH VTEU pilot study of Dryvax vaccine given to 90 previously vaccinated adults (33-50 years of age) was completed by the University of St. Louis VTEU (unpublished). Although results are still being analyzed, expected adverse reactions were considered to be less frequent and less severe in this group.

Dilutional studies of Dryvax were conducted in pediatric subjects in the early 1970s. In a study of 786 children 1 to 9 years of age, 97% of children who received full strength Dryvax and 74% of those who received a 1:10 dilution developed a "take." The area of site erythema was slightly less in children who received the 1:10 dilution compared with full strength (21mm versus 27mm). Moderate to severe complications in pediatric subjects usually occurred in infants which was one of the considerations for our decision to enroll children 2 to 5 years of age.

Listed below are potential adverse reactions/risks specific to pediatric subjects that may receive the vaccine.

The only product currently available for treatment of complications due to vaccinia vaccination is VIG, which is an isotonic sterile solution of the immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine. It is effective for treatment of eczema vaccinatum and certain cases of progressive vaccinia. It may be used for treatment of ocular vaccinia due to inadvertent inoculation but is contraindicated for vaccinal keratitis. VIG supply is limited and may only be obtained from CDC. A drug sheet for VIG has been provided in this packet.

Although there is no other recommended alternative to VIG in the treatment of vaccinia complications, FDA has requested that Cidofovir be available for each of the NIH adult and pediatric studies as a second option for serious vaccinia complications. This antiviral vaccine is currently licensed only for treatment of CMV retinitis in HIV-infected patients. There has been very limited experience in children. For this protocol, FDA has approved Cidofovir to be used off-label only if medically necessary to treat serious, life-threatening complications. A drug sheet for Cidofovir is included.

Project No. 10410-01(101)

Describe and assess potential risks and indicate the likelihood and seriousness of the risks. Use one line for each

| Drug/Procedure | Nature of Risk | Likelihood | Seriousness |
|----------------|-----------------------------------|------------|-------------|
| Dryvax | Anaphylaxis following vaccination | Serious | Rare |

| Drug/Procedure | Nature of Risk | Likelihood | Seriousness |
|----------------|---|---|---|
| Dryvax | Fever | Fever is more common in children than adults. 70% of children experience ≥ 1 day of temperatures $\geq 100F$ for 4-14 days after primary vaccination; 15-20% of children experience temperatures $\geq 102F$. After revaccination, 35% experience temperatures $\geq 100F$ and 5% experience temperatures $\geq 102F$. | Not serious |
| | Malaise Muscle aches, chills Headaches | Mild to moderate malaise, muscle aches, chills common (up to 20%). Headaches common. | Not serious |
| Dryvax | Pruritis (itching) at site | Common | Not serious |
| Dryvax | Erythema at site Induration at site | Common Common | Not serious Not serious |
| Dryvax | Bacterial infection at the site | $<0.06\%$ | Moderately serious |
| Dryvax | Lymphadenopathy | 20-30% in primary vaccination | Not serious |
| Dryvax | Transmission to susceptible persons | Rare when precautions are followed | Generally not serious; potentially serious if virus is transmitted to immune compromised individuals |
| Dryvax | Vaccinia necrosum | Rare: limited to those with immune system abnormalities | Moderately serious |
| Dryvax | Inadvertant autoinnoculation (eye, mucosa) | In children 1-4 years of age, rate of 0.0033% of primary vaccinations. For children 5-9 years of age, rate of 0.002% of vaccinations. Most common sites are face, eyelids, nose, mouth, genitalia and rectum. Rates may be lower with the use of dressings, good handwashing instructions and instructions to parents. | Most lesions heal without therapy. However, autoinnoculation is potentially serious if the eye is involved. VIG can be used for ocular implantation, but VIG is contraindicated if keratitis is present (may cause scarring). |
| Dryvax | Generalized vaccinia | For children 1-4 years of age, rate of 0.0017% of primary vaccinations. For children 5-9 years of age, rate decreases to (0.0013). No cases with revaccination recorded. | Moderate |
| Dryvax | Eczema vaccinatum | For children 1-4 years of age, rate of 0.0011% of primary doses. For children 5-9 years of age, rate of 0.0007% of primary vaccinations. Generally limited to vaccinees or those with eczema. | Potentially serious |
| Dryvax | Postvaccinial encephalitis | For children 1-4 years of age, rate of 0.00022% (2.2 cases per million) primary doses. For children 5-9, rate of 0.00032% of primary doses. No cases seen with revaccination. | Very serious |
| Dryvax | Death | For children, $<0.0002\%$ (2 per million) primary doses | Very serious |
| Phlebotomy | Pain, swelling and redness at the needle site where blood is taken. | Pain common. Swelling, redness infrequent. Infection rare. | Not serious. |

| Drug/Procedure | Nature of Risk | Likelihood | Seriousness |
|--|---|---|-------------|
| Collection of private information in relationship to study participation | Breach in privacy, confidentiality of records | Rare if records are kept in restricted, secure area | Moderate |

Please indicate what precautions you will take to minimize hazards or discomforts to the subject(s).

| Risk/Discomfort | Precaution to minimize risk/discomfort |
|---|--|
| Anaphylaxis | Vaccine will be administered in the clinic area where emergency medications and equipment are available. Parents will be asked to wait with their child for 30 minutes to observe for any immediate reactions and will be asked to contact Drs. Ward, Le or Marcy for any serious reactions. |
| Fever, malaise, muscle aches, headaches | Parents will be advised that acetaminophen or ibuprofen can be used to reduce these symptoms. |
| Site induration, pruritis | Cool packs and Benadryl may be used to reduce the discomfort at the site |
| Bacterial infection at the site | Change dressings every 2-3 days and monitor site closely. Parents will be instructed not to use any topical preparations on the site. |
| Transmission to susceptible persons | Children will not be vaccinated if they have household members or close contact with individuals who have eczema or atopic dermatitis, problems with the immune system, pregnancy or expected pregnancy. Parents will be instructed to keep a dressing on the vaccination site and to use good handwashing technique anytime the surrounding site is touched. Emergency dressing reinforcement kits (include gloves) will be given to the parent. Used dressing materials will be placed in a ziplock bag and returned to the CVR for biohazardous waste disposal. Physicians and nurses who are vaccinated will not be able to resume routine clinical care duties in the hospital or clinic until the site is healed and there is little or no chance of viral shedding at the site. |
| Vaccinia necrosum Eczema vaccinatum | Staff will not be vaccinated if they have problems with the immune system, or have a history of skin conditions such as eczema, dermatitis, burns, impetigo, or shingles. VIG (Vaccinia Immune Globulin) may be obtained from the CDC for treatment of individuals with these conditions. In the rare event of treatment failure, Cidofovir may be administered according to protocol. |
| Inadvertent autoinoculation | Parents will be instructed to prevent the child from touching the site and then the eye or any other mucosal membrane site. They will be instructed to maintain a dressing on the vaccination site at all times and to wash their hands with soap and water any time the site is touched or the dressing is changed. If a child or parent autoinoculates the eye, Drs. Ward, Le or Marcy will be notified immediately to assess the need for an ophthalmology consult. VIG may be used for ocular vaccinia that is not associated with keratitis. Viroptic ophthalmic solution may be administered. |
| Generalized vaccinia | The parent will be instructed to contact Dr. Le or Ward to be evaluated for satellite lesions or a rash that may indicate generalized vaccinia. VIG will be obtained from CDC as needed to treat the condition. |
| Post vaccinal encephalitis Death | Children will be screened for any serious health problems prior to administration of Dryvax vaccine. will be followed closely by study physicians for serious, life-threatening reactions after vaccination. VIG is not indicated for treatment of post vaccinal encephalitis. |
| Pain, swelling, redness at site where blood is drawn. | The UCLA CVR has several experienced pediatric phlebotomists who are able to maximize positioning and technique to minimize discomfort and other problems. |

Perform a risk:benefit analysis for the study. Balance risk to individual subjects to benefits to subjects or to society as a whole.

Children may directly benefit by developing immunity against vaccinia which provides protection against smallpox. The Dryvax vaccine has been found to be highly effective. Although smallpox was once thought to be eradicated, the prevailing national view is that a bioterrorist attack is a possibility and that efforts are needed to prepare for such an attack. Children who receive the vaccine would likely develop some protection against the smallpox virus that would be helpful in the event of such an attack. Society and the medical community will benefit from the knowledge obtained as additional dilutional studies of Dryvax are conducted.

There are expected mild to moderate side effects that occur commonly with Dryvax vaccination and generally resolve

without treatment. More serious side effects are rare but possible, and may be minimized by performing careful pre-vaccination screening to exclude those who may be susceptible to more serious risks and those who may expose other susceptible individuals.

SUBJECT DEMOGRAPHICS

The following information will be about the subject population to be included in the study.

| Number of Subjects to be: | Male | Female | Total |
|---------------------------|-----------|--------|-------|
| | Screened | 15 | 15 |
| Enrolled | 10 | 10 | 20 |
| Age Range of Subjects: | 2-5 years | | |

Please indicate if any of the following populations will be used in your research:

- | | |
|---|--|
| <input type="checkbox"/> Non-English speaking | <input type="checkbox"/> Mentally Disabled/Incapacitated |
| <input type="checkbox"/> Mentally Retarded | <input type="checkbox"/> Prisoners |
| <input type="checkbox"/> Fetuses | <input type="checkbox"/> Abortuses |
| <input checked="" type="checkbox"/> Normal Volunteers | |

If you checked off any of the preceding, explain how you will obtain informed consent. What precautions will you take? What is the rationale for using this population?

Normal pediatric volunteers will be enrolled. Due to the intense nature of education and follow-up for participants and contacts, and because this is a small pilot study, we will not enroll children who do not have access to an English-speaking parent in the household. Expanded pediatric studies will include non-English speaking children and their parents.

Current policy is to encourage the enrollment of women of childbearing age in research to increase the generalizability of research findings. If women of childbearing age are to be included in the study, explain how you will advise the subject of the possible risks to the fetus. What data are available regarding the risks to the fetus? If women of child-bearing age are NOT included, provide a scientific justification for their exclusion.

Pregnant women are not included. This is a pediatric study.

If pregnancy is an exclusion criterion, describe how you will determine and/or monitor the subjects for pregnancy status (initial screening and periodic screening). What steps will be taken if a subject becomes pregnant during the course of the study?

Pregnancy in the family of pediatric participants or intention to become pregnant within one month after vaccination is a study exclusion criteria. Live viral vaccines are contraindicated during pregnancy. Shedding of vaccinia virus could pose a danger to the fetus. Although less than 50 cases of fetal vaccinia infection have been reported, vaccinia virus has been reported to cause fetal infection on rare occasions.

WOMEN AND MINORITIES – Provide a description of the gender and ethnic distribution anticipated in your subject population and of the prevalence of the disease process under study in the general population by gender and ethnicity. **Provide a justification** if the anticipated study population's gender and ethnicity deviates markedly from these distributions within the general population. If the local distribution differs markedly from the national distribution, **described how this will be remedied.**

We anticipate enrollment of an equal number of males and females. The ethnic distribution will be similar to that in the surrounding community: 36% white, non-Hispanic, 44% Hispanic, 12% black, non-Hispanic, 7% Asian or Pacific Islander and 1% other of American Indian/Alaskan Native.

CHILDREN (<18 years old) Current policy is to encourage the enrollment of children in research to increase the generalizability of research findings. **Provide** the anticipated distribution of subjects by age in your subject population and the prevalence of the disease process under study in the general population by age. **Provide a justification** if the anticipated study population's age distribution deviates markedly from this distribution within the general population. **Attachment 5** describes the four federal categories of research that involves children (Sections 46.404, 46.405, 46.406 and 46.407). **Choose one and justify.**

46.404 46.405 46.406 46.407

This research involves greater than minimal risk to pediatric participants, but presents the prospect of direct benefit. Nearly all participants are expected to develop protective immunity against vaccinia which provides protection against smallpox (variola).

LOGISTICS

PLACEBO: If this study involves a PLACEBO, please complete Attachment 4.

DRUGS/DEVICES: If this study involves any drug which is **NOT** described in the PDR **OR** if it involves an experimental device, complete the Drug/Device Information Sheet (Attachment 1). If the drug **IS** described in the PDR, indicate below the publication date of the PDR being referred to and the page(s) on which the drug's description appears.

Dryvax is investigational, and is listed under BB IND number 8929.

RECRUITMENT: Describe the population you intend to recruit from (e.g., clinic population, general public).

Our primary source of recruitment will be the pediatric clinic at the Harbor City Kaiser Permanente Medical Center, where we have conducted past studies. Contact will be made through direct physician referral and parents will be approached during the child's well child care visit or recheck visit, consistent with recruitment methods for other studies. Secondly, we may enroll children from the surrounding community, with notification of the child's primary care provider.

Check the type of document(s) you will use in your recruitment process and understand that any type of advertisement must first be approved by the IRB.

Brochures Contact Letters Other (describe): Parent introductory letter (used for other studies): Final version pending
 Flyers: final version pending Internet Print Advertisements Radio Television Newsletters None

PAYMENT/REIMBURSEMENT:

| | | | | | | | |
|----------------------|-------|-------------------------|----|----------------------------|--|-------------------|---|
| Total Payment | \$120 | Number of Visits | 12 | Schedule of payment | \$10/visit Also, a \$40 gift certificate to a children's store if the child completes the study | Pro rated? | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Payment only for visits completed |
|----------------------|-------|-------------------------|----|----------------------------|--|-------------------|---|

ADDITIONAL COSTS – Are there additional costs to the patient other than routine patient care? Yes No If **YES**, explain.

LEAVING THE STUDY – Describe the consequences to the patient if either: 1) the Principal Investigator removes the subject; **or** 2) the subject withdraws (e.g., effect on payment/reimbursement, effect on future treatment, etc.).

If the principal investigator removes the subject, there will be no negative consequences for the child's routine pediatric healthcare. However, there may be follow-up telephone calls to make sure that there are no adverse reactions and that the site has healed adequately. If the parent withdraws the child, they will only receive reimbursement for the visits attended, and the \$40 gift certificate to a child's store for study completion will not be provided.

SPECIAL CHARACTERISTICS – Other special characteristics of the subject (e.g., old age, specific disease process, etc.).

Healthy children, 2 to 5 years of age.

LOCATION OF STUDY/EMERGENCY PROCEDURES – Indicate where the study will be carried out. If outside the MAIN UNIT (Unit I), **describe** your plan if a medical emergency happens.

The vaccine will be administered in the Outpatient GCRC, Liu Research Building, first floor.

COLLABORATING INSTITUTION(S) – Indicate the name and address of the collaborating institution(s); name and telephone number of the contact person. **NOTE** This does not refer to the funding agency or sponsor-initiated multicenter studies.

Investigators at Cincinnati Children's Hospital will enroll 20 subjects concurrently.

OFF-CAMPUS RESEARCH – If off-campus research is involved, **complete** Attachment 6, the Off-Campus Research Form (REI Form F-370)

CONSENT

A. If a consent form **IS** needed, attach your final draft.

There are 4 consent forms for this study: 1) main study consent form, 2) HIV testing consent form, 3) consent to administer VIG (Vaccinia Immune Globulin) in the event of a vaccinia-related complication, 4) consent to administer Cidofovir in the event of a severe vaccinia-related complication inadequately treated with VIG.

B. Discuss when (in relation to starting the protocol) and under what circumstances the subject will sign the consent form.

The parent will receive educational material and a thorough expectation about what to expect during the study and the risks and benefits to the child. The consent form will be signed prior to any study procedures.

C. If you feel that a consent form is **NOT** needed, explain. To justify a waiver, consult attachment 7.

NA

D. If any section(s) of the consent form were omitted, explain why.

None.

KEY PERSONNEL – List all key personnel including study coordinators, phlebotomists, etc. that will be involved in this study and indicate the date they were certified (passed the mandatory testing requirements) and who will be obtaining informed consent from study participants.

| Name (with degree) | Date Certified | Obtaining Consent |
|---------------------------------|----------------|---|
| Joel Ward, M.D. | 8/29/2000 | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Michael Marcy, M.D. | 9/29/200 | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Thuan Le, M.D. | 10/16/2000 | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Susan Partridge, R.N., C.C.R.C. | 8/28/2000 | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Pat Chatfield, N.P., C.C.R.C. | 9/15/2000 | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |
| Carol Farnworth, R.N., C.C.R.C. | 8/31/2000 | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No |

PROTOCOL DRUG/DEVICE INFORMATION (PDI)¹ - ATTACHMENT 1A

THIS FORM MUST BE TYPED – IT IS AVAILABLE ON THE REI INTRANET
(ONE DRUG/DEVICE PER FORM)

GENERAL INFORMATION:

| | |
|--|--|
| Sponsor Protocol #: None | REI Project Number: 10140-01(101) |
| Storage Location (include room #)ⁱⁱ: RB3 (Liu Bldg.) | Storage Requirementⁱⁱⁱ: Vaccine 2-8°C Diluent at room temperature |
| Drug Controller^{iv}: S Partridge | Telephone #: 781-3630 |
| Drug/Device Name: Dryvax Vaccine | E-mail: partridge@humc.edu |
| Manufacturer: Wyeth Laboratories | Other Names (if any): |

Drug/Device Acquisition (Check one): Supplied by Sponsor Purchased by Investigator Other

Special Handling Requirements (if any):

Limited, secure access. A dedicated, locked, monitored refrigerator will be used. The vaccine will be placed in a plastic ziplock bag within the refrigerator.

Is the compound cytotoxic? Yes No
If yes, discuss/attach information on emergency handling procedures and special precautions.

Drug to be administered by:

M.D. (Investigator) M.D. (Staff) R.N. (Research)
 R.N. (Staff) Patient Other – Specify:

Administration Procedures:

After dilution, Dryvax is given in the upper outer arm, using 5 intradermal punctures (for children) with a sterile bifurcated needle. The technique is called “scarification.” Training will be provided by CDC videotape and direct observation of experienced staff at St. Louis University.

Known Side Effects:

3-5 days after vaccination, a small bump develops at the vaccination site, followed by a blister which becomes pus-filled. The maximum size is reached at about 8-10 days, but can vary. Erythema, induration and soreness at the site is common, as is enlarged axillary lymph nodes. Fever, malaise, muscle aches and chills may occur, and is usually seen around days 7-10. Serious side effects following vaccination are rare but may include: vaccinia necrosum, eczema vaccinatum, inadvertent autoinnoculation (primary concern is ophthalmic), generalized vaccinia, post vaccinal encephalitis and death.

Investigator’s Name: | Joel Ward, M.D. **Telephone #** | 781-3636 **E-mail** | joeward@ucla.edu

24-Hour Contact Number for protocol inquiries:

| Research Coordinator: | Telephone # | Pager | E-mail |
|-----------------------|-------------|-------|--------------------|
| Susan Partridge | 781-3630 | | partridge@humc.edu |

Study Phase (Check One): Phase I Phase II – not really specified Phase III Post Marketing Trial (Phase IV)

REI Contract Officer: | Ashley Hogan **Telephone #** | 222-3621

- i. Information provided on this form will be used to track all drugs/devices used for protocols on campus, per JCAHO requirements.
- ii. The location must be a locked area that is non-accessible to non-study personnel.
- iii. Person responsible for maintaining control over drug inventory.
- iv. For example, locked cabinet, refrigerated, etc.



PROTOCOL DRUG/DEVICE INFORMATION (PDI)ⁱ - ATTACHMENT 1B

THIS FORM MUST BE TYPED – IT IS AVAILABLE ON THE REI INTRANET
(ONE DRUG/DEVICE PER FORM)

GENERAL INFORMATION:

| | |
|--|---|
| Sponsor Protocol #: None | REI Project Number: 10140-01(101) |
| Storage Location (include room #)ⁱⁱ: RB3 (Liu Bldg.) | Storage Requirementⁱⁱⁱ: 2-8°C |
| Drug Controller^{iv}: S Partridge | Telephone #: 781-3630 |
| Drug/Device Name: Vaccinia Immune Globulin (VIG) | Other Names (if any): |
| Manufacturer: | E-mail: partridge@humc.edu |

Drug/Device Acquisition (Check one): Supplied by Sponsor Purchased by Investigator Other

Special Handling Requirements (if any):

Can only be obtained from CDC. Store at 2-8° C in a locked refrigerator.

Is the compound cytotoxic? Yes No

If yes, discuss/attach information on emergency handling procedures and special precautions.

Drug to be administered by:

M.D. (Investigator) M.D. (Staff) R.N. (Research)
 R.N. (Staff) Patient Other – Specify:

Administration Procedures:

Recommended dosage is 0.6ml/kg body weight. Administer intramuscularly as soon as possible after onset of complications.

Known Side Effects:

Anaphylactic reactions following administration of VIG are rare but possible. Local tenderness and stiffness around the shot site may occur and may last 1 to 2 days.

Investigator's Name: Joel Ward, M.D. **Telephone #:** 781-3636 **E-mail:** joeward@ucla.edu

24-Hour Contact Number for protocol inquiries:

| Research Coordinator: | Telephone # | Pager | E-mail |
|-----------------------|-------------|-------|--------------------|
| Susan Partridge | 781-3630 | | partridge@humc.edu |

Study Phase (Check One): Phase I Phase II – not really specified Phase III Post Marketing Trial (Phase IV)

REI Contract Officer: Ashley Hogan **Telephone #:** 222-3621

- v. Information provided on this form will be used to track all drugs/devices used for protocols on campus, per JCAHO requirements.
- vi. The location must be a locked area that is non-accessible to non-study personnel.
- vii. Person responsible for maintaining control over drug inventory.
- viii. For example, locked cabinet, refrigerated, etc.

FOR FDA-APPROVED MARKETED DRUGS, ATTACH A CURRENT PACKAGE INSERT OR REFER TO PAGE NUMBERS IN CURRENT PDR

PROTOCOL DRUG/DEVICE INFORMATION (PDI)ⁱ - ATTACHMENT 1C

THIS FORM MUST BE TYPED – IT IS AVAILABLE ON THE REI INTRANET
(ONE DRUG/DEVICE PER FORM)

GENERAL INFORMATION:

| | | | |
|--|-----------------|---|---------------------------------|
| Sponsor Protocol #: | None | REI Project Number: | 10140-01(101) |
| Storage Location (include room #)ⁱⁱ: | RB3 (Liu Bldg.) | Storage Requirementⁱⁱⁱ: | Store vials at room temperature |
| Drug Controller^{iv}: | S Partridge | Telephone #: | 781-3630 |
| Drug/Device Name: | Vistide | Other Names (if any): | Cidofovir |
| Manufacturer: | Gilead | E-mail: | partridge@humc.edu |

Drug/Device Acquisition (Check one): Supplied by Sponsor Purchased by Investigator Other

If checked above, please specify source:

Special Handling Requirements (if any):

Dilute in 100ml of normal saline. Store at 2-8C and administer within 24 hours of preparation.

Is the compound cytotoxic? Yes No

If yes, discuss/attach information on emergency handling procedures and special precautions.

Prepare in a class II laminar flow hood biological safety cabinet. Wear gloves, gown with knit cuffs. Recommended method of disposal is high temperature incineration.

Drug to be administered by:

M.D. (Investigator) M.D. (Staff) R.N. (Research)
 R.N. (Staff) Patient Other – Specify:

Administration Procedures:

Intravenous infusion of 5mg/kg body weight over a one hour period once weekly for two weeks. (May be adjusted for pediatric patients after consultation with FDA.) Infusion of normal saline and oral probenidicid must accompany each dose of cidofovir.

Known Side Effects:

Dose-dependent nephrotoxicity. Contraindicated in individuals with elevated serum creatinine. Neutropenia. Decreased intraocular pressure. Anterior uveitis/iritis. Metabolic acidosis.

Investigator's Name: Joel Ward, M.D. **Telephone #:** 781-3636 **E-mail:** joeward@ucla.edu

24-Hour Contact Number for protocol inquiries:

| Research Coordinator: | Telephone # | Pager | E-mail |
|-----------------------|-------------|-------|--------------------|
| Susan Partridge | 781-3630 | | partridge@humc.edu |

Study Phase (Check One): Phase I Phase II Phase III Post Marketing – Off label use for emergency
2001 PDR page 1332

REI Contract Officer: Ashley Hogan **Telephone #:** 222-3621

- ix. Information provided on this form will be used to track all drugs/devices used for protocols on campus, per JCAHO requirements.
- x. The location must be a locked area that is non-accessible to non-study personnel.
- xi. Person responsible for maintaining control over drug inventory.
- xii. For example, locked cabinet, refrigerated, etc.

FOR FDA-APPROVED MARKETED DRUGS, ATTACH A CURRENT PACKAGE INSERT OR REFER TO PAGE NUMBERS IN CURRENT PDR



PROTOCOL DRUG/DEVICE INFORMATION (PDI)ⁱ - ATTACHMENT 1D

THIS FORM MUST BE TYPED – IT IS AVAILABLE ON THE REI INTRANET
(ONE DRUG/DEVICE PER FORM)

GENERAL INFORMATION:

| | | | |
|--|------------------------------|--|----------------------------------|
| Sponsor Protocol #: | None | REI Project Number: | 10140-01(101) |
| Storage Location (include room #)ⁱⁱ: | RB3 (Liu Bldg.) | Storage Requirementⁱⁱⁱ | 2-8°C |
| Drug Controller^{iv}: | S Partridge | Telephone #: | 781-3630 |
| Drug/Device Name: | Viroptic Ophthalmic Solution | Other Names (if any): | Trifluridine ophthalmic solution |
| Manufacturer: | Monarch | E-mail: | partridge@humc.edu |

Drug/Device Acquisition (Check one): Supplied by Sponsor Purchased by Investigator Other

If checked above, please specify source:

Special Handling Requirements (if any):

Is the compound cytotoxic? Yes No

If yes, discuss/attach information on emergency handling procedures and special precautions.

Drug to be administered by:

M.D. (Investigator) M.D. (Staff) R.N. (Research)
 R.N. (Staff) Patient Other – Specify:

Administration Procedures:

One drop into the cornea of the affected eye every 2 hours while awake from a maximum of 9 drops daily.

Known Side Effects:

Mild, transient burning/stinging and apbbebral edema.

Investigator's Name: | Joel Ward, M.D. **Telephone #** | 781-3636 **E-mail** | joeward@ucla.edu

24-Hour Contact Number for protocol inquiries:

| Research Coordinator: | Telephone # | Pager | E-mail |
|-----------------------|-------------|-------|--------------------|
| Susan Partridge | 781-3630 | | partridge@humc.edu |

Study Phase (Check One): Phase I Phase II Phase III Post Marketing – Current PDR Page 2104

REI Contract Officer: | Ashley Hogan **Telephone #** | 222-3621

- xiii. Information provided on this form will be used to track all drugs/devices used for protocols on campus, per JCAHO requirements.
- xiv. The location must be a locked area that is non-accessible to non-study personnel.
- xv. Person responsible for maintaining control over drug inventory.
- xvi. For example, locked cabinet, refrigerated, etc.

FOR FDA-APPROVED MARKETED DRUGS, ATTACH A CURRENT PACKAGE INSERT OR REFER TO PAGE NUMBERS IN CURRENT PDR