A MULTICENTER, RANDOMIZED DOSE RESPONSE STUDY OF THE SAFETY, CLINICAL & IMMUNE RESPONSES OF DRYVAX VACCINE ADMINISTERED TO CHILDREN 2 TO 5 YEARS OF AGE

The study was presented by . The study will evaluate the potency, dose and safety of the Dryvax smallpox vaccine which is available in the current stockpile. Subjects will be randomized to receive the vaccine either or at 1:5 dilution. The vaccine will be administered using 5 intradermal punctures in contrast to the 10 - 15 punctures used in the adult studies. The site will then be covered by a semi-occlusive dressing which differs from the conventional vaccination as administered 30 years ago. The variables that will be studied are related to the potency of the vaccine which has been in storage for 30 years, the number of intradermal punctures, the dilution of the vaccine and the use of a semi-occlusive dressing. Safety, the number of takes and immune responses will be studied.

Dr. commented on the clinical experience related to the administration of the vaccine over 30 years ago. The efficacy (i.e. "takes") the mild nature of the adverse events and the lack of spread to contacts was noted.

There was much discussion regarding the differences regarding potential contacts in the present-day community in contrast to the past. Much of the current population has never been immunized. There are more potential high risk contacts due to HIV, immunosuppression, steroid use, transplantation, etc.

The efficacy reported in the recent studies in adults involving undiluted 1:5 dilution, 1:10 dilution and 1:100 dilution was discussed.

The study is limited to children 2-5 years of age. Children will be excluded from day care or school for at least 30 days following vaccination. In the first stage subjects will receive the undiluted (20 infants) or the 1:5 dilution (20 infants). Pending these results there may be a second phase to this study following review by the DSMC, the NIH and the Institutional Review Board. A subset of subjects will have blood collected for antibody studies.

In the unlikely possibility that any subjects or contacts develop severe adverse events treatment will be offered with VIG and Cidofovir. The latter drug has been approved by the FDA but has not been approved for this indication.

The NIH protocol, the Cincinnati Children's Hospital Medical Center study protocol, the consent forms (3), Fact Sheet, Parent Information Sheet, consent form comprehension quiz, and the Dear Doctor letter were reviewed.

The major concern was related to the purpose of the study. Why is it necessary to do this study in children? In a previous multicenter study, 680 healthy young adults who had no history of previous smallpox vaccination were randomized. Of the 234 who were vaccinated with the 1:5 dilution 232 (99.1%) developed a clinical take. While the total of number of adults vaccinated in this study was small (680 subjects), the total sample size for the present trial will only be 40 subjects (20 volunteers per group). Is there any reason to expect that the response in children will be different than adults? What is the indication for performing this study in children? What additional information will be obtained?

Historically, the dose of smallpox vaccine administered to adults and children was the same. Despite limitations regarding the vaccine the immunization procedure was effective in eradicating this disease with no differences in the adverse events observed in infants, children and adults.

Based on the severity of the potential adverse events for the participants and other exposed individuals the study is classified as more than minimal risk.

As noted in the consent form "my child will receive no direct benefit from participating in this study." The potential benefits to society are questionable based on the comments noted above. Federal Regulations (45 CFR 46) state that research involving greater than minimal risk with no prospect of direct benefit to individual subjects are permissible only if the research "presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children." This raises the question regarding the justification for conducting this study in children and the scientific merit of the information that will be obtained.

Additional comments were noted:

1) Because of concerns regarding spread of the virus, children "must not attend day care or school for at least 30 days after vaccination or until the scab falls off." Dissemination of the virus is not limited to contacts in day care or school. Will these children be isolated from all contact with other children and/or adults (i.e. church, birthday party, playground, baby-sitters, etc.)? What if the virus is spread to a parent? Will the parent be unable to go to work? What about potential lost wages? If relevant, this should be included in the consent form.

2) The policy of Cincinnati Children's Hospital Medical Center regarding compensation for research related injury is noted in the consent form. Since the benefits, if any, appear to be societal what is the policy of the NIAID regarding compensation in the unlikely event that a serious devastating adverse event should occur in a normal healthy 2-5 year old enrolled on this study?
3) Has smallpox vaccination been discontinued universally? Are there any countries where smallpox vaccination continues to be practiced as part of routine immunizations?
4) The Dear Dr. letter requests that physicians provide the investigators "with a copy of the child's immunization records." This will require that the parent provide permission for the release of this medical information. Why is this information required? The inclusion criteria note only that the subject has received "no live attenuated vaccines within prior 30 days".
5) The consent form states that blood specimens will be stored for "future research only when they may help future tests or learn more about smallpox vaccine or other diseases." Elsewhere the consent form refers to the storage of "unused identified samples forever for future smallpox research." The Institutional Review Board cannot grant approval for the use of identified samples of future research for presently undefined "other diseases."

In summary the major concerns were related to the justification for conducting this study in children, the potential risks for the subjects and the contacts and the potential benefits for the subjects and society.

In lieu of extensive communications between the investigator and the Institutional Review Board and subsequent presentation of the responses on behalf of the investigator it was requested that the investigator attend an Institutional Review Board meeting in order to respond to these concerns directly.