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Response to the Proposal for a Smallpox Vaccine Trial in Children.

I have reviewed the proposed trial protocol and the accompanying documentation.

I suggest approval **under two Federal Regulations.**

1. I believe the trial can be approved under CFR 46.405. Both Cincinnati Children's Hospital and the Kaiser Permanente Southern California approved it under this heading under Subpart D of the Federal Regulations of Protection of Human Subjects. It missed approval under this heading by one vote at Harbor-UCLA. I am surprised that this study was not initially approved as meeting the test of providing benefit to the recipient. (CFR 46.405) While it is not yet clear whether the 1:5 dilution of vaccine will produce a Jennerian vesicle and produce immunognicity in all of the subjects, nearly all will respond to the undiluted and it is likely some or many will respond to the 1:5 based upon the adult data. These children would have benefit from the vaccination because they would be immune to smallpox.

   It is arguable whether immunity to smallpox is a great benefit at this time. In the absence of a known risk for a bioterrorism-related risk for smallpox dissemination the risk for any individual, while probably small, cannot be calculated. In this sense the benefit from the trial cannot be known. We do know, however, that there are many individuals who perceive the risk as being great enough for them to demand smallpox vaccine or at least to wish to be vaccinated and have their children vaccinated if the

vaccine is available. It is these people who will volunteer for this study. The study will attract such people and they will perceive immunization against variola to be valuable.

Informed medical people, epidemiologists and strategists differ in their assessment of the risk of smallpox dissemination, therefore it is reasonable for members of the public to differ also. If they perceive the risk as great enough to enroll their child in the study *they will benefit* if the child becomes immune or at least they and many informed individuals will see this as a benefit. The risk of severe sequelae from the vaccine being small I judge the benefits to be greater than the risks.

I distinguish the benefits and risks to the participants in this study to be different from mass vaccination of the general population where I believe the risks outweigh the benefits. In this study the participants are self selected for great interest in becoming immune to smallpox, they will have received considerable information about the risks, and will have been selected as having lower than average risk of sequalae by the inclusion criteria.

2. This study can also be approved under CFR 46.407

(i) I believe it "presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem afflicting the health or welfare of children."

There are two circumstance in which mass vaccination of children may occur. The first is in the event of an actual release of variola virus.

1. If there is a case of smallpox either the ring vaccination strategy will be used or some form of mass vaccination will be occur. In either case children will then be considered appropriate candidates for vaccination. Unless these studies are done the children who are vaccinated in an emergent situation will essentially be an experimental group. They will not be able to give informed consent, the opportunities for appropriate screening and follow-up will be poor and we may never know if they got an appropriate dose, dilution, and type of vaccine. If the vaccine used is not immunogenic in children they will be vulnerable to smallpox.
2. The government is currently considering voluntary vaccination. While this may or may not be a good idea, if it occurs decisions will have to be made about how children will be handled. Will they be subjects for voluntary vaccination in the midst of a mass vaccination program? What vaccine will they get? What dose? What dilution? What expectation for side effects? In order to provide information to physicians giving advice to parents and to provide information for health policy experts the information from this study and probably additional studies in children must be available. It is possible that the information gleaned from these 40 children will provide the basis for advising the parents of millions of other children. Thus there is no question that it meets this test of 407.
(ii). I believe the study is ethical in that while the vaccination presents some risk to the vaccinees, the risk is small as serious and permanent sequelae are rare with this vaccine. Although I am concerned about the risk of this vaccine for large numbers of people the risk to an individual is small. The minor discomforts of the vaccine are seen in many vaccinees but do not represent a major concern. The

protocol includes adequate information about both the minor and major side effects and allows parents to make an informed decision. It protects the subjects with regard to minimizing risk and includes the best plan possible for dealing with rare serious sequelae. Should parents wish to opt out of the study they are adequately protected. I agree with the IRB conclusions that assent from the children is not realistic.

(iii). I do believe adequate provisions are made for soliciting permission of parents and guardians.