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To: Dr. Greg Koski and Dr. David Lepay

Title: Summary Opinion concerning DMID 01-650 Protocol, "A Multicenter, Randomized, Dose Response Study of the Safety, Clinical and Immune Responses of Dryvax Administered to Children 2-5 years of Age, proposed by UCLA Center for Vaccine Research, and Cincinnati Children's Hospital Medical Center.

Introduction:

I have used the following factors in expressing my professional opinion as to this proposed study:

1. The threat of smallpox as a bioterrorist agent is real, probably very small, but not zero
2. It is prudent to vaccinate selected adults initially to provide teams immune to smallpox who can respond to an attack, if it occurs
3. In the event of an attack, it will be necessary to vaccinate a segment, or all of the civilian population, including children.
4. Smallpox vaccine is a safe, effective vaccine, but has predictable side effects in a small proportion of recipients, some of which are predicated on known susceptibility(ies) of the proposed vaccinee, and some which are not.
5. It has been at least 30 years since routine childhood vaccination was practiced in the United States.
6. There are at least two types of vaccines potentially available; a calf-lymph preparation stored since 1970 and currently not licensed, and a tissue culture vaccine currently being produced and tested. Neither of these vaccines has been tested in children; a small number of adults have received them in clinical trials this year. The calf lymph has also been used to vaccinate adult lab workers who work with orthopox viruses.
7. A limited amount of information has been published concerning the calf-lymph vaccine and its effect in adults from recent clinical trials
8. There is no effective treatment for smallpox although cidofovir has been suggested as a potential antiviral agent. The only preventive is smallpox vaccine (vaccinia).
9. At the present time, no immediate benefit accrues to any vaccinee from smallpox vaccine, in the event of a smallpox bioterrorist attack, vaccinated individuals will have a very high degree of protection and vaccination of those exposed, if carried out within 2-3 days offers significant degree of protection.

Opinion:

Summary: I believe this protocol should be approved., but have a question concerning undiluted vaccine use.

Reasoning:

1. The vaccine to be used has been stored since 1970 and appears to be quite effective in adults, even at a 1/5 dilution using 15 insertions with a bifurcated needle in a 5 mm area of the deltoid skin region (30 actual punctures). No children have been tested.
2. It is critical to know whether the vaccine given by 5 insertions with the bifurcated needle (10 punctures) in children will result in adequate response rate before we need to do this on a massive level should smallpox be introduced. I can conceive of panic and chaos and the need for multiple vaccinators, few of which will be experienced with vaccination, who would be immunizing children without a clear-cut protocol to follow. This study has the potential of providing a protocol to use in the future.
3. In the near future we will have a tissue culture derived vaccine and this study can provide benchmarks by which controlled trials in children with the tissue culture vaccine can be undertaken. Without these trials we would delay these benchmarks to the new vaccine trials and should smallpox intervene, be at a disadvantage.

4. The major concerns for this trial are three and my responses are in parentheses after each concern:
 - a. There is no direct, immediate benefit to the children (this is true, but is counterbalanced by the societal benefit now, and the potential benefit in the event of a smallpox bioterrorist introduction)
 - b. There are significant safety concerns for the child vaccinee (again true, but counterbalanced by the design of the study and the site care proposed)
 - c. Since this vaccine is identical to those used in the past, it is unnecessary to re-test it in children today (this is also true, but we have a huge time gap between studies conducted in the 50's and 60's and today, the current vaccine is NOT licensed which could pose a problem in its use in children absent clinical trials, and we need to know if 5 insertions with the bifurcated needle using the current protocol achieves the same results.)

5. I am concerned about the need to use undiluted vaccine. It is clear from the adult trials that a rigorous response has been encountered in many vaccinees with the 1/5 dilution and 15 insertions. I think it prudent to test this vaccine first in children at the 1/5 dilution and the 5 insertion level before any undiluted vaccine is used. If the 1/5 dilution is successful (i.e. achieves a satisfactory local response at the same high rate as in adults) one need not ever use undiluted. If it is not successful then a second trial could be undertaken using undiluted vaccine at 5 insertions and the 1/5 dilution with 15 insertions. I doubt these later trials would be necessary, given the adult data (In fact, I would opt for less than 15 insertions, even in adults, given the reaction seen at that level).