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Panel Review of Research Involving Children under Subpart D; "A Multicenter, Randomized Dose Response Study of the Safety, Clinical and Immune Responses of Dryvax® Administered to Children 2 to 5 Years of Age"

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General Remarks:

An ethical problem, like any other sort of problem, is best resolved by bringing the facts to bear on the issue, and by eliminating uncertainty. Uncertainty, unfortunately, is one variable that cannot be fully eliminated in the analysis of this (or any) study. The possibility of a bioterrorist attack against the United States is real. Its probability can be guessed at by experts, but the likelihood of such an event is ultimately unquantifiable. Recent experience has heightened the appreciation of laypersons and expert advisors alike to the merits of preparedness to prevent or limit the harmful sequelae of a terrorist event. Bioterrorism with the use of smallpox as a weapon is a possibility that the government and the American people face. Even if the probability is low, the potential for harm in such an event is large, as smallpox infection carries a 30% mortality rate. The study under review is one component of a public health preparedness response.

The study poses concerns of justice. The primary motivation behind the study is to maximize potential distribution of a [currently] scarce resource – 15 million doses of smallpox vaccine that have been stockpiled for twenty years since the eradication of the disease worldwide. Fair distribution of potential risks and benefits among potential study populations is a separate justice issue that inheres in any study. The potential for abuse or exploitation increases when subjects cannot make their own assessments of the relative risks and benefits of the proposed research. They are, in effect, vulnerable to abuse by others. The study population at hand, children ages 2-5, are by definition, a vulnerable class of research subjects.

The research question at hand is relatively straightforward. It is a randomized dose response study. The vaccine has been tested before and administered in a large scale fashion to children in the US. Its risks are, for the most part, known. Recent studies in the adult population have shown that the vaccine has not lost its potency in storage. Dose response among the pediatric population at the 1:5 dilution has not been studied,

and is necessitated by the limited availability of the vaccine. If the dilution provides adequate immune response, then limited supplies can be distributed to more people than would be possible with a 1:1 dilution.

The ethical analysis of the study is complicated by the fact that a second generation vaccine is under development. The new vaccine - sterile, derived from cell culture, will be safer and can be mass produced quickly. Clinical trials in adults are apparently underway but not complete. Whether there are plans for trials in children is unknown to this reviewer. The issue, then, is the temporal window between completion of the dose response study under consideration and the availability of pediatric clinical trials of the safer vaccine. Placing healthy children at risk of harm for no individual benefit merits serious ethical consideration. Some might argue that it should never be allowed. The rejoinder to that argument is that, in this context at least, children will become research subjects by default in the event of a bioterrorist attack; subjects in less controlled and safe circumstances.

Applicability Under the Common Rule:

45 CFR §46.404 (21 CFR §50.51). Research not involving greater than minimal risk.

The study is not approvable under this category as the known risks from the vaccine are greater than minimal for both the subject and others who might be exposed via contact with the subject.

45 CFR §46.405 (21 CFR §50.52). Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

The study is not approvable under this category. While benefit may, in theory, accrue to individual subjects, it is contingent upon a bioterrorist attack occurring in the US in a locale in which the child might be exposed. The observation could be made that the child might benefit in the future if he or she derives altruistic pleasure from having participated in the study. Although altruism is an important motivation, and certainly one that confers individual benefit, this sort of "substituted judgement" is impossible to make. Such value judgements should only be acted on by those capable of making them.

45 CFR §46.406 (21 CFR §50.53). Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

The prospective subjects in this study are normal volunteers. No disorder or condition entails. The risks posed by the vaccine constitute more than a minor increase over minimal risk to the subjects and to those who might be exposed via contact with the subject.

45 CFR §46.407 (21 CFR §50.54). Research not otherwise approvable which represents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

The study is approvable under this category.

1.The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

The risk of a biological attack with smallpox as a weapon constitutes a serious problem that would affect the health of children in the US. One can assess the seriousness of the problem using the criteria that one uses for assessing risk: probability and magnitude. The probability of a bioterrorist attack is unknown but real. Even a remote probability, however, must be balanced by the magnitude of the problem, or harm that would result from it. A 30% mortality rate among those infected constitutes a serious problem.

2. The research will be conducted in accordance with sound ethical principles;

The investigators have taken great care in selecting their prospective research population. No subjects or classes of subjects are being systematically selected because of easy availability, compromised position, or manipulability. The potential subjects have been selected for reasons directly related to the problem being studied. Recruitment in each of the settings will/should reflect the demographics of the area population.

All children in the US (and in other countries) stand to benefit from the research in the event of a bioterrorism attack with smallpox as the weapon.

While there are provisions to treat research related injury, there is some exculpatory language in the draft consent documents. Any research subject who is injured as a direct result of participating in this study, should be compensated. Compensation should include the costs of medical care and rehabilitation. Compensation for research injury,

especially within the 45 CFR §46.407 (21 CFR §50.54) is a moral duty owed by the sponsors of the research.

Compensation to parents/guardians for time and travel expenses is reasonable. However, the gift certificate to the child should NOT be predicated on completion of the study. Any child who receives the study vaccine should receive a gift certificate. This is fair, as each child will individually assume the risk and burden of the vaccine whether or not she or he completes the study. Predicating the gift certificate on study completion is unfair to the child (punishes him/her for the actions of parents/guardians), and may be coercive.

3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.

The age range (2 to 5) of prospective subjects precludes assent procedures. The reviewing IRBs are not consistent regarding the requirement of permission from both parents. Permission of both parents - or guardian(s) – (if available) is required and should be consistent at each of the sites. All consent and educational documents should be available in the languages spoken by the participants and their families. Native American, Asian and Hispanic families must be accommodated and translators should be available during the consent process and during visits. All parents/guardians should be given educational materials prospectively (not just upon request). All parents/guardians should be queried about their understanding of the study, its risks and probable lack of benefit. They should demonstrate understanding prior to signing a consent document.

Written Consent Document:

1. Use of the term “treatment” in the consent documents for the vaccine trial, or in conversations about the study, implies empirically derived standard therapy. The term “treatment” has no place in this trial relative to the administration of the study vaccine or other study interventions.
2. All consent documents should be examined for readability levels. My understanding is that the American public reads at a 5th (not 8th) grade level.
3. The consent document needs editing.
4. The dilutional scheme needs better explanation.
5. All references to “the child” should be replaced with “your child.”
6. A member of the study team should be available 24hrs/day in case of question or emergency. This contact number should be in the consent document. The parent should not have to resort to the

emergency room/staff unfamiliar with the study unless directed to by study personnel or in case of a true emergency.

7. The “benefits” section of the consent document should clarify that that vaccination against the virus is a benefit only in the event of a bioterrorism attack with smallpox as the weapon. Since smallpox has been eradicated, it is otherwise not a threat.
8. Lack of charge for participation in this study is not a benefit and should be deleted.
9. Continued routine and sick care from primary care providers is not a benefit and should be deleted.
10. The alternatives section is strangely worded. These are well children being recruited. Their alternative is not to participate in the study. Period.
11. The request for tissue storage for unspecified future research to “even out tests,” etc. is untenable and should be deleted. This reviewer is shocked to see language such as “By signing below you will be agreeing to allow the researchers to decide what to do with any surplus tissue removed from your child during the research above….”!
12. As per above, the exculpatory language regarding lack of financial responsibility on the part of the sponsor or investigating institution for research related injury is unethical and should be eliminated.

Other:

1. Parents/Guardians should demonstrate the application of dressing materials prior to leaving the clinic; not just be told or given information on how to do it.
2. There is no plan discussed for disseminating the study results to the parents of the subjects. This should be outlined in the protocol and approved by the IRB.
3. The Data and Safety Monitoring plan is not well articulated in the protocol. Its responsibilities and composition need to be spelled out more clearly.