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Dear Doctor Koski and Doctor Lepay:

I have appreciated the opportunity to review the protocol for a multicenter randomized dose response study of the safety, clinical and immune responses of Dryvax smallpox vaccine in children. The circumstances giving rise to the proposal of this trial are disappointing given the great hope we all shared in the eradication of smallpox from human populations. Nevertheless, modern realities and societal prudence necessitate consideration of measures necessary to protect people anew in the case of a smallpox event.

Having reviewed the protocol, informed consent documents and scientific background, I conclude that the trial of the Dryvax vaccine in children is not approvable under 45 CFR 46.404, 46.405, or 46.406 (also 21 CFR 50.51, 50.52, or 50.53). I believe the research is approvable under 45 CFR 46.407 (and the corresponding 21 CFR 50.54), with some modification of the protocol and informed consent. My discussion addresses why I perceive these protocols to entail more than minimal risk without adequate corresponding prospect of benefit, thus excluding the protocol from approval under 46.404, 46.405 and 46.406. I go on to address why this special research case can be approved under 46.407, given the need for this research to be conducted in children rather than mere extrapolation from adult studies and the history of smallpox vaccination in this country. In order for the current protocol to meet ethical standards required by the regulations, I propose three significant changes that should be made for this research to be approvable under 46.407.

I. Research not approvable under 45 CFR 46.404, 46.405, or 46.406 (also 21 CFR 50.51, 50.52, or 50.53)

Because this protocol involves, to my reading, more than minimal risk with very remote prospect of direct benefit to healthy volunteers, I do not believe it meets any of these provisions for approval under the federal rules. Regarding risk, it seems clear that this protocol involves the prospect of complications more serious "than those ordinarily encountered [by children] in daily life." 46.102(i). In reaching this conclusion, I do not believe the risk of extremely dire outcomes, such as death or paralysis, are appreciably greater than those encountered in daily life, for instance in walking to school. The risk of death based on earlier data is targeted at less than 3 per million children in this age range. However, a significant proportion of the trial participants will suffer moderate to severe symptoms of headache, fever, fatigue and rash, with some requiring medical treatment. The risk of these experiences is greater than a child would normally encounter. They are not pleasant or without suffering and thus qualify this protocol as being of more than minimal risk. The protocol should also be seen as posing more than minimal risk because individuals beyond the vaccine recipient may suffer physical harms due to vaccinia exposure. Though risk of third party transmission is minimized in the conduct of the trial, the possibility sets this protocol apart and contributes to an assessment of more than minimal risk. Finally, the increased susceptibility of the population since routine smallpox ceased has increased, with burgeoning percentages of individuals afflicted with immune deficiency and skin conditions. As such, risks to both recipients and third parties may be greater than risks in earlier decades.

To classify this protocol credibly one should not overstate the prospect of direct benefit. At best the protocol is of unknown benefit to these child participants. In the absence of precise predictive information from the government, the risk of a smallpox attack in this country seems small,

though possible. The slim chance that the children in this protocol will be in close proximity to the occurrence of a smallpox case makes the prospect of direct benefit through prophylactic vaccination even more remote. As such, I do not believe the uncertain benefit the protocol offers can be construed to offset the risks of some harm that the protocol certainly entails.

II. Research approvable under 45 CFR 46.407 (and 21 CFR 50.54), with protocol/informed consent modifications

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

Some ethicists considering the question of enrolling children in research have suggested that benefit to society cannot morally outweigh exposing children to more than minimal risk without prospect of therapeutic benefit, as children should not be used as a means to an end even with parental permission. I do not believe this research protocol comes under this moral objection. Rather, the research falls in the gap of research that offers quite small and unpredictable prospect of direct benefit but also imposes considerable risk of at least mild to moderate physical harms. Given the balancing in this case, the protocol does not clearly fall under the other approvable categories, for instance where prospect of benefit outweighs more than minimal risk. However, the children are not simply being used as means to ends. It is unusual in this circumstance that the agent under investigation has previously been given to millions of children in the United States until three decades ago. As such the risks, though real and more than minimal, seem bearable even if they cannot be readily applied to our current population with more immunocompromised individuals and more people suffering dermatological conditions. Also, while the likelihood of a renewal of smallpox exposure is unknown, there is real concern about the safety and effectiveness of inoculating children with diluted vaccine, an issue requiring reassurance. Such experience cannot be reliably derived from adult studies given children's distinct susceptibilities. This study might also provide valuable information about any difference in the safety profiles between the full and diluted doses in children. Also, the trial would demonstrate the efficacy of using fewer pricks in children (which could have an impact on vaccine take), as well as the safety/tolerability of using the new site dressing in children. All of this information would be uniquely helpful in preparation for and prevention of harm to children in particular in the event of a smallpox incident.

B. With the following modifications, the research can be conducted in accordance with ethical principles.

1. The investigators should adopt a two-tiered consent process for enrollment into the trial.

As the protocol reads at present, the parents of the potential research participant are extensively screened related to the child's and the family's ability to participate in the trial. However, the parents are asked to sign the informed consent allowing their child to be admitted to the trial prior to review of the child's medical record, processing the child through the inclusion/exclusion criteria, and the results of blood tests including for HIV status. The informed consent for the trial should be obtained after these preliminary steps are complete and before the administration of the vaccine. A separate consent should be completed earlier, with parents giving permission only for their child to be screened for the trial. Some parents of potential research participants may gain understanding of the trial as their child is processed through the clinical eligibility criteria, as well as by the experience of an initial blood draw. This experience can enhance their all-important appreciation of the risks and burdens of the trial. If the parents have already signed the consent for enrollment and receipt of the vaccine, it becomes much more difficult to extricate their child, despite assurances that consent may be withdrawn at anytime. While this change poses an additional burden for the investigator, such two-tiered consent has been incorporated into other trials, with the initial consent pertaining to permission for reviewing medical records and conducting laboratory tests and the second consent applying to enrollment and administration of the experimental intervention. This would enhance the informed consent process in this trial.

2. The investigators must remove all language from the informed consent and trial recruiting documents inflating the likelihood of a terrorist attack and implying a duty of good parental care.

The model recruitment letter provided has as its first sentence: “As a parent it’s important to know how to keep your child healthy and to avoid serious illness.” This line sets the tone for the clinical trial and the message is that a responsible parent would get their child this vaccination to maintain health. This is certainly not the message to convey in the context of research that is, at best, of unknown benefit. Parental instinct to protect a child should not be played upon as an impetus to enroll in this trial. Language in the consent form should be similarly toned down (not “widespread illness and harm”), noting only the remote possibility of the use of smallpox in a terrorist attack. And in the benefits section of the consent form “protection against smallpox” should be clarified and perhaps replaced by a statement such as “While such an event is of unknown likelihood, if a release of smallpox occurred in proximity to your child, s/he would be protected against the virus.” Benefits to society (let alone “humanity”) are almost never listed in the informed consent document. Despite the reasoning behind approval of this research, I do not believe such justification should appear here.

3. The investigators must establish a mechanism to cover the cost of treating reactions/injuries resulting from the smallpox vaccine.

The informed consent document states: “If your child is injured because of this research, emergency medical care will be available. The care will not necessarily be free of charge” (original emphasis). While the federal regulations do not require investigators, sponsors or institutions to cover the cost of injuries in clinical trials, the National Bioethics Advisory Commission (NBAC) recently advocated development of a system to compensate participants for medical and rehabilitative costs resulting from research-related injuries. In the context of smallpox vaccine research on otherwise healthy and non-assenting children, I believe provision must be made for coverage of injury-related expenses. The principle reason is the prospect of harm to the trial participants if assurances that costs of related care will be covered are not in place. There is at least the possibility that a parent will be reluctant to seek medical care for moderate to severe symptoms related to vaccine administration if they face the prospect of bearing the costs associated with emergency room treatment or hospital admission. It is certainly unlikely that any private insurer would cover such research-related costs. Expense should simply not be a factor where any delay in treating an adverse event resulting from vaccination poses the risk of irreparable harm to the child. A mechanism for covering these costs, at least in the critical period, must be established. Third-party reactions to vaccinia exposure should also be covered. And given the real but remote chance of long-term injury, such as from an encephalitis event, the possibility of a fund for support of such individuals should at least be explored with the country’s existing mechanism for vaccine injury compensation as a model.

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

Obviously this protocol involves children aged 2-5 who are not mature enough to assent to research participation. However, conducting the research in this age range is most helpful in assessing dose response in young children, while also removing the very young children with heightened risk of reaction to the vaccine from trial eligibility. The vast majority of children in this age range would already have exhibited signs of the various exclusionary criteria, including immune suppression and eczema, such that enrollment of children specially at risk is unlikely to occur. The federal regulations make provision for the parents to give permission on behalf of their child when the IRB determines that the child is not capable of assent. Prospect of direct benefit is not required. As such, sound informed consent from the parents is sufficient to enroll a child in the smallpox vaccine trial. It is worth noting that if the protocol is approved under 46.407 both parents, if living and with custody, must provide consent for their child’s enrollment.

III. Other comments

1. Regarding study procedures, individuals and contacts in receipt of transplants, solid organ or cell, should be explicitly listed among the excludable conditions. Also, the risk to third parties who may enter the orbit of the vaccinated child must be made very clear in counseling enrollees' parents. Regarding provision of a handout for visitors, parents should be instructed that this information must be provided for visitors' review and consideration in advance of their proximate exposure to the child or his/her environs.
2. Possibly reconsider the \$40 bonus gift certificate on completion of the study. While compensation for the trial is nominal in general, such bonuses may have the effect of keeping the participant in the trial even if it is, in some sense, not in their child's interest.
3. Remove language in the risks section (part 4) clarifying, "As with all vaccines or drugs" and calling allergic reaction "rare." In fact, reactions to the smallpox vaccine are more common than with other vaccines and drugs. The comparison is misleading and falsely reassuring.
4. From my review of the VIG information this treatment is not necessarily without its own side effects and thus calling it "safe and effective" in the vaccination consent form without any statement of risks may be misleading. Also related to VIG treatment, I note that the doses will be retained at CDC. Given the possibility that any delay in treatment could result in irreparable harm to trial participants, parents and investigators should be encouraged to flag adverse events quickly and not delay judgments that may necessitate a request for VIG. Perhaps release of some treatment doses to the study sites could also be explored.
5. In the benefits section, part 5, the statement "There will be no costs to you or your child" should be removed. There may indeed be costs, for instance withdrawal from daycare could result in babysitting expenses or appointments may result in loss of work pay.
6. In part 7 regarding sample retention, the informed consent document consistently refers to "you" when it should indicate you, on behalf of your child. From a lay standpoint, I do not understand use of samples to "even out future tests." Finally, and most important, the NBAC discussed consent for future use of identified samples suggesting that it may be limited, for instance to research on the condition being treated. For future research on "other diseases" besides smallpox/vaccinia, I believe the investigators here should seriously consider implementing coding of stored samples.
7. In part 8, the researchers' authority over disposition of unused tissue seems to conflict with the prior consent on sample retention. Also, any personal (financial) interest of the investigator should not only be disclosed verbally but should be stated in the consent form.
8. Even though the institutions conducting the trial serve some populations that may be perceived to be disadvantaged, based on the protocol I believe the investigators are committed to drawing trial participants fairly from a diverse population. The requirements for understanding the complex trial may screen out potentially more vulnerable research subjects. And the nominal compensation is unlikely to be coercive to individuals, even those from lower income groups.

In conclusion, I support the pursuit of research to ensure the safe and effective vaccination of children in the event of a smallpox case. If follow-up research is pursued, I recommend that the additional enrollment of children for testing of the Dryvax vaccine should be limited, with only the numbers required to obtain sufficient data to resolve remaining, important research questions. Finally, I hasten to emphasize that the results of this research should not be extrapolated to assure the safety of children in a program of greater population inoculation. In this small study, the chance of a serious adverse event occurring is thankfully limited due to what will no doubt be vigorous screening of potential trial participants and their contacts for pertinent risk factors. It would be virtually impossible to replicate this intensive and controlled circumstance in a non-research setting. As such, any results indicating the relative safety of the vaccine dose in the research population should not be readily applied to consideration of broader vaccination schemes. Once again, I am grateful for the chance to comment on this important research protocol and I hope these thoughts are a helpful contribution to a productive public discussion.

Sincerely,

Rosemary B. Quigley, JD, MPH