Analysis&Perspective

The Process of Federal Panel Review of Research Protocols Involving Children

Case Study: A Multi-Center, Randomized Dose Response Study of the Safety, Clinical, and Immune Response of Dryvax® Administered to Children 2 to 5 Years of Age

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A notice in the Oct. 31 issue of the *Federal Register* solicited public review and comment on a proposed research study of the safety, clinical, and immune response of administering Dryvax® (a smallpox vaccine) to children between 2 and 5 years of age, with the comment period closing on Dec. 2 (67 Fed. Reg. 66403). The research, sponsored by the National Institute of Allergy and Infectious Diseases, proposes to evaluate the vaccine at its full, licensed strength and at a 1:5 dilution. Use of Dryvax® in this protocol is being performed under a Food and Drug Administration investigational new drug (IND) designation primarily because there are no data to support the efficacy of the 1:5 dilution of this product in children.

One reviewing institutional review board felt that administration of the vaccine was greater than a minor increase over minimal risk (thus not approvable under Department of Health and Human Services human subject protection regulations at 45 C.F.R. § 46.404/21 C.F.R. § 50.51 or 45 C.F.R. § 46.406/21 C.F.R. § 50.53), and did not offer the prospect of direct benefit for the individual subjects given the unlikelihood of a terrorist attack using smallpox (and thus not approvable under 45 C.F.R. § 46.405/21 C.F.R. § 50.52). However, finding that the research presented a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, the IRB referred the research to the HHS secretary and the FDA commissioner for review under 45 C.F.R. § 46.407 and 21 C.F.R. § 50.54.

The primary objective of the proposed research is to evaluate the cutaneous responses (''take rates'') after vaccination in 40 children, half of which would be given undiluted and the other half diluted (1:5 dilution) vaccine. Thus, the primary study endpoint is the clinical formation of a vesicle/pustule at the site of primary vaccination, and assumes efficacy based on this surrogate endpoint. Among the secondary objectives are: (a) to evaluate the immunological responses in children given undiluted or diluted (1:5 dilution) vaccine; (b) to ascertain the clinical and immunological responses and safety of five intradermal punctures with a bifurcated needle; and (c) to assess the safety profile in the vaccinated individual and assess the risk to contacts. The statement of rationale for the study clarifies that a major concern is the risk of autoinoculation and secondary transmission from young vaccinees to contacts, and the study therefore incorporates evaluation of the use of a semi-occlusive dressing to prevent such spread. The protocol also states that the study is underpowered to examine any but the largest differences between the groups receiving the undiluted and diluted (1:5 dilution) vaccine. In addition, the study also is too small to provide any meaningful safety data.

The federal regulations require both ''consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law)'' and the ''opportunity for public review and comment'' (45 C.F.R. § 46.407/21 C.F.R. § 50.54). For this consultation, the documents were mailed to the individual consultants who then delivered their separate reports. Although we understand that the individual consultants were permitted to contact each other, we suspect that this process did not allow for substantive exchange between panel members, either on points of scientific disagreement or for clarification of ethical arguments and/or claims. We have indicated in our focused analysis below where a substantive exchange on key scientific and ethical issues would have allowed for a more informed judgment about the research.

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Scientific and Ethical Analysis: The Findings of Risk and Benefit

With the exception of one of the 10 consultants, who felt that the study should be approved yet failed to discuss the level of risk exposure, all agreed that administration of the smallpox vaccine presents greater than a minor increase over minimal risk and thus could not be approved under 45 C.F.R. § 46.404/21 C.F.R. § 50.51 or 45 C.F.R. § 46.406/21 C.F.R. § 50.53. In effect, all of the consultants agreed that the study either must offer the prospect of direct benefit to the children enrolled in the trial (45 C.F.R. § 46.405/21 C.F.R. § 50.52), or meet the requirements for approval under 45 C.F.R. § 46.407/21 C.F.R. § 50.54. We agree with this assessment.

In addition to the assessment of risk, the children to be enrolled in this study do not to have a ''disorder or condition,'' which is a requirement for approval under

45 C.F.R. § 46.406/21 C.F.R. § 50.53. This specific point was discussed by a minority of the consultants since the risk determination alone disqualified the study from consideration under this category.

In our opinion, administration of the smallpox vaccine does not offer a realistic prospect of direct benefit to the children to be enrolled in this research study. Indeed, only two of the 10 consultants thought that the research offers such a direct benefit to enrollees. One consultant did not discuss the 45 C.F.R. Subpart D categories, which outline subject protection requirements specifically applicable to children, yet clearly stated that the research offers ''no direct, immediate benefit to the children.'' Another consultant argued for the prospect of direct benefit based on an analogy to the use of oral polio vaccine in spite of the known but small risk of vaccine-associated polio. However, we argue that this analogy is not useful. The oral polio vaccine was (and is) administered to children at the same time that polio disease occurs in many areas of the world. The benefits of that vaccine are, therefore, not theoretical. A third consultant argued that being immune from smallpox is a direct benefit even in the absence of a known bioterrorism-related risk for smallpox dissemination. Turning ethical concern for the ''therapeutic misconception'' on its head, parental perception of direct benefit based on the fear of smallpox dissemination was argued to be seen as sufficient justification for an IRB to determine that the prospect of direct benefit, in fact, exists. Contrary to this claim, one consultant appropriately asserts that the ''parental instinct to protect a child should not be played upon as an impetus to enroll in this trial.'' We do not know whether a conversation between consultants would have resulted in agreement on this point, as an opportunity for such a panel discussion never was provided.

We agree with the majority of consultants that the research could *not* be approved by an IRB under certain human subject protection regulations (45 C.F.R. § 46.404/21 C.F.R. § 50.51, 45 C.F.R. § 46.405/21 C.F.R. § 50.52 or 45 C.F.R. § 46.406/21 C.F.R. § 50.53).

Sound Ethical Principles

Although all of the consultants recommended that the research potentially could be approved under 45 C.F.R. § 46.407 and 21 C.F.R. § 50.54, there was little discussion of the ''sound ethical principles'' according to which the research must be conducted (apart from three of the four consultants with ethical and/or legal expertise). These ''sound ethical principles'' can be considered under two general categories: (1) the ethical principles that must be met for the research to be conducted in children at all, and (2) the ethical principles that must be met for the proper and ethical conduct of the research, assuming the use of children is ethically appropriate. Although the consultants' discussion focused primarily on the second category, we must first ask and answer the first question of whether the research should be conducted in children at all. The primary ethical principle in conducting research involving children is that the scientific question(s) cannot be answered by using adults who are capable of consent. Assuming that consenting adults cannot be used, a secondary ethical principle in conducting research involving young children is that the scientific question(s) cannot be answered by using children who are capable of assent.

Is there a need to test children based on the possibility of a different immune response? Can one expect a different immunological response from children ages 2-5 years? Three of the six infectious disease experts appear to disagree. Absent a panel discussion among them, it is unclear if they would have reached consensus on this point. However, the weight of opinion appears to favor the view that children would be expected to have the same immunological response to smallpox vaccine as would adults. As such, the only difference that actually is being tested is the five-prick inoculation method (versus the 15 pricks used in the adult studies).

One expert asserted that children's ''immune responses may be different from those documented in adults. There are other vaccines where it is already known that the responses in adults do not mimic those in children, for example in the cases of diptheria toxoid and pneumococcal conjugate vaccines.'' However, another expert claimed that ''there is no biologically plausible reason to expect children 2-5 years of age to respond less well to this or any other live viral vaccine than adults if the vaccine virus and administration methods were the same.'' Asserting that ''above two years of age there is no impairment of the immune response to any other live viral vaccine as compared to adults and children often respond better than adults,'' this expert cited as evidence the fact that ''there is no impairment in the immune response to measles vaccine, oral polio vaccine, yellow fever vaccine, mumps, or rubella vaccine in children ages 2-5 as compared to adults.'' Two other experts appeared to agree with this assessment. We do not know whether a conversation between consultants would have resulted in agreement on this point, as the opportunity for such a panel discussion never was provided.

Is there a need to test diluted vaccine? The need to test diluted vaccine is based on the public health concern that an adequate supply of vaccine be available in the event of a terrorist attack. Whether the vaccine supply will remain scarce for the foreseeable future is a question of fact that could not be answered from the information provided. It thus is difficult to assess the need for this study absent facts concerning the reality of a terrorist attack, and the timeline for alternative vaccine development. Even so, unless one assumes that children would respond differently to the smallpox vaccine (addressed below), there would be no need to test the diluted vaccine on children.

Is there a need to test the five-insertion scarification method (i.e., five intradermal punctures with a bifurcated needle)? If the speed and efficiency of the five-prick versus the 15-prick (or other) method is why the five-prick method was selected, this hypothesis can be tested without introducing the risks of smallpox vaccine. It is possible that parents would not volunteer their child simply to be ''stuck'' without the presence of the vaccine; however, this hesitation illustrates the ethical problem with the parental perception of benefit from the vaccine. Testing the five-prick method alone would make clear the public health benefit of the intervention without the prospect of direct benefit to the child. Furthermore, the comparative effectiveness of the five-prick method in producing a vesicular response with either undiluted or diluted vaccine can be answered using adult subjects.

Is there a need to evaluate a new semi-occlusive dressing applied to the site, in order to prevent secondary viral

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spread? The previous adult study (sample size, 740) did not show an increase in adverse viral reactions or bacterial superinfection with the use of the semi-occlusive dressing. One would not expect there to be a difference between adults and children in the frequency of dressing-related adverse events, nor is the proposed pediatric trial sufficiently powered (sample size, 40) to detect a difference in the incidence rate of such adverse events. In addition, previous studies in adults demonstrated that two layers of the semi-occlusive dressing are required to obtain negative cultures from the top of the dressing. There is no reason to assume that viral penetration of the semi-occlusive dressing would vary between adults and children.

Thus the main reason to study the semi-occlusive dressing in children is to see if the behavioral differences result in a higher rate of autoinoculation and contact transmission. The rate of contact transmission will not be studied directly, as the children are being isolated in a way that will minimize such contacts when compared to the ''real world'' situation. The question then would be whether children of varying ages would be able to keep the semi-occlusive dressing in place during the 30-60 day period of post-vaccination viral shedding. Answering this question may not require vaccination with an active smallpox vaccine, unless one postulates that the presence of the vesicle would cause sufficient skin irritation to increase the likelihood that the child would remove the dressing. There is no discussion of whether there are alternative methods for mimicking a vesicle in order to reproduce the appropriate trial conditions without administering active smallpox vaccine.

Are children as research subjects required to answer the research objectives? Apart from the question of maintaining the intactness of the semi-occlusive dressing, there does not appear to be a reason that use of children as subjects is necessary to answer the other study objectives. This assumes that the immune response of a 2- to 5-year-old child to a live smallpox vaccine is similar to that of an adult. Since there may be alternative methods for assessing the ability to maintain the intactness of the semi-occlusive barrier, it is unclear whether the administration of smallpox vaccine to children is necessary. Given the lack of a face-to-face panel meeting, the individual members were unable to query each other about the need to perform this study in children.

The Individual Panel Member Process Is Fundamentally Flawed

From the current documents, one cannot conclude that a concern raised by one consultant would or would not have been a concern for one or more of the other nine consultants. By way of analogy, the use of a focus group (of which a convened panel is a specific instance) is often recommended for qualitative research so that ideas raised by one panel member can be considered and developed further by the other panel members. This same approach applies to inform the review of a research protocol by a convened meeting of an IRB made up of members with different perspectives. Frequently, only one member of an IRB expresses a concern which is then supported by the majority or a consensus of the IRB membership. It would be a serious error to conclude that a recommendation made by only one or two panel members reflects the opinion of only a minority of the panel.

The lack of public discussion among panel members renders it impossible to determine whether the apparent differences of opinion would have been resolved, or to assess the relative merits of arguments for or against the divergent opinions. The scientific question of whether children aged 2 to 5 years have a different immune response from adults is absolutely essential in determining whether the research should be performed in children. The ethical and legal consultants did not have the benefit of hearing these different perspectives, nor did any of the panel members benefit from hearing a discussion among those with different views of the issue. In effect, it leaves the FDA and HHS in the position of picking and choosing among the individual consultants' advice in order to support conclusions drawn by unnamed experts within either department, thereby undercutting the moral justification of research conducted under 45 C.F.R. § 46.407/21 C.F.R. § 50.54.

The FDA has considerable experience in the use of public advisory panels to provide a forum for deliberation and advice on issues concerning FDA-regulated products. Such a process should be established and used for research falling under sections 45 C.F.R. § 46.407 and 21 C.F.R. § 50.54. As the FDA indicated in adopting the additional safeguards for children: ''FDA anticipates that this panel may include an advisory committee supplemented, if needed, by appropriate experts'' (66 Fed. Reg. 20594, 4/24/01). As schedules may conflict and prevent the participation of appropriate experts, written comments could be solicited ahead of time for consideration by the panel, with the ability to establish an audio-conference link with individuals whose schedules do not permit personal attendance. It is unclear why the existing FDA advisory panel structure, supplemented by individuals with appropriate subject-specific expertise, was not used for this panel. In fact, a meeting of the FDA Pediatric Advisory Subcommittee of the FDA Infectious Disease Advisory Committee already was scheduled for early November 2002 and cancelled due to lack of an agenda.

The irony is that the consultative process of using individual experts without the benefit of panel discussion may have been selected to avoid violating the Federal Advisory Committee Act (FACA). FACA is founded on the important principles of open government and public participation, especially when panel deliberations will have an impact on governmental policy. Although the public has adequate opportunity and access to the source documents in order to comment on this research, the manner in which the expert panel was conducted undercuts the moral legitimacy of the overall process.