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The Food and Drug Administration's Federal Review of a Pediatric Muscular Dystrophy Protocol

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The United States' federal regulatory requirements for pediatric research, "Additional Safeguards for Children in Clinical Investigations" provide an ethical framework for whether and under what conditions children can be enrolled in clinical trials.¹ These protections place limits on the amount of risk to which a child can be exposed if there is no prospect of direct clinical benefit. This risk has been defined as "minimal risk"² and "no more than a minor increase over minimal risk."³ When reviewing pediatric research protocols, institutional review boards (IRBs) should consider "individually as well as collectively" the risks of interventions or procedures included in the protocol. This type of review is referred to as "component analysis."⁴ Pursuant to the regulations, IRBs are not permitted to approve a protocol if there is no prospect of direct clinical benefit to the child and the risk exceeds "a minor increase over minimal risk." However, there may be studies involving an intervention or procedure consistent with sound ethical principles, even though the research protocol is "not IRB approvable." Such studies may proceed following review by a federal panel of appropriate experts, an opportunity for public comment, and a determination by the commissioner of the U.S. Food and Drug Administration (FDA) and/or the secretary of the Department of Health and Human Services (HHS) that the study addresses "a serious problem affecting the health or welfare of children" and can "be conducted in accordance with sound ethical principles."⁵ Prior to 2017, a federal panel reviewed 10 pediatric protocols, with the most recent review occurring in 2008. For that protocol, the initial referral was received on October 1, 2008, the HHS determination was dated May 22, 2009, and the final approval to proceed was issued on June 7, 2010—a delay of nearly 21 months.⁶

At a public hearing on May 18, 2017, the FDA's Pediatric Ethics Subcommittee (PES) and Pediatric Advisory Committee (PAC) met to review a pediatric research protocol on referral from the IRB at the University of California, Los Angeles (UCLA). The protocol, A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy (DMD) (ESSENCE), required weekly peripheral intravenous (PIV) infusions of the study product or placebo over 96 weeks, followed by an open-label 96-week extension phase. The referral asked whether placement of a central venous catheter rather than a PIV

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for study-drug infusion (including for participants in the placebo control group) would be acceptable during the initial 96-week study period. In this commentary, we highlight several lessons learned from the referral of the ESSENCE protocol to the FDA and from the federal panel review process for pediatric protocols that IRBs are not permitted to approve.

The ESSENCE trial was originally reviewed by the FDA in 2015. At that time, the protocol allowed the use of a totally implantable central venous access catheter device (TICVAD) to provide the study drug (including placebo) to patient-participants. Using component analysis, the FDA determined that for pediatric patients in the treatment arm, use of a TICVAD was acceptable given the prospect of direct clinical benefit to patients receiving the active study drug. However, for patients in the placebo arm, there was no direct clinical benefit from the placebo and consequently no benefit to justify the risks of placing a TICVAD. Generally, placebos are considered minimal risk unless there is an increased risk of harm from not receiving known effective treatment or if administration of the placebo involves an invasive procedure. When considered together, these risks must not exceed a “minor increase over minimal risk,” as there would be, for example, when using a PIV or an intramuscular injection to administer a placebo. Use of a TICVAD exceeds a “minor increase over minimal risk” and thus is not approvable by an IRB for patients randomized to the study’s placebo arm. The study’s commercial sponsor was aware that a federal panel could potentially approve the protocol but decided, when informed that the IRB could not approve it pursuant to the regulations, to amend the protocol to remove the option to use a TICVAD.

In February 2017, the UCLA IRB was contacted by a parent of a patient participating in the ESSENCE trial who was having difficulty with continued PIV access. The parent asked the IRB why a TICVAD was not allowed in the study. The IRB reviewed the protocol and determined that it was not IRB approvable pursuant to the pediatric research regulations. However, the IRB believed that an amended protocol met the criteria for referring a protocol to the FDA for review. Working with the sponsor and the investigator, the IRB submitted an amended protocol to the FDA that included TICVADs and other options for central venous access, such as central venous catheters and peripherally inserted central venous catheters.

The FDA received the official referral from the IRB on March 15, 2017, and initiated the federal panel review process. The FDA asked the PES and PAC to determine whether alternative central venous access methods should be allowed in the study and, if yes, to discuss other considerations and stipulations that might be required for the study to proceed. The PES and PAS voted unanimously (fourteen voting yes and zero no) to allow the use of a TICVAD, favoring a TICVAD over other forms of central venous access because of lower complication rates and longer dwell times than with other central venous access devices.⁷ The panel agreed that the decision for placement of a TICVAD should be left to the discretion of parents and the study investigator and chose to place no other restrictions than requiring that the expertise of the consulting surgeon placing the TICVAD be documented and that the parental permission and child assent forms should include information on the possibility, risks, and benefits of using a TICVAD.

One lesson learned from the ESSENCE protocol review is about the initiation of a federal review panel and the amount of time for completion of the review. Parents of children enrolled in the study and representatives from the DMD advocacy community who testified at the hearing were unanimously in favor of allowing the use of central venous access devices in the trial despite the potential for their children to receive a placebo and the known risks associated with the devices. If the FDA had initiated federal review of the protocol with the opportunity for public comment and participation sooner, rather than waiting for a referral from an IRB, the decision permitting the use of a TICVAD to provide the study drug would have been made sooner, thus potentially eliminating any pain and suffering children in the study experienced from multiple PIV infusions. Indeed, panel members raised concerns about the harms to children who did not get access to the TICVAD. One panel member questioned whether multiple PIV attempts every week constituted only a “minor increase over minimal risk,” and another opined that withholding a TICVAD was “cruel and unusual punishment.” The speed with which the FDA determination was issued is unprecedented: the letter allowing the study to proceed was issued on May 25, 2017, one week after the advisory committee meeting and less than 10 weeks from the time of the initial IRB referral. This suggests that the FDA recognized that a prompt review and decision was warranted so that patient-participants who might be required to withdraw from the study because PIV access could not be maintained would instead receive access to the study drug with use of the TICVAD.

Another lesson from the ESSENCE review process has to do with confidentiality of product information in a process open to the public. The ESSENCE protocol was the first federal panel review of a commercially sponsored pediatric protocol. In initiating the review process, the FDA realized that for review of a commercial study, a balance would need to be struck between protecting the confidential commercial interests of the sponsor and providing adequate transparency about the study to the public. The FDA decided to redact documents it posted on the publicly accessible FDA website while giving members of the PAC and PES access to un-redacted documents under a confidentiality agreement.

As a result of these lessons learned from the review process of the ESSENCE protocol, the FDA is exploring ways in which its advisory committee can be used more efficiently and effectively to review pediatric protocols that the regulations stipulate are not IRB approvable. The agency has solicited discussion and feedback from the Secretary’s Advisory Committee on Human Research Protections (SACHRP) on the advantages and potential disadvantages of having the FDA initiate an expert panel for selected protocols prior to an IRB referral. In addition, it is possible that a protocol substantially similar to that of the ESSENCE trial could be proposed by a sponsor, raising the same issue about the use of a TICVAD for the placebo control group. The FDA also solicited discussion and feedback from SACHRP on the advantages and potential disadvantages of issuing a determination pursuant to the regulations for protocols that are determined by the FDA to be “substantially similar” to previously reviewed protocols, after an appropriate opportunity for public comment on a draft FDA determination based on a prior expert panel review. SACHRP agreed that both these approaches would streamline the review process if implemented; however, careful consideration would be required to ensure that independent IRB review is maintained before moving forward with any changes to the process.

References

1. 21 CFR 50, subpart D; 45 CFR 46, subpart D.
2. 21 CFR 50.51; 45 CFR 46.404.
3. 21 CFR 50.53, 45 CFR 46.406.
4. 43 FR 2084 at 2086.
5. 21 CFR 50.54; 45 CFR 46.407.
6. Previous protocols reviewed under the 21 CFR 50.54 and 45 CFR 46.407 are archived here on the website of the Office for Human Research Protections: <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-407-review-process/index.html>.
7. The documents from the PAC and PES meeting and the FDA determination letter can be found at <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm536086.htm>.