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IRBs and Long-Term Safety Studies In Neonatal Research Projects (#1)

Research with very young human subjects has always posed special protocol review challenges for IRBs. That situation is not changing. However, what is changing in an increased emphasis by FDA on using the results of long-term studies to inform future research in an effort to reduce risks for neonates who participate in very early research projects.

The relevant new guidance, containing numerous recommendations for IRBs and researchers, is titled "Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development: Guidance for Industry."

"This guidance is intended to provide a framework for considering whether and what type of long-term neurologic, sensory, and developmental evaluations could be useful in supporting a determination of safety of a FDA-regulated 'medical product' (i.e., drug, biological product, or medical device) for use in neonates" (89 Fed. Reg. 83892, October 18).

Research Requirements Part of Federal Law

"Although short-term safety evaluations may be appropriate for adults or other populations, such evaluations may not identify important adverse events in the neonatal population, as medical treatment during the neonatal period coincides with a time of critical growth and physiologic development and latent effects may not be evident until later in life following early-life exposures.

Consideration of the potential for long-term neurologic, sensory, and developmental effects in the neonatal population early in a development program is important for establishing safety of a medical product intended for use in neonates ....

Historically, most medical products used to treat neonates and young infants were not approved for use in these populations, and thus have not undergone comprehensive evaluation of safety or efficacy for use in neonates" (supra at pages 83820-83893).

The 11-page guidance contains a number of quite detailed issues for IRBs and associated researchers to consider when planning a research project with neonates.

"In 2012, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) were made permanent under Title V

NOTE #1: Quoted materials in this newsletter appear exactly as originally published in source documents, including any misspellings, grammatical errors, or missing words. However, we will on occasion insert words or edit text and/or formating in brackets [ ] to make the material easier to read.

NOTE #2: Emphases are added to articles by HRR by underlining or adding ***bold/italics*** to selected text, unless stated otherwise.

NOTE #3: Articles **T**o **B**e **C**ontinued in subsequent issues are marked at the end of the article with **{TBC}**.

Also In This Issue

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of the Food and Drug Administration Safety and Innovation Act (FDASIA). FDASIA contained several provisions to encourage medical product development in neonates" (guidance, October, p. 2; https://www.fda.gov/media/165239/download).

Possible Long-Term Harm to Subjects

"Clinical investigators and sponsors of neonatal studies should consider and assess potential short-term and long-term effects of an investigational therapy ....

Short-term clinical improvement, such as that observed after high-dose corticosteroids for infants with bronchopulmonary dysplasia, may be followed by unexpected long-term harm.

While adjunctive neurological assessments (e.g., neuroimaging, electroencephalography) may provide information on early safety concerns, they cannot replace clinical assessments of long-term functional outcomes.

Although there is no universal definition of 'long-term,' for the purpose of this guidance, the time frame can be generally thought of as at least 2 years of age or at such time when relevant clinical neurodevelopmental parameters can be reasonably assessed ...; the minimum duration of follow-up will depend on different population- and product-specific factors ....

Prospectively designed long-term follow-up is often important to understand medical product safety in neonates" (guidance at pp. 2-3).

Neonates Should Be Subjects in Studies Originally Designed for Older Subjects

"Neonates should have access to medical products adequately evaluated for safety, effectiveness, and, when appropriate, dosing for that population. There are conditions unique to term or preterm neonates, such as necrotizing enterocolitis and retinopathy of prematurity, that will not have analogous development programs in older populations.

As new medical products are developed for these and other unique neonatal conditions, novel development programs and first-in-human studies may be initiated in neonates, and these development programs should also demonstrate long-term neurologic, sensory, and developmental safety.

Neonates should also be enrolled in clinical studies for medical products and diagnostic tools initially developed in other populations that will be used for neonates. Inclusion of neonates in such studies may be useful to establish dosing, safety, and efficacy or effectiveness, and these studies may also warrant long-term safety evaluations" (supra at p. 3).

Special Study Design Issues for Neonates

"III. Neurodevelopmental Follow-Up for Product Development Programs That Include Neonates ....

Sponsors should communicate as early as possible with the relevant FDA review division to reach alignment on an appropriate approach for long-term safety evaluations.

A. Determining the Need for Long-term Neurodevelopmental Safety Evaluations

Sponsors should assess whether a long-term neurodevelopmental safety evaluation for neonates enrolled in clinical studies should be conducted. This assessment should be initiated early in product development and should be reevaluated as new information becomes available.

1. General Considerations

a. *Central Nervous System (CNS) Exposure*: Any route of administration may result in a systemic exposure. The degree of systemic exposure, which should be quantified in early pharmacokinetic or animal studies if possible, may inform the need for long-term safety assessment.

In general, higher levels of systemic exposure may be associated with higher CNS exposure and potential risk for long-term sequelae. The degree of CNS exposure may vary independently of systemic exposure.

b. *Timing of Exposure:* The timing of exposure to a drug, biological product, or device relative to a particularly vulnerable stage of organ and tissue development may inform the need for and the type of long-term safety assessment.

c. *Duration of Exposure:* Repeated dosing, prolonged exposure[,] and medical products with persistent effects may be associated with higher risk for long-term sequelae; however, long-term safety assessments may also be required after single doses or short durations of investigational therapies ...." (supra at pp. 3-4). © {TBC}

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