U.S. FOOD & DRUG ADMINISTRATION

Considerations for Long-Term Clinical Neurodevelopmental Safety Studies in Neonatal Product Development

DRAFT GUIDANCE FOR INDUSTRY

What is covered in this guidance?

This draft guidance provides a framework for considering neurodevelopmental evaluations that could be useful to assess long-term safety of a medical product intended for use in neonates.

Why is this guidance important?

Treatment with medical products during the neonatal period coincides with a time of critical growth and physiologic development. Short-term safety evaluations typical for adults or other populations may fail to identify important adverse effects in the neonatal population, as latent effects may follow early-life exposures.

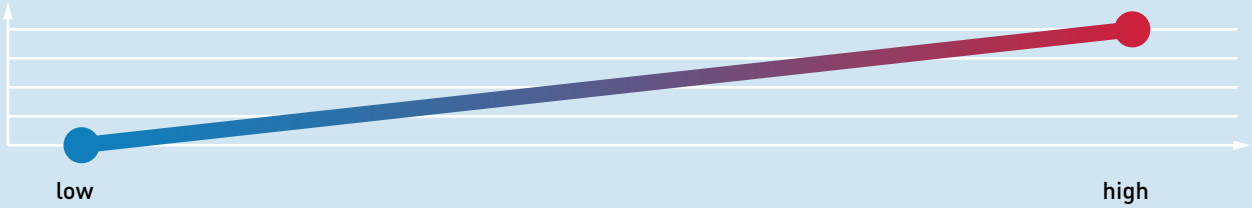
Domains for evaluating neurodevelopmental clinical outcomes for safety

General	Neurodevelopmental
Physical health	Sensory
Health conditions	Motor
Feeding problems	Cognition
Somatic growth	Emotional and behavioral health
Sleep	Communication
Quality of life and global function	Social functioning
Receipt of developmental interventions and educational services	Adaptive functioning

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about the considerations for long-term clinical neurodevelopmental safety studies in neonatal product development, **read the guidance**.

Examples of considerations when determining the need for long-term neurodevelopmental safety evaluations

Systemic (and CNS) Exposure



Timing of Exposure

Less vulnerable stage of organ/tissue development

Vulnerable stage of organ/tissue development

Duration of Exposure

HOURS | DAYS | WEEKS | MONTHS

Population Characteristics

- Older gestational age
- Higher birth weight
- Underlying disease does not increase neurologic risk

- Younger gestational age
- Lower birth weight
- Underlying disease increases neurologic risk

Product Information

Product components (e.g., active ingredient, excipients, impurities) and nonclinical toxicity, clinical pharmacology, and clinical experience data

Data do not suggest potential adverse neurological effects

Data suggest potential adverse neurological effects

Increasing likelihood that long-term neurodevelopmental safety evaluations will be needed

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Key points when developing a plan to evaluate long-term neurodevelopmental safety and considering what to measure, when, and for how long

A **controlled** study design is recommended to allow for more reliable discrimination of drug or device-related patient outcomes from outcomes caused by other factors

Neurodevelopmental outcomes should be evaluated up to **at least 2 years adjusted age**; evaluation of some outcomes may also require assessment later in childhood

A **general evaluation of all key neurodevelopmental domains** is recommended, with additional evaluations based on domains of concern; physical, mental, and social health should also be included

Neurodevelopmental safety evaluations should be **well-defined, reliable, and relevant**; clinical outcome assessments should include **validated** tools, when available

Sponsors should ensure reliable and **consistent evaluations** across study sites and examiners

Data should be collected on co-variates that may affect neurodevelopmental outcomes (e.g., perinatal factors, comorbidities, socioeconomic factors, etc.)

Certain objective developmental measures with established reference standards (e.g., growth, vision, and hearing screening) captured during routine care may be used when collected reliably, but **general developmental screening and formalized assessments of neurodevelopment are not interchangeable**

Long-term functional assessments provide the most meaningful outcome information; in general, **adjunctive assessments and biomarker measures** (e.g., neuroimaging and neurophysiologic studies) may be useful to support the evaluation of neurodevelopmental safety in certain circumstances, but **may not substitute for functional evaluations**

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Community acceptance, inclusivity, and engagement

✓ **Collaborate with families and additional stakeholders**

- Stakeholders such as caregivers, healthcare providers, educators, and developmental specialists can help identify clinically meaningful outcomes and assess study feasibility

✓ **Understand patient family perceptions on clinical trial participation**

- Engage with patient families and community leaders to get input on the clinical trial protocol and help promote participation of historically underrepresented communities

✓ **Minimize the burden of study participation for patients and families**

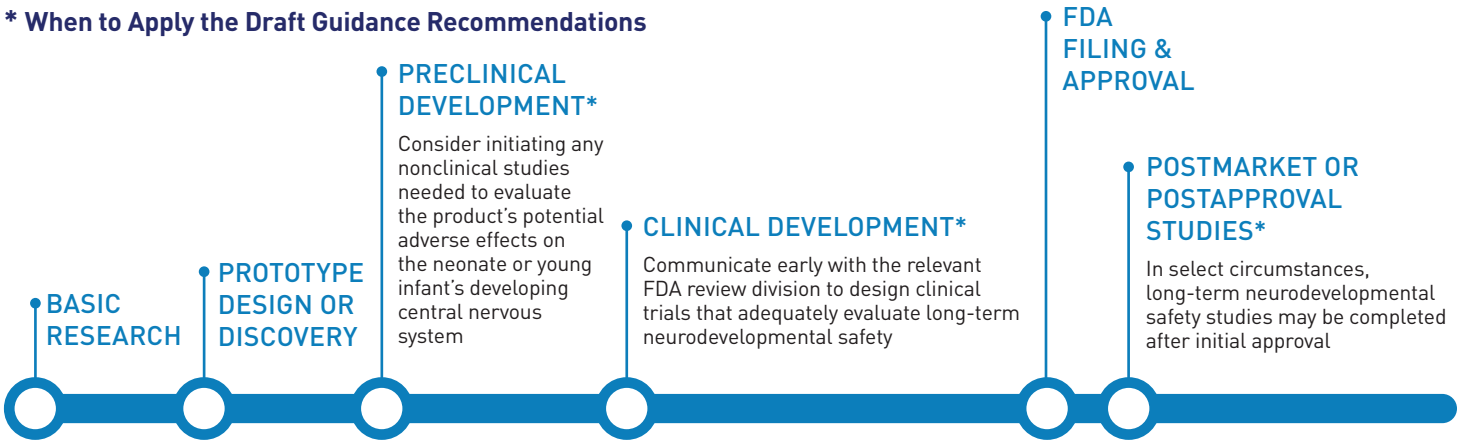
- Streamline evaluations to avoid duplication and help ensure pediatric patients will be willing to complete the tests
- Integrate data from community-level services and providers (e.g., early intervention programs), when appropriate
- Use mobile technologies or other streamlined methods for information collection

✓ **Connect early and keep in contact with families**

- Include long-term follow-up plans as a component of the initial study enrollment and stay in touch with patient families to help reinforce the importance of long-term follow-up

Medical Product Development Timeline

*** When to Apply the Draft Guidance Recommendations**



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Speakers: Gerri Baer, MD | An Massaro, MD

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To see additional Guidance Snapshots, **check out the pilot program**.