

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

Guidance for Industry



What is covered in this guidance?

This 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.



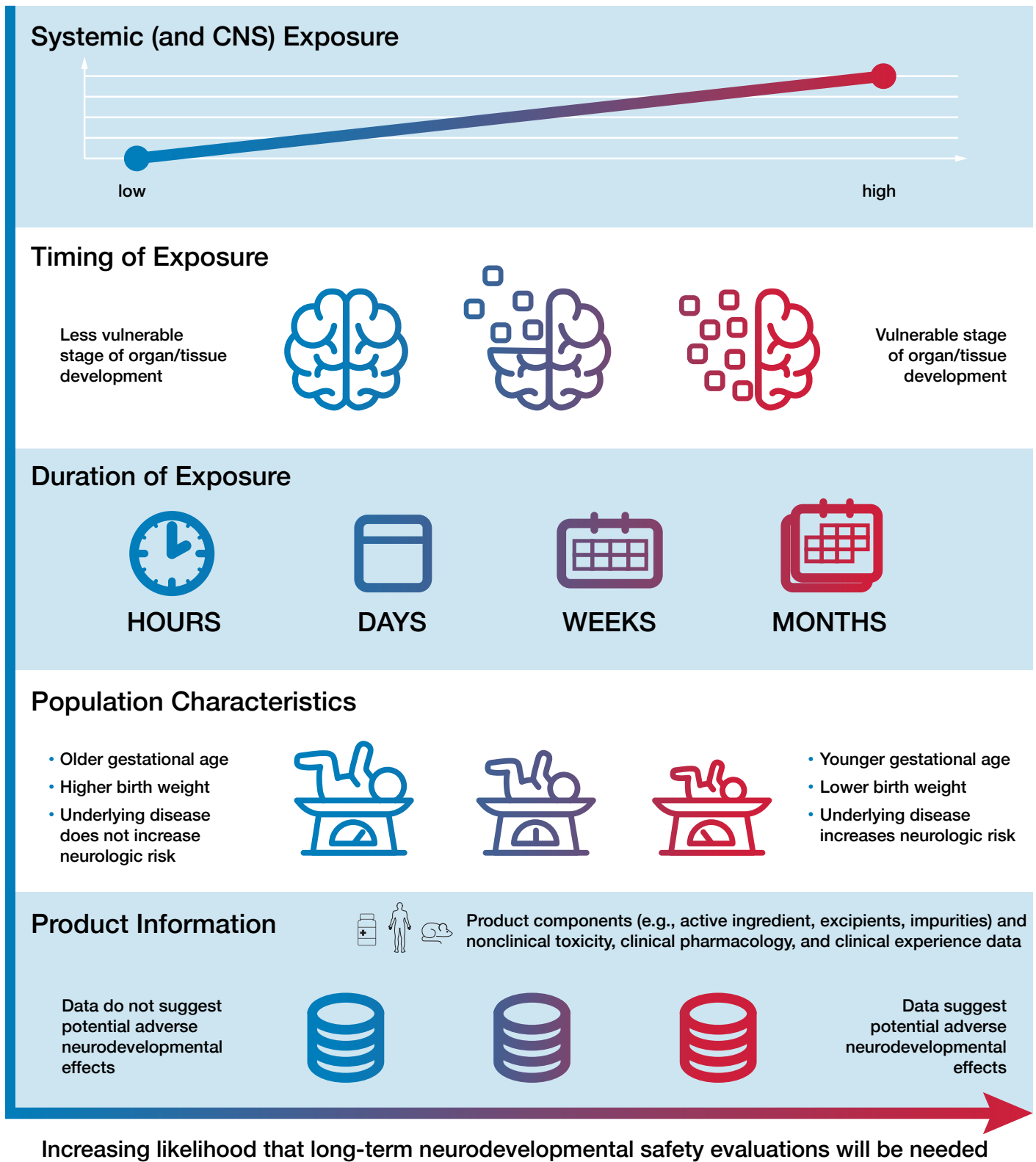
Why is this guidance important?

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	

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



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 generally should be evaluated up to **at least 2 years adjusted age**; evaluation of some outcomes (e.g., cognitive, executive functioning and social-emotional 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-variables that may affect neurodevelopmental outcomes (e.g., perinatal factors, comorbidities, parental or caregiver education, 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**

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

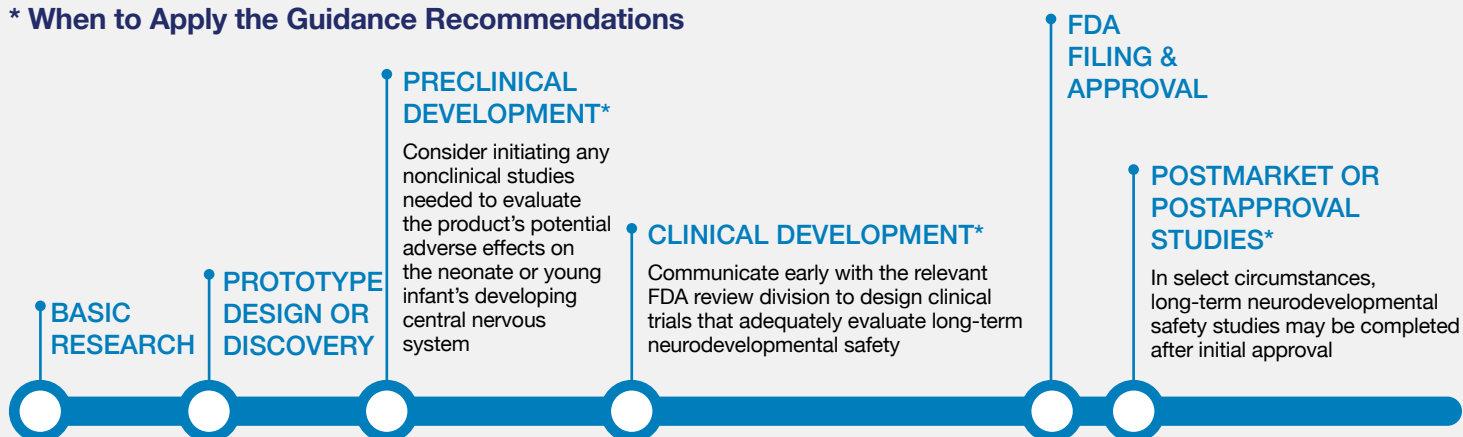
- Streamline evaluations to avoid duplication and help ensure pediatric patients will be willing to complete the tests
- Integrate data from community-level services and providers (e.g., early intervention programs), when appropriate
- Use mobile technologies or other streamlined methods for information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



Guidance Recap Podcast

Hear highlights straight from FDA staff

Speakers: An Massaro, MD, Lead Neonatologist for the Neonatology Program in the Office of Pediatric Therapeutics

Gerri Baer, MD, Neonatologist and Team Lead in the Center for Drug Evaluation and Research



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