

Measuring Clinical Benefit in Neonatal Randomized Clinical Trials: Challenges and Opportunities

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Hybrid Public Workshop: National Press Club, Washington D.C. and Virtual

Discussion Guide

Introduction

Beginning in the 1990s, legislative achievements such as the Best Pharmaceuticals for Children Act (BPCA), the Pediatric Research Equity Act (PREA), and Title V of the FDA Safety and Innovation Act (FDASIA) prompted significant improvements in pediatric access to safe and effective medical products. As a subset of the pediatric population, neonates have benefited from the pediatric legislation and clinical studies, particularly in the therapeutic areas of anti-infectives and anti-viral drugs. However, many drugs that are commonly used in neonatal intensive care units (NICUs) are not specifically labeled or approved for use in neonates. In addition, medical conditions specific to neonates frequently lack approved therapies that have been proven safe and effective.

Often cited challenges inherent in conducting neonatal randomized controlled clinical trials (RCTs) include: the heterogeneity of the population (both with regards to baseline differences and comorbidities, as well as within subject temporal changes in neonatal physiology), lack of standardization (with regards to laboratory normative values, neonatal adverse event adjudication, and clinical practices during trials), and recruitment difficulties.

Despite these challenges, designing and conducting neonatal RCTs is both possible and necessary for developing and evaluating drugs and other medical products in neonates. For a drug or biologic to be approved for marketing, it must be deemed safe and effective for its intended use – in other words, its potential benefits must outweigh its potential risks. Clinical trials are conducted to show that a treatment delivers this positive balance of benefits and risks. In clinical trials designed to measure efficacy, primary endpoints are used to reflect the intended effects of the drug and demonstrate whether it provides clinical benefit.

Types of RCTs and Endpoint Selection

Neonatal RCTs can be designed and conducted to achieve different objectives. Investigators may conduct a neonatal RCT to compare differences, for example, in resuscitation protocols, respiratory support strategies, or nutrition practices. For most of these RCTs, the U.S. Food and Drug Administration (FDA) does not need to review the study protocol. Clinical study protocols involving drugs and biological products may require FDA review. Investigator-initiated RCTs that are designed to evaluate the impact of a drug on patients with a disease or condition, often require an investigational new drug (IND) application submission and review by FDA staff.¹ Investigator-initiated INDs undergo a review primarily to ensure participant safety according to regulations. After establishing proof of concept and preliminary efficacy, an investigator or industry sponsor may initiate later phase clinical trials designed to

¹ “Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators – Draft Guidance for Industry.” U.S. Department of Health and Human Services, Food and Drug Administration; May 2015.

demonstrate efficacy for patients with a disease or condition. These trials may then be submitted as part of a new drug application (NDA), supplemental NDA or biologics licensing application (BLA) for FDA review and potential approval.

One of the key questions that arises early in efficacy trial design is: *which study endpoint should be measured to assess the effects of treatment?* The specific endpoint chosen for a given study depends on the nature of the condition, the clinical trial design and feasibility, and the anticipated effect of the treatment. Investigators may use clinical outcomes, surrogate endpoints, biomarkers, clinical outcome assessments or a combination of endpoints to measure treatment benefit.

The FDA's statutory requirement for approval requires demonstrating substantial evidence of effectiveness, which includes "adequate and well-controlled trials." In an adequate and well-controlled clinical investigation, the method of assessing a research subject's response must be well-defined and reliable. The response may be assessed by clinical endpoints, or surrogate endpoints when appropriate, but it must be "clinically meaningful."² If a surrogate endpoint is considered for efficacy assessment, it needs to be supported by clear mechanistic rationale and clinical data providing strong evidence that an impact on the surrogate predicts a specific clinical benefit.

Progress has been made, yet more work is needed to develop efficacy endpoints and outcome measures that are specific to neonates and are acceptable to investigators, regulators, drug developers, and patients and families. This creates challenges – and opportunities – for researchers to understand what to measure and how to measure clinical benefit in response to treatment in the neonate. At the foundation of finding solutions to this challenge is understanding what is clinically important by talking to clinicians, investigators, regulators, and most importantly, the families and patients who have been impacted by conditions that present in the newborn period.

The Duke-Margolis Center for Health Policy under a cooperative agreement with the FDA is convening this meeting to promote discussion and collaboration between researchers, clinicians, industry, parents, and regulators on efficacy endpoint considerations for neonatal RCTs, and to provide a forum for patients and families to share what clinical benefits they find important. Featuring multistakeholder perspectives, the meeting will cover topics including:

- Current approaches to measuring efficacy in neonatal randomized clinical trials;
- Challenges experienced in evaluating efficacy in neonatal trials for conditions with high unmet clinical need including bronchopulmonary dysplasia (BPD), neonatal seizures, neonatal opioid withdrawal syndrome (NOWS), and pain;
- Key considerations for selecting endpoints to be included in neonatal trials including perspectives of patients and families;
- Novel approaches to measure clinical benefit in neonatal clinical trials.

Session 1: Current Approaches to Measuring Efficacy in Neonatal Randomized Control Trials

Neonatal multicenter RCTs frequently are designed with composite, dichotomous primary endpoints, such as "death or severe neurodevelopmental impairment," or "death or bronchopulmonary dysplasia." One main reason for this approach is the importance of accounting for deaths in populations of very preterm or ill neonates, because patients who do not survive cannot be assessed for later outcomes.

² "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products – Draft Guidance for Industry;" U.S. Department of Health and Human Services, Food and Drug Administration; December 2019.

Although dichotomous composite endpoints may be statistically efficient, these endpoints are not able to capture a range of severity of outcomes. Primary efficacy endpoints for trials involving preterm neonates (except when neurodevelopmental testing is part of a primary endpoint) are typically captured at or around 36 weeks post-menstrual age (PMA), as most preterm patients will be nearing or ready for discharge. However, for most outcomes an assessment at 36 weeks PMA may not be an adequate predictor of longer-term clinical outcomes.

For the purposes of regulatory approval, trials need to demonstrate efficacy on clinical endpoints that measure how a person “feels, functions, or survives” or on surrogate endpoints that reliably predict clinical benefit. Lack of established validated efficacy endpoints is a stumbling block for many neonatal drug development programs. This workshop was designed to stimulate discussion about efficacy endpoints amongst stakeholders with multiple viewpoints and a common goal of improving the health and well-being of patients. This session will feature presentations on current approaches to measuring efficacy in neonatal RCTs to lay the foundation for the workshop’s subsequent discussions.

Session 2: Challenges in Measuring Efficacy for Neonatal Conditions with Unmet Clinical Needs

While there are several examples of primary efficacy endpoints that have been generally accepted to support regulatory approvals for neonatal products (e.g., mortality, severe neurodevelopmental impairment at 2 years), defining efficacy endpoints in conditions where reducing severe outcomes is not the only or primary treatment goal remain a challenge. Also, severe outcomes can often be rare in certain conditions, or take years to manifest, causing difficulty with feasibility and sample size. Approaches to define endpoints that can measure clinically relevant endpoints are crucial to promoting product development in neonatal conditions with unmet clinical needs.

Key challenges for establishing efficacy of neonatal therapies include population heterogeneity, lack of standardization of clinical practices, difficulty demonstrating durability of effect, and a myriad of intercurrent issues (e.g., social, environmental, access to care, comorbid conditions) that can all introduce confounding. Selection of efficacy endpoints for neonatal RCTs must factor in these considerations and, when at all possible, be robust to confounding effects and other sources of bias. Neonatal-specific conditions present a unique challenge since analogous endpoints cannot be generalized from adult conditions and judgments regarding what may represent a clinically relevant benefit have to be made without the benefit of the direct patient perspective.

This session will begin with presentations from experts in four different neonatal conditions of unmet clinical needs: pain, bronchopulmonary dysplasia (BPD), neonatal seizures, and neonatal opioid withdrawal syndrome (NOWS). The presenters will discuss the condition-specific challenges and considerations for efficacy measurement, including methods used to develop proposed endpoints.

Discussion Questions:

- What challenges exist in measuring efficacy and selecting endpoints for neonatal RCTs? How have these challenges impacted meaningful evidence generation?
- What are the best approaches for developing core outcome sets for key neonatal conditions and how can core outcome sets be used in demonstrating efficacy?
- What are the best approaches for justifying proposed efficacy endpoints for a neonatal trial?

Session 3: Key Considerations for Endpoint Selection for Neonatal Conditions

Endpoint selection and refinement should involve a variety of stakeholders, each of whom provides vital input on ensuring that the proposed endpoint meets the scientific expectations while balancing patient-focused priorities. Patient and (in the case of neonates and infants) parent and caregiver experience data needs to be collected to best understand the impact of the condition on how the child feels and functions. Patients and their families provide essential perspective on the lived experience of children who survive preterm birth and other neonatal conditions. Data on symptoms and their impact on functioning, quality of life, and the perceived importance of various outcomes are best collected from persons who experience those outcomes or their caregivers. Clinicians who help manage patients during and after the neonatal period also can provide an understanding of clinical outcomes and feasibility of assessments. From a scientific perspective, a robust efficacy endpoint needs to be clinically relevant, reliably measured, and sensitive to the impact of treatment. Regulators are focused on understanding and ensuring that a given treatment is responsible for a clinically meaningful effect, and industry partners provide important perspectives on operationalizing protocols and feasibility of measures.

In this session, panelists with diverse views and experiences will discuss key aspects of endpoint selection for neonatal conditions, including timing of outcome measurement, interpretability, and other important considerations.

Discussion Questions:

- What does each stakeholder believe are the most important factors to consider for measuring efficacy?
- When designing a clinical trial, how can investigators/sponsors determine the degree of improvement that would be clinically meaningful?
- How can study investigators/sponsors balance feasibility and meaningfulness when selecting outcome measures?

Session 4: Novel Approaches to Measure Clinical Benefit in Neonatal Clinical Trials

Given the challenges with current approaches to measuring efficacy discussed in the preceding sessions, clinical trialists, industry stakeholders, and consortia are exploring new approaches for measuring clinical benefit in RCTs. Emerging methodologies for measuring clinical benefit will be discussed, such as hierarchical combinations of clinical outcomes of interest (e.g., Global Rank Score). These and other statistical methods can address problems related to the lack of power associated with classical categorical endpoints, a major challenge in neonatal trials where conditions are relatively rare and enrollment is challenging due to the vulnerability of the population.

Presenters will provide background information on innovative methodologies, and the panel will discuss additional approaches, including the utility of real-world data, to develop novel endpoints for neonatal clinical trials.

Discussion Questions:

- What new approaches are investigators considering for measuring clinical benefit in neonatal RCTs?
- What are the best approaches for validating an innovative measure of clinical benefit?
- How can innovative efficacy endpoints be efficiently incorporated into neonatal clinical trials?

Recommended Reading

- [Bronchopulmonary dysplasia appropriateness as a surrogate marker for long-term pulmonary outcomes: a systematic review](#) (Corwin et al., 2018)
- [The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-Based Approach](#) (Jensen et al., 2019)
- [A Core Outcome Set for Neonatal Opioid Withdrawal Syndrome](#) (Kelly et al., 2020)
- [Drug Labeling and Exposure in Neonates](#) (Laughon et al., 2014)
- [Recommendations for the Design of Therapeutic Trials for Neonatal Seizures](#) (Soul et al., 2019)
- [Chronic Pulmonary Insufficiency of Prematurity: Developing Optimal Endpoints for Drug Development](#) (Steinhorn et al., 2017)
- [Do We Measure the Right Endpoints? A Systematic Review of Primary Outcomes in Recent Neonatal Randomized Clinical trials](#) (Zhang B, Schmidt B, 2001)