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Methodological issues in the design and analyses of neonatal research studies: Experience of the NICHD Neonatal Research Network

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ABSTRACT

Impressive advances in neonatology have occurred over the 30 years of life of The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN). However, substantial room for improvement remains in investigating and further developing the evidence base for improving outcomes among the extremely premature. We discuss some of the specific methodological challenges in the statistical design and analysis of randomized trials and observational studies in this population. Challenges faced by the NRN include designing trials for unusual or rare outcomes, accounting for and explaining center variations, identifying other subgroup differences, and balancing safety and efficacy concerns between short-term hospital outcomes and longer-term neurodevelopmental outcomes. In conclusion, the constellation of unique patient characteristics in neonates calls for broad understanding and careful consideration of the issues identified in this article for conducting rigorous studies in this population.

Introduction

Impressive advances in neonatology have occurred over the 30 years of life of The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN). However, improvement in survival for extremely premature babies has plateaued in recent years despite the more aggressive use of antenatal steroids,

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antibiotics, and surfactant, while in-hospital morbidities such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), intracranial hemorrhage (ICH), and sepsis remain high[1–3] as premature births have increased.[4] Although this has led to an increase in the number of infants at higher risk for long-term neurodevelopmental impairment (NDI), most investigators have reported that rates of neurologically intact survival (among live births) at 18 months–2 years remain unchanged. Allowing for the complexities in interpreting a composite outcome (survival free of NDI), which is discussed later, overall this illustrates both the progress made in improving outcomes and the substantial room for improvement that remains.[5,6] These trends collectively have widespread implications for health care delivery and point to the continued need for targeted and rigorous research to develop better treatment and management strategies for neonates that improve long-term rehabilitation and outcome.

Reducing the high rates of in-hospital morbidity and later NDI among extremely premature infants remains a significant public health challenge, highlighting the importance of ongoing evidence-based research in this area. In addition, although late preterm births currently account for 75% of all neonatal intensive care unit (NICU) admissions, little evidence-based research occurs for these infants.[7,8] Thus, critical gaps in neonatal research remain, and many of the more severe diseases [such as necrotizing enterocolitis (NEC) or neonatal encephalopathy] are relatively infrequent conditions that require multicenter involvement to study them. Significant methodological challenges also exist in designing rigorous trials for unusual or rare outcomes, accounting for and explaining center variations, identifying other subgroup differences, and balancing safety and efficacy concerns between short-term hospital outcomes and longer-term neurodevelopmental outcomes. These challenges require innovative trial design and analysis strategies to address them. Over the past 30 years of its existence, the NRN has conducted important studies to fill critical evidence gaps in the field and tackled several methodological issues in study design and data analyses in this area (Table). The following discussion briefly highlights some of the special methodological concerns in neonatal studies and the NRN experience in addressing them.

Statistical considerations for neonatal research

Designing studies in neonatal populations involves particular challenges, some of which apply almost universally across all NRN studies (e.g., the need to balance both proximal and distal outcomes to evaluate safety and efficacy), and some of which arise during the planning of specific studies [e.g., switching drug administration mode from IV to oral as an infant matures in a pharmacokinetics (PK) study]. In this section, we give examples of statistical innovations we have used to overcome specific challenges in recent NRN studies, and we describe methods emerging from the research of statisticians at RTI and elsewhere that can be applied to challenges we foresee for future studies. The approaches discussed here augment standard statistical techniques used in more straightforward studies and analyses, which are not discussed here.

Competing outcomes

An important issue in designing randomized clinical trials (RCTs) for high-risk patients is the selection of an appropriate primary outcome when death is a competing outcome. In this situation, some patients will die before the outcome that the intervention is expected to prevent can be diagnosed, e.g., BPD. For this reason, the primary outcome in such trials is often a composite outcome, e.g., death or BPD even if the intervention is not expected to affect mortality.

As illustrated by the Network SUPPORT trial, an important advantage of including deaths in the primary outcome is that mortality might unexpectedly be affected. This trial assessed whether use of an oxygen saturation goal in the lower half of the recommended range would reduce severe ROP among infants born at 24–27 weeks' gestation. Based on the best available evidence before the trial, no effect on mortality was hypothesized or expected by the investigators, contrary to what critics unfamiliar with the issue of competing outcomes have assumed about this study.[9] The lower saturation goal did reduce severe ROP. However, this benefit was offset by an unexpected increase in death with no significant effect on the primary outcome of death or severe ROP. Had the primary outcome been severe ROP alone (among survivors), the primary outcome would not have captured the most important effect of the lower saturation goal, and the finding of a mortality difference that prompted the recommendation to use a high saturation goal.[10]

In general, unless death is part of the primary outcome for a trial in a population that is likely to experience a substantially high death rate before the true outcome of interest can be assessed (again, because death is a competing outcome for any later morbidity in the NICU population), interpreting downstream events is complicated and inferences about the effects of treatment on these risks may be biased. This is because differential death rates in the comparison groups make the survivors in these two groups a non-random sample of the randomized population, resulting in a biased and nonrandomized comparison of outcome rates.

In addition to accounting for mortality, certain composite outcomes in neonatal research have considerable public health significance in their own right. Since the survival of extremely premature babies with profound impairment often has lifelong significance for these children, their families and society at large, survival free of neurodevelopmental impairment (or, neurologically intact survival) is a clinically meaningful outcome in its own right that is frequently used as a primary outcome for many NRN trials. For example, the ongoing Transfusion of Prematures (TOP) trial aims to examine whether the clinically relevant composite primary outcome of death or significant neurodevelopmental impairment in survivors at 22–26 months of corrected age is less common among preterm infants who, by transfusion practice, are maintained at higher hemoglobin levels.[11]

Although competing outcomes are an unavoidable problem, some investigators resist the use of composite outcomes, including those that include death as a competing outcome, because outcomes of differing importance are given equal weightage. In principle, this is not an inherent problem for composite outcomes. A potential solution is to weigh the