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Article type : A Different View

Use of Composite NICU Research Outcomes for Goals of Care Counseling Creates Ethical Challenges

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/apa.16018](https://doi.org/10.1111/apa.16018)

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P: 206.987.4760. F: 206.987.2685

Short title: Ethical Concerns of Using NICU Composite Outcomes

Funding source: No funding was secured for this study.

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Abbreviations:

Neurodevelopmental Impairment (NDI)

Quality of life (QOL)

Retinopathy of prematurity (ROP)

Contributors' Statement Page

Dr. Weiss conceptualized and designed the project, drafted the initial manuscript, and reviewed and revised the manuscript.

Drs. Barrington and Kukora provided key conceptual input into the project and critically reviewed and revised the manuscript.

The use of composite outcomes has become standard in neonatal research. Limited alternatives to this approach to data analysis are feasible or widely accepted. In this paper, we suggest reasons why using results based on this standard measure to guide goals of care discussions for individual patients can be ethically problematic. Specifically, it implicitly suggests that neurodevelopmental impairment (NDI) is equivalent to death. We do not claim that most clinicians caring for neonates feel this way. However, discussing prognosis based on composite outcomes without careful consideration of the granular components risks creating such an equivalency.

Extremely preterm infants are at high risk of both death and long-term survival with permanent impairment. There is persistent concern that neonatal intensive care may result in survivors with unacceptably severe impairments. A combined outcome, previously called "intact survival" and now referred to as "survival without neurodevelopmental impairment (NDI)"—has been developed to aid research into therapies for preterm infants. Because prospective clinical research studies represent the strongest empirical evidence available in neonatology, the findings heavily influence clinicians' decision-making, perspective, and communication with families. As a result, findings from such studies frequently guide decision-making for individual patients, whether explicitly or implicitly. These include assisting in goals of care discussions, in which parents may consider redirection from intensive support to comfort care for their preterm infant.

In this piece, we will: a) describe the benefits of composite outcomes for neonatal clinical research; b) explain the imperative of neonatologists to use the best available data to guide goals of care decision-making; c) detail the ethical problem with applying the best data currently available to guide goals of care decision-making; and d) propose actions to improve the ability of neonatologists and parents to use the best available evidence to guide goals of care decision-making.

The composite outcome "survival without NDI" has the following benefits for the research endeavor. First, it allows the determination of whether a specific intervention with a highly

heterogeneous outcome (e.g., neurological status) is beneficial. Improvement in neurodevelopmental status is the primary goal for many interventions targeting preterm neonates, so this advantage could hardly be overstated. Second, death may compete with the primary outcome of interest. NDI assessment is typically made after hospital discharge. Failing to include death in the composite outcome will result in a failure to account for infants that would have developed NDI had they survived. Third, it reduces the required sample size, enabling research that might otherwise be unfeasible. Fourth, it allows for the comparison of benefit across studies of widely different interventions. Fifth, it enables aggregate assessment of trials of similar interventions via meta-analyses. Composite outcomes can also be criticized for research purposes because when contributing outcomes are affected in different directions (e.g., decrease mortality and increase severe morbidity) interpretation becomes fraught. Neonatologists in practice also embrace the composite outcome approach to gain valuable insight into quality improvement work, resource allocation decisions, and education of trainees.

Clinical research includes the wide spectrum of activities, from randomized controlled trials to comparative effectiveness research to observational cohort studies. Although they have different primary outcomes (e.g., comparing effectiveness of interventions vs. generating epidemiologic outcomes) different risks,¹ and some lend themselves to direct counseling better than others, they all approach outcomes in this same mentality. This, in turn, sets the framing for how neonatologists think about outcomes and how outcomes are used to guide decision-making with parents. Historically, the choice to not focus on quality of life (QOL) measures within neonatology clinical trials was a deliberate decision made by the research community.²

American Academy of Pediatrics guidelines endorse explicit discussion of evidence-based outcomes about morbidity and mortality as part of goals of care discussions for parents of extremely preterm infants.³ British Association of Perinatal Medicine guidelines are more specific in that they recommend clinicians discussing goals of care with parents use a specific severe NDI category which includes severe cerebral palsy, blindness and profound hearing impairment in addition to severe cognitive impairment.⁴

The paramount ethical concern with using “survival without NDI” to guide goals of care discussions is that parents of an infant with a high likelihood of death or NDI may decide to pursue comfort care without fully understanding that this categorization may include clinical outcomes they consider acceptable. Outcomes such as isolated blindness or deafness, severe cerebral palsy with normal cognition, or moderate cognitive delay fall in the "bad" category in trials but may represent a quality of life many families would prefer over death. Conversely, some babies with the “good” outcome of “survival without NDI” may have clinical outcomes that would be unacceptable to families, such as severely disabling behavioral abnormalities.⁵ Detailed information about the range of possible outcomes, with a focus on individual components rather than composites, will help support decision-making congruent with values.⁶

Even though we rarely use the words “intact survival” or explicitly refer to composite outcomes, these frame our thinking as clinicians. We utilize data from these studies to inform our discussions and recommendations. Parents’ decisions for their infant’s goals of care may be influenced by advice from clinicians and as a result they may be swayed towards a decision inconsistent with their true values.

Consider the example outcome of studies targeting reduced visual impairment from severe retinopathy of prematurity (ROP). Supplemental oxygen is needed for the survival of extremely preterm infants; however, excessive exposure leads to blindness. Researchers continue to try to find the right balance, but too little oxygen may cause the most fragile infants—who may otherwise have lived with blindness—to die. Therefore, studies attempting to decrease severe ROP must combine the two unacceptable outcomes of severe ROP and death, because the aim is to decrease the latter without increasing the former. In this context, the combined outcome is essential. At the bedside, though, the acceptability of outcomes for parents considering deciding between comfort care and intensive supportive therapy may be quite different from the acceptability of outcomes for research. If parents feel that survival with blindness would be acceptable for their child, counseling them using the combined outcome conflate an acceptable outcome (severe ROP) with an unacceptable one (death).

Implications for Researchers Endeavoring to Improve Decision-Making in the NICU

What does this mean for those who want to improve the ability of neonatologists and parents to use the best available evidence to guide goals of care decision-making? We identify four areas of particular interest in this arena that would benefit from further research: 1) identification of outcomes best suited to assist parents make these decisions, including QOL and how it is perceived in the context of diverse values; 2) presentation of data, including choice of denominator and consideration of biases; 3) how parents make these types of decisions; 4) adaptation and resilience of families. First, researchers must assess what outcomes are best suited to assist parents making goals of care decisions. Input should be solicited from a wide range of stakeholders: funders, trialists, clinicians, and, particularly, parents. Former preterm infants conceptualize disabilities and evaluate QOL differently from their parents⁷, from physicians⁸, and from clinical researchers.⁹ Outcomes that differ from those currently studied, such as functional communication ability, may be particularly important to parents tasked with these decisions.¹⁰ Over the past decade, investigators have reported that former premature infants rate their QOL lower than term controls in later childhood or into adulthood.¹¹⁻¹³ These findings of statistically significant but clinically modest lower QOL are important indicators that we, as a specialty and as a society, still have much to do to better support their needs. These findings should not be presumed to suggest that most parents would alter goals of care decisions in the neonatal period because of them or that NICU survivors would wish they had done so.

Second, researchers must assess how the presentation of information influences these decisions. Framing,¹⁴ order choice,¹⁵ and default option presentation¹⁶ influence perinatal decision-making around resuscitation. Cognitive biases are likely frequently used in such decision-making.¹⁷ Additionally, more empirical research is needed to clarify which denominator is appropriate to use for these conversations. In our experience, parents are typically more interested in rates of severe NDI among survivors than in a composite outcome including death. For high mortality populations this drastically changes the numbers presented.

Third, we need a better understanding of how parents make goals of care decisions. Hope, cultural and religious beliefs, and personal values can be more influential than statistical outcomes.¹⁸ Fourth, more research is needed into the adaptation and resilience of families with a

severely impaired former preterm infant as well as the condition of families that choose to pursue palliative comfort care.

Implications for Clinical Trialists

We acknowledge that some strides have been made towards presenting data to better inform clinical discussions. Tyson, for example, presents data using composite outcomes of both “death or profound impairment” and “death or [any] impairment.”¹⁹ Schmidt, likewise, includes a more granular table of outcomes.²⁰ Although these actions may give clinicians some additional context, they remain inadequate to guide decision-making for an individual patient. Recently, papers reporting these clinical outcomes have cautioned that these studies should not be used for guiding decision-making at the individual level, particularly for goals of care discussions. For several years the predominant outcomes estimate calculator has featured a disclaimer indicating that the data are not intended for individual prediction purposes.²¹ Though these qualifications are warranted, necessary, and well intentioned, they have not stopped clinicians from using the results in a way we find concerning.²² In March 2020, the calculator was changed to include more granular data in its output. Such changes and other work towards refining how we present outcomes data to families facing extremely preterm birth represent important steps in the right direction.²³

Once we have better defined which outcomes are most important for parents tasked with these decisions, we hope that clinical trialists will routinely include them as secondary outcomes. There is a growing appreciation among neonatal clinical trialists that medical, functional, and social outcomes beyond NDI are critically important.⁵ Only when relevant outcomes become part of the most robust evidence base can we make substantial strides addressing these concerns.

Implications for Clinicians

Employment of a dichotomous outcome created and intended for research purposes at the bedside during goals of care discussions has ethically problematic consequences. Work must be done to learn what functional outcomes of babies with NDI may better inform values-based goals of care decisions. Until then, neonatologists must be explicitly aware that morbidity outcomes from most neonatal research are inadequate to thoughtfully inform life and death decisions for

individual preterm infants. They must attempt to tailor their counseling to include how potential outcomes (of various likelihoods) are perceived by parents in order to best align goals of care decisions to parental values.

Acknowledgements:

We would like to acknowledge Jeanne A Krick, MD, Madigan Army Medical Center, Tacoma, WA for her intellectual contributions in earlier discussions of these topics. We also thank Katherine F Guttman, MD, MBE, Icahn School of Medicine at Mount Sinai, New York, New York, John D Lantos, MD, Children's Mercy Bioethics Center, Kansas City, MO, and Nicolas Bamat, MD, MSCE, Children's Hospital of Philadelphia, Philadelphia, PA for commenting on earlier drafts.

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