PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

FINAL RESEARCH REPORT

Looking at the Effect of Treatment Duration for Newborn Infants Who Have Seizures

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ABSTRACT

Background: Treatment duration for acute symptomatic neonatal seizures is highly variable. Antiseizure medication (ASM) may be discontinued before or maintained at the time of discharge from the neonatal seizure admission.

Objectives: We assessed whether ASM treatment duration after acute symptomatic neonatal seizures alters the following:

- The risk of abnormal functional neurodevelopment or postneonatal epilepsy by 24 months corrected age (aim 1)
- The hospital length of stay (LOS) for the neonatal seizure admission (aim 2)
- Parent well-being (aim 3)

Methods: We conducted a prospective, observational comparative effectiveness study of ASM duration for 303 survivors of acute symptomatic neonatal seizures (seizure onset <44 weeks postmenstrual age, excluding transient, genetic, and congenital infectious causes of seizures) who were born between July 2015 and March 2018 and were enrolled at 9 Neonatal Seizure Registry sites. At 24 months, functional development was assessed using the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS) instrument (primary outcome). Clinical neonatal data, including LOS, were extracted from the neonatal records. Parent-reported well-being measures were collected at hospital discharge and at 12, 18, and 24 months. To enhance causal inference, we adjusted the risk of each outcome for the propensity to receive ASM at discharge. We hypothesized that WIDEA-FS scores of children whose ASMs were discontinued before hospital discharge would be noninferior to scores of children whose ASMs were maintained at discharge. The study was powered to demonstrate noninferiority if the lower bound on the CI for the WIDEA-FS was <0.5 SD of the WIDEA-FS score (7%, or 12 points).

Results: ASMs were prescribed at discharge for 64% (higher propensity for those with high seizure burden, complex clinical course, and abnormal discharge examination) of infants. Among infants whose ASMs were discontinued before discharge, ASMs were prescribed for a median of 6 (interquartile range [IQR], 3-11) hospital *days*, compared with a median of 4 (IQR, 3-8) *months* for infants whose ASMs were maintained.

- *Aim 1:* Unadjusted 24-month WIDEA-FS scores (measured in 270/300 [90%] of survivors) were 4 points (2%) higher for children whose ASMs were discontinued before hospital discharge than for children maintained on ASMs (median, 165 [IQR, 150-175], compared with median, 161 [IQR, 129-174], respectively; $P = .09$). In propensity-adjusted analysis, WIDEA-FS scores were noninferior for children whose ASMs were discontinued before hospital discharge compared with children whose ASMs were maintained (average difference, +3 points; 90% lower CI of −4 was within the a priori noninferiority margin of −12 points). Epilepsy (recurrent unprovoked seizures) developed in 13% (37/282) of infants before age 24 months; 5% had infantile spasms (13/282). The risk of epilepsy did not differ

by ASM treatment duration (11% for infants whose ASMs were discontinued, compared with 14% for those maintained on ASM; odds ratio [OR], 0.8; 95% CI, 0.4-1.6; *P* = .49; propensity-adjusted OR, 1.5; 95% CI, 0.7-3.4; *P* = .3).

- *Aim 2:* The median LOS was 15 (IQR, 9-29) days. The point estimate of the LOS was shorter for children whose ASMs were discontinued (median, 13 [IQR, 8-25] days) than for those maintained on ASMs upon discharge from the neonatal seizure admission (median, 17 [IQR, 10-32] days; *P* = .07]. After propensity adjustment, LOS was similar between groups. In a stratified analysis, the effect was most pronounced for newborns with seizures due to ischemic stroke (average estimated effect, 36% shorter hospital stay; 95% CI, 59% shorter to 2% longer; *P* = .06).
- *Aim 3:* Parents reported high rates of symptoms of depression (54%) and anxiety (32%) at the time of hospital discharge. Several characteristics of parents (eg, higher maternal education and greater impact on family) and infants (eg, hypoxic-ischemic encephalopathy) were associated, with medium-to-large standardized effect sizes (ranging from 0.52 to 0.78), and with poorer parent and family quality of life and well-being. At 24 months, in both the unadjusted and adjusted analyses, there were no consistent differences in well-being measures between parents of children whose ASMs were discontinued before discharge and those whose children were maintained on ASM. In a comparison of parent well-being over time for children whose ASMs were discontinued with parents of children whose ASMs were maintained on discharge from the neonatal seizure admission, a multivariate analysis showed that the impact of being discharged on ASMs differed based upon the specific dimension of parent well-being. Answers to open-ended questions provided rich information for families and clinicians.

Conclusions: Discontinuing ASMs before discharge from the neonatal seizure admission for infants with acute symptomatic neonatal seizures is safe, as this practice is not adversely associated with risk of functional neurodevelopmental impairment, postneonatal epilepsy, or LOS, and it variably affected parent well-being.

Limitations: Although the study was well powered to determine noninferiority for the primary outcome of functional development at age 24 months, postneonatal epilepsy was a relatively rare outcome: only 13% of the cohort developed epilepsy. Thus, although there was no significant difference in epilepsy development between the treatment duration groups, the analysis suggests the possibility of up to 3.4 times the odds of developing epilepsy among infants whose ASMs were discontinued before hospital discharge, compared with those whose ASMs were maintained. Parent-measured outcomes were limited by self-report at each time point, and responses were mostly from the mother, with a minority of responses from the father.

BACKGROUND

Seizures affect approximately 16 000 newborns per year in the United States and have lasting adverse effects on affected children and their families. About 15% of newborns with seizures die, and at least 50% of survivors have 1 or more long-term disabilities, including cerebral palsy, intellectual disability, and/or epilepsy.[1] Many survivors require costly lifelong therapies as well as social and academic support. More than 20% develop epilepsy within the first 12 to 18 months of life, and those with comorbid cerebral palsy are at highest risk.[2,3] For the 1 in 26 Americans who have epilepsy, a history of neonatal seizures is a major risk factor for nonremittance (lack of complete response to medications).[4] As such, neonatal seizures have a major effect, not only on the health of newborn infants but also on their long-term neurological morbidity and chronic epilepsy.

Despite the wide-ranging impacts of seizures in the newborn, alarmingly significant knowledge gaps persist. The most common current management paradigm for neonatal seizures is to treat clinical events, with or without confirmation of electroencephalogram (EEG) seizures, which can lead to both under- and overtreatment. To avoid these pitfalls, the American Clinical Neurophysiology Society (ACNS) recommends EEG monitoring for neonatal seizure diagnosis[5]; all sites in the present study follow this guideline. Phenobarbital, the most commonly prescribed antiseizure medication (ASM) for neonatal seizures, is often maintained for several months after hospital discharge because of clinicians' and parents' concerns that early discontinuation of ASM might cause seizures to recur.[6,7] However, continued exposure to phenobarbital is sedating, which may prolong the time it takes for a newborn to establish oral feeding, and this medicine may have deleterious long-term effects on the developing brain.[8,9] Results from small, nonrandomized, single-center studies suggest that discontinuation of ASM after the resolution of acute symptomatic seizures and before hospital discharge is not harmful (no worsening of developmental outcomes or increase in seizure recurrence),[6,10-12] but the optimal duration of therapy remains unknown.

Parents of infants with neonatal seizures, including those involved in this study, highlight the lack of certainty regarding treatment duration as a major concern. The present

PCORI-funded research aimed to provide critical data where very little existed to guide key decision-making for clinicians and families of these highly vulnerable infants. This patient-centered approach highlights the main concerns of >150 parents who responded to our online survey request for input on the most important research topics related to neonatal seizures.[13]

> *The question of . . . how long to continue phenobarbital after neonatal seizures is one that weighs heavily on families.*
>
> —Elizabeth (Libby) Hill, MD, parent partner

No published studies have examined the impact of antiseizure treatment on parent well-being. A few studies have focused on parents' experience after their infant's discharge home from the neonatal intensive care unit (NICU).[14] Parents of preterm and term infants may experience apprehension and lack of confidence and have a deep sense of responsibility for their infant's medical and developmental care. They are acutely aware of their infant's special needs but seek to develop a sense of normalcy for their family and to gain perspective about their experience over time. However, approximately a third of parents will experience posttraumatic stress disorder (PTSD) related to their child's hospitalization, and this has a negative effect on the family.[15,16] It is unknown whether ongoing ASM use contributes to difficulties in parent and family functioning.

According to the FDA and National Institute of Neurological Disorders and Stroke (NINDS), understanding the best management for neonatal seizures is a priority. In 2005 and 2007, the FDA and NINDS sponsored workshops on improving the treatment of neonatal seizures. There was a consensus that

> *high priorities for research included investigations to understand adverse effects of* [antiseizure medications] *and . . . to determine the relationship between efficacy for seizure suppression and long-term outcome.*[17]

Nearly 15 years later, the neonatal neurology community has not yet addressed either priority.

Traditional research approaches have failed to answer important questions about neonatal seizure treatment duration. In 2009, the Eunice Kennedy Shriver National Institute of

Child Health and Human Development (NICHD) funded a multicenter, randomized, double-blind, placebo-controlled trial to examine the very question we pose here by randomly assigning neonates with seizures that resolved within 7 days to receive either phenobarbital or placebo for 4 months (PROPHENO, ClinicalTrials.gov identifier NCT01089504; https://clinicaltrials.gov/ct2/show/NCT01089504). Although adequate numbers of potential participants were identified, a high proportion of parents at every participating center refused to consent, and the study was closed early after enrolling only 13 neonates. We concluded that another randomized trial was not feasible. Yet, we hypothesized that a well-conceived, large-scale observational study with a propensity score analysis strategy would provide the needed data and causal inference to answer the question of the optimal duration of medical treatment for acute symptomatic neonatal seizures.

The Neonatal Seizure Registry is an established, multicenter collaborative of pediatric hospitals from across the United States.[18-21] Unique among neonatal seizure studies, the Neonatal Seizure Registry was designed to enroll newborns at 9 US children's hospitals with level IV NICUs, all of which have the capability to perform long-term, multichannel neonatal EEG monitoring and to follow the ACNS guideline for neonatal EEG[5]; they are also National Association of Epilepsy Center level IV pediatric epilepsy centers.

Because of the dearth of evidence regarding optimal treatment duration, substantial practice variability continues for acute symptomatic neonatal seizures. Among 488 newborns enrolled in the Neonatal Seizure Registry preliminary study, 364 had seizures due to an acute symptomatic cause and survived until the time of hospital discharge.[22] The data regarding phenobarbital treatment duration reflected 2 main clinical practices: (1) short duration (whereby medication was discontinued before discharge from the neonatal seizure admission) and (2) prolonged duration (whereby medication was maintained at least until the first outpatient follow-up, typically at 2-4 months of age). Among the newborns enrolled in the Neonatal Seizure Registry, 23% had ASM discontinued before discharge from the neonatal seizure admission (range by site, 3%-75%), while 77% were maintained on ASM at the time of hospital discharge. Phenobarbital was the most commonly prescribed ASM (89% of those

maintained on medications). Although the Neonatal Seizure Registry sites are similar in patient acuity and conditions treated, the approach to acute symptomatic neonatal seizures differed across sites and between providers at each site. In adjusted analyses that included seizure etiology, seizure burden, and maximum phenobarbital levels, *the study site was the only independent predictor of discharge to home with continued ASM* after resolution of acute symptomatic neonatal seizures ($P < .001$). The present study took advantage of this heterogeneity in practice to address key knowledge gaps regarding appropriate treatment duration for acute symptomatic neonatal seizures.

Our long-term goal is to improve neurodevelopmental outcomes following acute symptomatic seizures in newborns. The objective of this study was to examine whether the duration of ASM treatment has an impact on neurodevelopmental and epilepsy outcomes, as well as parent well-being, after acute symptomatic neonatal seizures. Our collaborative research team established the Neonatal Seizure Registry, a multicenter association of institutions across the United States, and partnered with a parent advisory panel and patient and parent advocacy groups to develop the patient-centered questions and outcomes outlined in this report.

We planned to take advantage of the heterogeneity of treatment duration for acute symptomatic seizures within the Neonatal Seizure Registry sites to *determine the comparative effectiveness* of 2 common approaches to ASM prescription for the treatment of acute symptomatic neonatal seizures for 300 enrolled neonates: (1) short duration of treatment (discontinuation of ASM before discharge from the neonatal seizure admission) and (2) prolonged duration of treatment (maintenance of ASM at the time of discharge from the neonatal seizure admission). Importantly, based on specific stakeholder feedback, we also examined parent well-being in both treatment plans. The central hypothesis of this study was that the duration of medical management would have little to no effect on neurodevelopmental outcome or the development of postneonatal epilepsy after acute symptomatic neonatal seizures (aim 1) but would be directly associated with hospital length of stay (LOS) (aim 2) and worse parent well-being (aim 3).

Aim 1

To determine how ASM discontinued before discharge from the neonatal seizure admission (short duration) compared with ASM maintained at the time of discharge from the neonatal seizure admission (prolonged duration) affects (1) neurodevelopmental outcome and (2) incidence of epilepsy at ages 12, 18, and 24 months.

Hypothesis: There will be no differences in (1) functional developmental outcome or (2) incidence of epilepsy between the short-duration antiseizure treatment (ie, ASM discontinued before discharge from the neonatal seizure admission) and prolonged antiseizure treatment (ie, ASM maintained at the time of discharge from the neonatal seizure admission), and the results of an EEG during convalescence can be used to predict the risk of epilepsy in both groups.

Aim 2

To determine whether duration of antiseizure treatment during NICU admission affects hospital LOS among neonates with acute symptomatic seizures, a factor highlighted by stakeholders as important for family well-being.

Hypothesis: Discharge home on ASM is associated with increased exposure to ASM and longer LOS.

Aim 3

To determine how ASM discontinued before discharge from the neonatal seizure admission (short duration) compared with ASM maintained at the time of discharge from the neonatal seizure admission (prolonged duration) affects parent well-being.

Hypothesis: Shorter treatment duration is associated with improved parent well-being.

PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS

Planning the Study

The research team included key clinician stakeholders. In addition to pediatric neurologists, the research team included neonatologists, epileptologists, and a nurse. Together, these researchers worked with clinicians at their own sites to understand the local landscape of treatment approaches for acute symptomatic neonatal seizures.

We established several critical partnerships to develop the proposal. One key stakeholder group, Hand to Hold, is a parent peer group for families whose newborns require NICU care (www.handtohold.org). Hand to Hold connects with NICU families to provide information, support, and ongoing education to mitigate the impact of a NICU stay and prepare them to meet the needs of their medically fragile child after they leave the NICU. Kelli Kelley, founder and executive director, assisted the study team in designing and posting a parent survey regarding priorities for neonatal seizure research on the Hand to Hold site and provided a parent perspective to the development of the study design.[13] A second key partner in study planning was Marty Barnes, founder and director of Casey's Circle (www.caseyscircle.org). Casey's Circle aims to improve the quality of life (QOL) for children with medically complex conditions, their families, and their providers by providing education, tools, and resources to help in the day-to-day care of these children. They host social events designed for children with complex medical needs that are fun for the entire family, and they provide bereavement events designed to celebrate the lives of children who have died from illness. Mrs Barnes also assisted the study team in designing and posting the parent survey regarding priorities for neonatal seizure research[13] on the Casey's Circle website and provided a parent perspective on the development of the study design.

The parent advisory panel helped design the study and selected the most relevant outcome measures. Given that newborn infants are unable to act as direct patient stakeholders, parents must serve as proxy stakeholders. We worked with the University of Michigan (UM) Patient and Family Research Council to develop the research idea and refine the overall study design. We then recruited parents of children who experienced neonatal seizures

to form our parent advisory panel (Table 1). Most parents were recruited from the study sites by the local site investigator to mitigate concern regarding the exclusion of parents who are not part of online social media platforms. These parents were chosen for their interest in research or advocacy and based on willingness to participate in monthly calls. Several parents were recruited via their connections with Hand to Hold, Casey's Circle, and Hope for HIE (ie, hypoxic-ischemic encephalopathy). These parents came from all regions of the United States, had diverse racial and ethnic backgrounds, and had a range of experiences with neonatal seizures. Parents participated in conference calls and email discussions to provide input on the overall study design and to select the methods and measures for aim 3. They were asked open-ended questions about major concerns related to the management of their child's seizure during neonatal hospitalization and after discharge and were asked how they believed research could address their concerns. Major themes included uncertainty about prognosis, treatment variability, and long-term effects on the family. The parent advisory panel members were fully supportive of the plans for aims 1 and 2. They also confirmed the pertinence of the outcome measurement time points (NICU discharge and when the infant is 12, 18, and 24 months corrected age). Parents discussed the pros and cons of different well-being surveys, agreed that no single instrument measured all the necessary topics, and arrived at consensus on the domains and validated questionnaires selected for aim 3. The panel was also instrumental in the proposal to extend the primary outcome from 12- to 24-month developmental assessment scores.

Table 1. Neonatal Seizure Registry Stakeholders: Parent Advisory Panel

Name	Organization representative	Home state
Dana Annis	DC National Children's Hospital	Maryland
Marty Barnes	Casey's Circle	Texas
Trisha Brogi	Stanford University (Lucile Packard Children's Hospital)	California
Claire Brown	Hand to Hold	Texas
Karla Contreras	Hand to Hold	Texas
Katie Grant	Cincinnati Children's Hospital Medical Center	Kentucky
Lisa Grossbauer	Children's Hospital of Philadelphia	Pennsylvania
Jennifer Guerriero	Boston Children's Hospital	Massachusetts
Elizabeth Hill	UM (Mott Children's Hospital)	Michigan
Kelli Kelley	Hand to Hold	Texas
Gwen Ma	Stanford University (Lucile Packard Children's Hospital)	California
Kamil Pawlowski	UCSF Benioff Children's Hospital	California
Betsy Pilon	Hope for HIE	Michigan

Abbreviations: HIE, hypoxic-ischemic encephalopathy; UCSF, University of California San Francisco; University of Michigan.

In Fall 2019, a representative of another important stakeholder group joined the parent advisory panel. Betsy Pilon, president of Hope for HIE (www.hopeforhie.org), joined our panel. Hope for HIE is the largest collective of HIE-focused help, support, resources, and HIE families anywhere; serves families worldwide; and is completely run by parent volunteers. Since joining our team, Ms Pilon has been active in advising about strategies for dissemination of study findings.

Co-learning

During the study planning and throughout the project, the research team educated parents and other stakeholders about the scientific evidence and options of research protocol design. Parent advisory panel focus groups contained a specific educational segment on patient-centered research and PCORI. Likewise, the parent advisory panel members were critical in informing the research team about parents' priorities and the best assessment

instruments for use in the parent well-being outcome assessments, as well as best practices for communication with participating families.

Parent Advisory Panel Compensation

Parent advisory panel members were offered financial compensation in recognition of their participation in monthly telephone conference calls, focus groups, review of study documents, data interpretation, and manuscript review. Parents of children with special needs, especially those with seizures, are busy people. They balance multiple childcare, health care, and professional commitments. We specifically discussed the level of commitment required and compensation available, and each parent advisory panel member agreed to the commitments outlined above.

Additionally, 2 members of the parent advisory panel reported listing on their résumés that they were members of the panel and co-authors on published papers. They reported that these accomplishments were influential in obtaining admission to a PhD program and in being hired by a health care organization.

Conducting the Study

The parent advisory panel remained engaged and active throughout the term of the study. They participated in monthly meetings through teleconference calls and by email. The minutes of the meetings were circulated and were submitted separately to PCORI. During the study period, the parent advisory panel focused on the following activities:

- **Development of study-related documents (eg, consent forms, brochures).** The parent advisory panel reviewed and sometimes co-created all participant-facing study documents to ensure that the content and formats were sensitive and welcoming to potential study participants.

- **Provision of guidance on optimal recruitment and retention practices.** The parent advisory panel provided advice on recruitment and retention strategies and discussed challenges that arose. They contributed significantly to decisions about the timing of the approach for initial consent to join the study. The parent advisory panel helped create a study newsletter that was distributed to all study participants 2 times per year. Over the

course of the study, almost all of the parent advisory panel members were featured in a newsletter along with their reason for being involved in the study. We attribute our great success in recruitment and retention in large part to the work of the parent advisory panel on study planning and development of participant documents that were engaging and focused on what mattered most to parents, as well as a result of their ongoing advice on strategies for maximizing retention.

- **Optimization of study procedures.** The parent advisory panel provided consultation to optimize study procedures for the comfort and benefit of potential participants. For example, in the first 6 months of the study, they discussed approaches to informed consent discussions, communications with families at various time points in the study (including acknowledgment of a family whose child died unexpectedly), and strategies for clinical research coordinators to provide resources for parents in the event they became distressed when answering telephone surveys. The parent advisory panel also offered advice on ways to trigger greater recall for parents during telephone follow-ups. Dr Hill, UM parent partner, represented the parent advisory panel at an investigator meeting (May 2017). Mrs Barnes, a representative from Casey's Circle, joined Renée A. Shellhaas, MD, MS, at the PCORI conference to represent the parent advisory panel perspective (September 2019).

- **Review of study results.** Early drafts of study findings (abstracts and papers) were shared with the parent advisory panel. Parent advisory panel members were active collaborators and co-authors on the presentation and publication of findings from aim 3,[23,24] and they were engaged in a review of the preliminary results for parent well-being and in hypothesizing underlying mechanisms and potential future interventions. Parent advisory panel members were also instrumental in advising that the analysis plan include the interactions between parent mental health and child neurodevelopment.

We discussed the analysis plan and preliminary results with the full parent advisory panel and worked with a subset of parents to interpret the findings, suggest additional analyses, and reinterpret the data once those became available. Parents contributed unique perspectives that enabled a deeper and more inclusive interpretation of the findings. For example, in the thematic analysis, they endorsed many of the emerging themes and helped us reconsider some initial interpretations (eg, in the early coding for our parent experience analysis, nonparent analysts identified codes around parent "acceptance of the new normal"). Parent advisory panelists reviewed the primary data and challenged the team to reframe the

idea of acceptance and instead reflect the process of parent adaptation. Iterative analysis of the data revealed that this concept of adaptation was a primary theme that was endorsed by two-thirds of respondents).

Several parent advisory panel members were co-authors on Franck et al[23] and Lemmon et al,[24] and the full panel was acknowledged in both articles. All parent advisory panel members reviewed abstract submissions to Pediatric Academic Societies, and 2 were co-authors. Parent advisory panel members also guided development of the workshop "Studying What Matters: Engaging Parents in Research," which was accepted to the 2020 Pediatric Academic Societies conference. This workshop planned to highlight multiple members of the Neonatal Seizure Registry team, including 2 parent advisory panel members and program officers from PCORI and the NIH. Unfortunately, the conference was canceled because of the COVID-19 pandemic.

Ideas for New Studies and Review of Ancillary Studies

The parent advisory panel contributed ideas for a long-term follow-up grant and the most appropriate measures for this study with respect to parent well-being and parent-completed assessments of child health and development at early school age (now funded by NIH grant R01 HL147261); literature searches on parent documentation tools; and how to ask parents questions about seizures in general, infantile spasms in particular, and postneonatal epilepsy.

Disseminating the Study Results

Parent advisory panel members were actively involved in all plans to disseminate key findings to professional and parent/family partners. They reviewed abstracts before submission to professional conferences and provided feedback on manuscripts before submission for publication. Mrs Barnes co-presented a poster on stakeholder engagement in research at the PCORI annual conference (September 2019). During spring 2020, 2 parent advisory panel members representing 2 larger parent stakeholder groups (Casey's Circle and Hope for HIE) began to compile ideas for the dissemination of findings specifically to parent and community groups. Ideas include postings on parent support organization websites and social media

platforms, webinars, infographics, template slide decks, and video interviews. Work is ongoing to draft these products in parallel with manuscript preparation so that dissemination can occur rapidly once peer-reviewed papers are published. The parent advisory panel also contributed to the summary of the findings that was sent to all study participants. Each study investigator has been encouraged to include their parent partner in presentations, and slide templates and guidance for the parent advisory panel have been provided. Parent advisory panel members report that they also informally speak to other families of children with neonatal seizures or epilepsy about the importance of parent involvement in research to accelerate the development of new knowledge that will improve outcomes for children and their families.

Principles for Engagement

Reciprocal Relationships

One parent from each study site served on the parent advisory panel, which met monthly by teleconference throughout the study period. Monthly meeting agendas included updates on the project's progress, discussion of major decisions, review of results, and discussion of dissemination of findings. The principal investigators (PIs) and parent advisory panel established a pattern of discussion and partnership for decision-making. The parent advisory panel, in collaboration with Linda S. Franck, RN, PhD, and in consultation with the PIs, had both an overall study advisory role and a specific role in the development and analysis of aim 3. The parent advisory panel was instrumental in decision-making regarding the design, conduct, analysis, and dissemination of the results (Table 2).

Table 2. Timeline of Work Performed by the Parent Advisory Panel in Collaboration With Investigators

		Time, mo						
	Presubmission	1-6	7-12	13-18	19-24	15-30	31-36	37-48
Planning								
Recruit parents to the parent advisory panel	✓							
Initial and follow-up focus groups to discuss well-being domains and select validated instruments	✓	✓	✓	✓	✓	✓	✓	
Monthly teleconferences		✓	✓	✓	✓	✓	✓	✓
Document review								
Review manual of operations and case report forms		✓						
Creation of newsletters			✓	✓	✓	✓	✓	✓
Dissemination								
Review of data re: parent responses to open-ended questions					✓	✓	✓	✓
Presentation at society conferences							✓	✓
Updates to websites (eg, Hand to Hold)							✓	✓

Trust, Transparency, and Honesty

From its conception, this study included both clinicians and parent stakeholders. We worked in close collaboration with the parent advisory panel to create a proposal that served (1) the infants who are treated with medicine for seizures; (2) the clinicians who must make treatment decisions in the absence of scientific evidence; and (3) the parents of affected infants, who must nurture these children and live with the day-to-day impact of the seizures, their treatment, and their neurodevelopmental consequences.

> *There was no one who I had really met at the time who got what I was going through. I learned early on to ask all the questions to the doctors and not to think twice about reaching out if I had more. . . . Starting with this group where we each bring something different to the table helped me feel like I'm not alone and empowered me more to keep pushing and thinking outside the box. I have a sense of pride when I bring up that I'm the parent partner for* [our site] *and that our research is being published. Every time I see our ideas from the phone calls work out, it makes me feel like I have accomplished something that one day will help make another parent's life a little easier. I really am happy to be part of the team!*
>
> —Katie Grant, parent partner

As a fully integrated study team of parents, stakeholders, and researchers, we committed to continued trust, transparency, and honesty about the study design, implementation, and reporting of results. The physician investigators, parent partners, and stakeholders remained committed to sustained parent and stakeholder integration throughout the study's planning, implementation, analysis, and dissemination phases.

METHODS

Study Overview

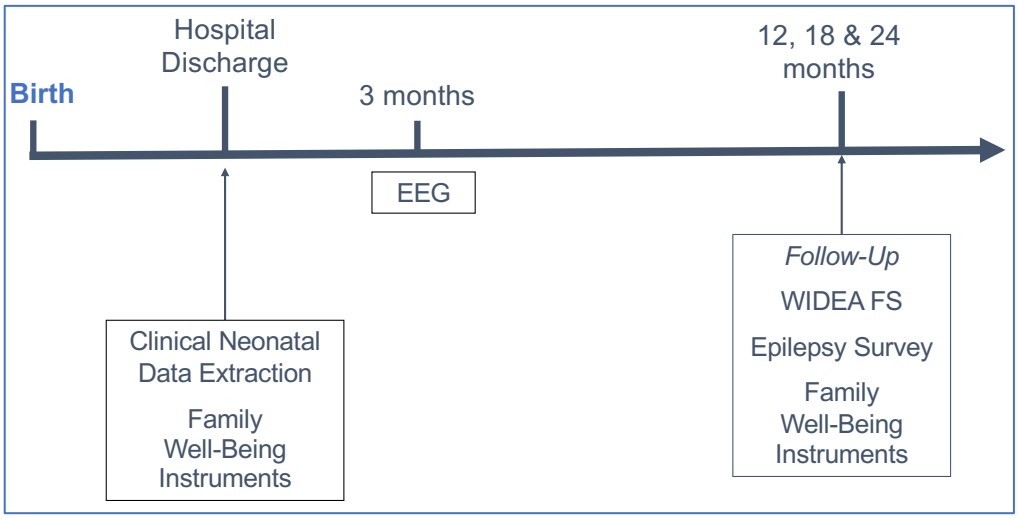
Our collaborative research team used the Neonatal Seizure Registry, a multicenter association of institutions across the United States, along with a parent advisory panel and parent advocacy groups to develop patient-centered questions and outcomes to examine whether the duration of treatment with ASMs (and particularly with phenobarbital) has an impact on neurodevelopmental and epilepsy outcomes, as well as parent well-being, after acute symptomatic neonatal seizures. *The long-term goal of this research is to improve neurodevelopmental outcomes following acute symptomatic seizures in newborns.*

The study was designed to take advantage of the heterogeneity of treatment duration for acute symptomatic seizures within the Neonatal Seizure Registry to determine the comparative effectiveness of 2 common approaches to ASM prescription for the treatment of acute symptomatic neonatal seizures: (1) ASM(s) discontinued before discharge from the neonatal seizure admission (short duration), and (2) ASM(s) maintained at the time of discharge from the neonatal seizure admission (prolonged duration).

Our central hypothesis was that the duration of ASM would have no effect on neurodevelopmental outcome (primary outcome) or the development of postneonatal epilepsy (secondary outcome) after acute symptomatic neonatal seizures (aim 1) but would be associated with NICU LOS (aim 2) and parent well-being (aim 3).

Infants with acute symptomatic neonatal seizures and their parents were recruited from Neonatal Seizure Registry sites either before hospital discharge (inpatient recruitment group) or after discharge but before age 24 months (outpatient recruitment group). Children were then assessed at ages corrected ages 12, 18, and 24 months for neurodevelopment and epilepsy outcomes. The 12-, 18-, and 24-month assessments were prospective; if a participant was recruited after age 12 or 18 months, those time points were omitted (all participants had a prospective 24-month assessment). Parent well-being was also assessed at each time point (Figure 1). Families were provided with $50 gift cards at each time point.

Figure 1. Study Overview



Abbreviations: EEG, electroencephalogram; WIDEA FS, Warner Initial Developmental Evaluation of Adaptive and Functional Skills.

Study Setting

The study sites were tertiary and quaternary children's hospitals at 9 medical centers across the United States. Study sites were selected based on the following:

- Ability to perform continuous, video-EEG as recommended by the ACNS[25]
- Neurophysiologist(s) with experience interpreting neonatal and pediatric EEG
- Technologists with experience in applying the neonatal EEG montage
- State-of-the-art neonatal neurology and pediatric epilepsy care

Participants

Target population:

- Neonates with seizures due to an acute symptomatic cause who were treated at a Neonatal Seizure Registry site

Inclusion criteria:

- Neonates aged <44 weeks postmenstrual age (PMA) at seizure onset

- Seizures with an acute symptomatic cause (including HIE, stroke, or cerebral hemorrhage)
- Parent(s) who were English or Spanish literate (with assistance of interpreter)
- For outpatient enrollment, participants aged <24 months at the time of enrollment

Exclusion criteria:

- Neonates at risk for adverse outcome *independent of* seizures and underlying brain injury (including but not limited to inborn errors of metabolism, fetal infection, brain malformation, or genetic syndrome)
- Neonates with transient cause for seizures (eg, mild hypoglycemia, hyponatremia, hypocalcemia)
- Newborns with neonatal-onset epilepsy syndromes
- Neonates who did not survive the initial hospital admission

Inpatient enrollment:

- **Enrollment.** A total of 150 participants were enrolled as inpatients from among eligible infants during their neonatal admission from July 2016 to March 2018.
- **Participant recruitment.** A study investigator or clinical research coordinator identified eligible newborns during the neonatal admission at each of the participating study sites via daily screening of inpatient admission and EEG lists. After approval from the treating medical team, a study investigator approached the parents/guardians of eligible patients during the NICU admission and, using a consent form approved by the local IRB, described the anticipated risks and benefits of the study.

Outpatient enrollment:

- **Enrollment.** A total of 155 participants were enrolled from among eligible infants evaluated as outpatients from July 2016 to March 2018.
- **Participant recruitment.** A study investigator or clinical research coordinator identified eligible infants who were previously enrolled in the Neonatal Seizure Registry or who fulfilled inclusion and exclusion criteria based on screening of inpatient and outpatient

logs (for the 2 sites that did not participate in the Neonatal Seizure Registry before PCORI funding). A study investigator or clinical research coordinator approached the parents/guardians of eligible patients during clinical follow-up or by telephone or mail to introduce the study. Using a consent form approved by the local IRB, the study investigator or clinical research coordinator described the anticipated risks and benefits of the study.

- **Reasons for study decline.** Parents who declined to participate were asked their reasons for nonparticipation. Sample reasons are presented in Table 3.

Table 3. Sample Reasons for Nonparticipation

Reason	No.
Unable to reach before 25 mo corrected age	48
Did not want to participate in research	28
Unable to reach before enrollment ended	20
Too much of a time commitment	12
Already been through so much/don't want to remember	8
"Researched out"/in too many other studies	1
Could not make a decision	1
Using faith-based care	1
Transferred care to nonstudy center	1
Not interested because of 3-mo EEG	1
Not stated	18

Abbreviation: EEG, electroencephalogram.

Comparators

The primary comparator for this comparative effectiveness study was duration of ASM for the treatment of acute symptomatic seizures.

The treatment approach as a dichotomous predictor (aims 1, 2, and 3) was determined by medical record review, as follows:

- ASMs discontinued before discharge from the neonatal seizure admission (short duration) *compared with*

- ASMs maintained at the time of discharge from the neonatal admission (prolonged duration)

These comparators were chosen to address the fundamental and unanswered question of how long to treat acute symptomatic neonatal seizures.

- **The selected comparators are relevant to clinicians.** The current management paradigm is typically to *maintain* ASMs for several months; however, some clinicians *discontinue* medication immediately after resolution of seizures (typically after 72-96 hours). The rationale for early discontinuation is based on preliminary evidence that suggests this practice is not harmful.[6,10] Furthermore, continued exposure to phenobarbital is sedating, which may prolong the time it takes for a newborn to establish oral feeding and may have deleterious long-term effects on the developing brain.[8,26,27]

- **The selected comparators are highly relevant to parents and stakeholders.** According to Mrs Barnes, mother of a child with seizures since birth and director of Casey's Circle, and Ms Kelley, a collaborative stakeholder partner at Hand to Hold, sedating ASMs have an impact on the whole family. A parent whose child had neonatal seizures commented: "The decision about continuing phenobarbital weighed heavily on [our family] . . . Was the medicine I was giving my child really for the best?" and "Every additional minute in the hospital . . . feels like an eternity. . . . The sooner you get home, the better." The 153 respondents to our online parent survey overwhelmingly indicated concerns regarding immediate adverse effects (especially sedation and its potential impact on LOS [aim 2]) and long-term outcomes (development and epilepsy [aim 1]) for their children who had been treated for neonatal seizures.[13] This was confirmed during focus group discussions with our parent advisory panel.

Study Outcomes

Primary Outcome: Functional Development

The primary outcome was functional development as assessed by the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS).[28,29] The WIDEA-FS is a simple, free, 1-page, 50-item, criterion-specified questionnaire designed to assess adaptive skills, including mobility, communication, social-cognitive, and self-care skills (see Appendix A). The WIDEA-FS is significantly associated with Bayley Scales of Infant and Toddler Development

III in all domains and has been shown to be a useful tool for following children at high risk for neurodevelopmental disability.[30] The WIDEA-FS was administered by research staff who were blinded to the child's medical history and treatment duration at 12, 18, and 24 months corrected age. At 24 months, the normal population mean score is 172, with an SD of 10. A child was considered to have functional impairment when the WIDEA-FS total score was >2 SDs below the mean for age.

We chose functional development as the primary outcome measure because our parent advisory panel, stakeholders, and survey respondents have all told us that neurodevelopment and milestones are what matter most to parents in the first year of life. One respondent wrote:

> *If the patient is taking medications, the parent will want to know about the risk and how those risks can impact milestones. . . . We are all consumed, almost to the point of obsessed, with milestones early on. Each one that we don't make is another heartbreak.*

Furthermore, parents value outcome measures that are simple and can be rapidly administered.

There is no widely accepted standard for the minimally clinically important difference for the WIDEA-FS. For other standardized neurodevelopmental evaluations, 1 SD is considered relevant,[31,32] whereas referral to developmental services requires a developmental delay of >33% in most states.[33] To ensure that the noninferiority analysis excluded a clinically relevant difference, we conservatively defined our noninferiority limit as 0.5 SD.

Secondary Outcomes

Epilepsy. Postneonatal epilepsy was defined per 2014 International League Against Epilepsy criteria[34]: (1) at least 2 unprovoked seizures occurring >24 h apart; (2) 1 unprovoked seizure and a probability of additional seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years; or (3) diagnosis of an epilepsy syndrome after 44 weeks PMA.

Diagnosis and timing of epilepsy was determined by a telephone survey to a parent or guardian when the child reached a corrected age of 12, 18, and 24 months. The survey comprises standardized questions to derive a modified Engel Classification, which is a validated way to describe the severity of epilepsy (see Appendix B).[35] The survey was corroborated by medical record review to extract detailed data regarding epilepsy syndromes and treatments. Final adjudication of the presence and timing of epilepsy was based on a review of the entire record by the study PIs.

Epilepsy is an important outcome for both clinicians and parents. A history of seizures in the newborn is a major risk factor for nonremittance of postneonatal epilepsy,[4] and many affected children have very difficult-to-treat epilepsy, such as infantile spasms.[36] *Parent survey respondents indicated major concerns about the risk of epilepsy*.[13]

Motor function. As an exploratory outcome, motor function was assessed at 24 months using a modified Gross Motor Function Classification System (GMFCS). During the telephone follow-up, the parent was asked to best describe the child's level of function as follows: GMFCS I, walks 10 steps independently with gait abnormalities (eg, wide-based gait, frequent falling, tiptoe walking); GMFCS II, does not walk independently but crawls, pulls to stand, and cruises; GMFCS III, does not crawl, pull to stand, or cruise but can sit independently; GMFCS IV, cannot sit independently but has head control; and GMFCS V, cannot control head [37] GMFCS has previously been used to simplify gross motor function assessment in large trials to objectively operationalize outcomes.[38,39] Functional motor disability was defined as GMFCS ≥II at age 24 months.

Hospital LOS. The duration of the first hospital admission for acute symptomatic neonatal seizure diagnosis and treatment was measured in days. This is an important outcome for parents, clinicians, and insurance providers.

Parent-Reported Outcomes

Parent well-being. A parent well-being assessment was conducted in conjunction with hospital discharge and again at the 12-, 18-, and 24-month evaluations. The instruments administered at each time point were as follows:

- The Hospital Anxiety Depression Scale (HADS) is a well-validated, 14-item measure of symptoms of anxiety (7 items) and depression (7 items), with each item rated on a 4-point scale. Total subscale scores of 0-7 on each subscale are considered normal. Scores of 8-10 suggest borderline anxiety (HADS anxiety subscale) or depressive (HADS depression subscale) symptoms, and scores of >10 are considered "abnormal (cases)." Scores in the borderline and abnormal ranges represent clinically important symptoms of anxiety or depression.[40,41]

- World Health Organization Quality of Life-BREF (WHOQOL-BREF) assesses 4 domains of health: physical, psychological, social relationships, and environment. It also includes 2 general questions on self-perceived QOL and general health.[42] It includes 24 items (rated 1-5) as follows: physical health (7 items), psychological health (6 items), social relationships (3 items), and environment (8 items). It also includes 2 general questions on self-perceived QOL and general health. The scores are transformed into a scale ranging from 0 to 100, with 0 indicating worst QOL and 100 indicating best QOL.

- The Impact on Family Scale (IOF) measures a parent's perception of the impact on the family of having an ill child.[43,44] The score represents a construct of personal, family, and social impact. The revised IOF is a 15-item measure of parental perception (each rated on a 1-4 scale) of the impact on the family of having an ill child. The overall score represents a single construct of personal, family, and social impact (15 items), with higher scores indicating a greater impact on the family. Additionally, 2 subscales, financial strain (4 items; higher scores indicate more financial strain) and coping (6 items; higher scores indicate worse coping), are measured separately but are not included in the overall score.

- The Impact of Events Scale–Revised (IES) is a validated 22-item self-report measure of posttraumatic stress symptoms (PTSS).[45] IES scores are reported either as total scores ranging from 0 to 88 or as mean scores ranging from 0 to 4, with higher scores indicating greater posttraumatic stress. A total score of ≥34 has been used to indicate ''elevated PTSS'' and is consistent with a probable diagnosis of PTSD.[46]

- The Posttraumatic Growth Inventory (PTGI) is a 21-item scale that measures the extent to which survivors of traumatic events perceive personal benefits related to their attempts to cope with trauma. It is a commonly used, validated measure of *resilience* that has been incorporated into studies of parents of sick neonates and children.[47-49] A higher total score indicates greater posttraumatic growth. There are 5 domains comprising the score: relating to others, new possibilities, personal strength, spiritual enhancement, and appreciation. The scores across the subscales are suggestive of which areas of self-development are predominant and which areas might have scope for self-improvement.[50]

- Open-ended, free-text questions to explore the specific impact of ASM on family well-being.

Our parent advisory panel helped select the parent well-being instruments, and as such, they are all very relevant to parent stakeholders. Instruments were chosen during focus groups co-led by a study co-investigator (Dr Franck) along with a parent advisory panel member (Dr Hill, who is both a parent of a child with neonatal seizures caused by ischemic stroke and a primary care pediatrician). The parent advisory panel discussed the most relevant domains of family well-being, reviewed the pertinent validated instruments (eg, measures of QOL, anxiety and depression, family coping, parent posttraumatic stress and posttraumatic growth, parenting confidence and competence, and family functioning) and then selected the most relevant and valid measures (see Appendix C). Questions specific to the impact of ASM on family well-being were developed together by the parent advisory panel and investigators (see Appendix C).

Covariates

Basic clinical and family demographics, as well as clinical variables and EEG features associated with ASM use, neurodevelopmental outcome, and epilepsy, were prespecified and defined as described below. All listed covariates were considered for inclusion in the propensity score.

- **Preterm birth.** Classified according to the WHO definitions (extremely preterm, <28 weeks; very preterm, 28 to <32 weeks; moderate to late preterm, 32 to <37 weeks; term ≥37 weeks).

- **Sex.** Defined as male or female.

- **Race.** American Indian/Alaska Native, Asian, Black/African American, White, Native Hawaiian/other Pacific Islander, more than 1 race, unknown/not reported, decline to answer, other.

- **Ethnicity.** Hispanic or Latino, not Hispanic or Latino, unknown/not reported, decline to answer.

- **Maternal education.** Some education (high school not complete), high school graduate, some college, college graduate, graduate study, unknown/unavailable, decline to answer.

- **Insurance type.** Public, private, unknown.

- **Mode of delivery.** Vaginal, operative vaginal (vacuum or forceps), scheduled cesarean section, emergent cesarean section, unknown.

- **Apgar scores.** At 1 and 5 minutes.

- **Patient location at the time of neonatal seizure evaluation.** NICU, pediatric intensive care unit, cardiac intensive care unit, other.

- **Complex clinical course.** Considered present for any of the following: preterm birth (<37 weeks gestational age at birth), congenital heart malformation, need for extracorporeal membrane oxygenation.

- **Seizure etiology.** Categorized as HIE, ischemic stroke, intracranial hemorrhage (ICH), other.

- **Hypothermia.** Treatment with therapeutic hypothermia for HIE.

- **Abnormal discharge neurologic examination.** Considered present if a child had any of the following findings on neurologic examination at the time of discharge: abnormality in consciousness, tone, or reflexes.

- **Worst EEG background in the first 24 hours at the study center.** Determined by clinical report and categorized as normal, mild/moderately abnormal, severely abnormal (burst suppression, depressed/undifferentiated, flat tracing), status epilepticus at onset of recording, cannot assess.

- **Seizure burden.** Determined based on number of seizures recorded at the study center during the neonatal seizure admission (period of acute symptomatic seizures) and categorized as none, few (<7), many (≥7), frequent recurrent seizures not fulfilling criteria for status epilepticus, and status epilepticus. Seizures were defined as sudden, abnormal EEG events with a repetitive and evolving pattern with amplitude ≥2μV and duration ≥10 seconds, with or without a clinical correlate.[51] Status epilepticus was defined as >30 minutes of seizures within any 1-hour epoch.[52]

- **Days of EEG seizures.** Calendar days on which EEG seizures were present.

- **Initial ASM used for seizure treatment.** Categorized as phenobarbital, fosphenytoin/phenytoin, levetiracetam, or no loading dose given.

- **Seizures refractory to initial loading dose of ASM.** Defined as seizures lasting >30 minutes after treatment with adequate dose of ASM.

- **Multiple medications.** Requiring ≥2 ASMs for neonatal seizure treatment.

- **Disposition from the study center neonatal seizure admission.** Home, transferred to another hospital for ongoing care, hospice, long-term-care facility.

- **Follow-up EEG at 3 months corrected age.** Children enrolled as inpatients were eligible for the follow-up EEG. This timing was selected to mirror the typical clinical practice of outpatient evaluation at age 3 months. These 1-hour EEGs were centrally reviewed by 2 clinical neurophysiologists for slowing and epileptiform discharges. Differences in scoring were resolved through consensus reviews.

  Overall result:

  - Abnormal with epileptiform abnormalities: yes, no.
  - Abnormal with hypsarrhythmia (chaotic, slow background with amplitude >200 μV and frequent multifocal spikes): yes, no.

Sample Size Calculations and Power

The study was powered for a noninferiority analysis. For the primary outcome of WIDEA-FS score (Aim 1a), we set a very conservative margin at 0.5 SD, or 7%, which is considered highly clinically relevant given that 2 SDs below the mean is required for referral to early intervention services. Our initial proposal was for 12-month follow-up based on a standard 3-year grant period. Using a 12-month WIDEA-FS mean score of 109 with an SD of

16.5, we calculated that 192 participants were required to be 80% sure that the lower limit of a 1-sided 95% CI (or 2-sided 90% CI) would be above the noninferiority limit of −7 points. Therefore, we proposed N = 300 newborns, which allowed us to take into account loss to follow-up (conservatively estimated at 15%) and propensity score adjustment analysis to address causal inference (as discussed below), which required that we inflate the sample size by 9%.[53] Once PCORI extended the contract to 4 years, we proposed adding 18- and 24-month follow-up evaluations. With 24-month WIDEA-FS score as the new primary outcome measure, the noninferiority limit changed to −12 points (7% of the average 24-month score of 172 ± 10 points). Under this assumption, we calculated that only 116 children were required for the study to have 80% power that the lower limit of a 2-sided 90% CI would be above the a priori noninferiority limit of −12 points (7%). We retained the planned enrollment of 300 children to have sufficient power to assess secondary and longer-term outcomes (ongoing).

We also provided power assessments for secondary outcomes:

- **For aim 1b (epilepsy).** With epilepsy incidence among infants who survive acute symptomatic neonatal seizures conservatively estimated at 20%,[36] we had sufficient participants to be 80% sure that the upper limit of a 1-sided 95% CI (or, equivalently, a 2-sided 90% CI) would exclude a difference of >13% between groups.[54]

- **For aim 2 (LOS).** Using the SD of the log-transformed LOS from our preliminary data of 0.71, our sample size gave a detectable difference (with 80% power) of 0.28 on the log scale, corresponding to a 32% difference in LOS. The median LOS is 14 days, so our sample was powered to detect a difference of >4.5 days, a duration that is clinically meaningful to families and important for health resource use considerations.

- **For aim 3 (parent well-being measures).** We planned on well-being measures being available for the N = 150 prospectively enrolled families at the time of hospital discharge. Using the sample sizes of $N_1 = 36$ (ASM discontinued) and $N_2 = 84$ (ASM maintained; accounting for expected dropout among the prospectively recruited N = 150) for families with both hospital discharge and 12-month outcome data, we had 80% power to detect a standardized difference of 0.56, which we determined was adequate power to detect moderate-sized differences in standardized survey scores between groups.[55]

Time Frame for the Study

Participants were enrolled and evaluated at 12, 18, and 24 months corrected age. These time points were chosen as clinically relevant and feasible within the time frame of the study. The 18- and 24-month time points mirror the primary outcome time point for the major hypothermia neuroprotection trials.[56-59] Children enrolled as outpatients were evaluated at the same time points; for children aged >12 months at enrollment, the parent-reported data were collected only for the remaining time points (eg, 18 months and/or 24 months).

Data Collection and Sources

Two data sources were used. First, the medical records were reviewed by a clinical research coordinator at each site and confirmed by a study investigator to determine clinical variables related to the seizures (etiology, burden, treatments) and neonatal admission. Then, the parent-reported outcomes for aims 1 and 3 (functional development as measured by the WIDEA-FS, epilepsy, and parent well-being) were determined by parent report at 12, 18, and 24 months corrected age. WIDEA-FS and epilepsy outcome assessments were conducted by telephone by a clinical research coordinator who was blinded to the neonatal clinical course and seizure treatment duration.

Epilepsy diagnosis and medication use were corroborated by concurrent medical record review at each time point. LOS (aim 2) was determined by medical record review.

Retention Strategies

The local clinical research coordinator made primary contact with the family during each 3-month follow-up window. Families were initially contacted by their stated preferred method (email, phone call, text). If that was not effective, the clinical research coordinator would reach out again using a backup contact method. If that did not work, the clinical research coordinator would reach out to the secondary contact provided by the family. This workflow was highly effective and enabled the team to maximize our study retention rate.

To further engage families and minimize loss to follow-up, the study team at each site sent each child a birthday card each year to let them know we were thinking of them, as well as 2 newsletters each year to report our progress (Appendix D).

Study Withdrawal

At the time of the 12-month study visit, 1 family decided to withdraw, as they were no longer interested in being part of the study. No other families withdrew.

Loss to Follow-up

A child was considered lost to follow-up if the parent did not complete *any* of the 12-, 18-, or 24-month evaluations for the primary outcome.

Analytical and Statistical Approaches

Primary and secondary outcomes were adjusted by propensity for ASM to be prescribed at the time of discharge from the neonatal seizure admission.

Propensity Score Adjustment

Propensity adjustment was used to improve causal inference and address confounding by indication by accounting for covariates that predicted treatment approach (ie, estimating the effect of discontinuing ASM before discharge compared with maintaining ASM upon discharge from the neonatal seizure admission).[60,61]

To develop the propensity score, we examined each of the neonatal covariates described above (including all collected demographic, clinical, and EEG factors) for its association with treatment approach (ie, discontinue or maintain ASM at the time of hospital discharge). The clinical neonatal variables with $P \leq .1$ were considered for inclusion in the propensity score. Propensity for ASM at discharge was then estimated using logistic regression. Backward stepwise logistic regression (to retain variables associated with treatment approach by $P \leq .1$) was used to build the propensity model for seizure treatment approach from the

remaining covariates. Backward logistic regression was chosen because it eliminates the chance of missing predictors due to negative confounding.[62]

The final model included seizure etiology (categorized as HIE, ischemic stroke, ICH, or other), gestational age (categorized by WHO gestational age criteria), therapeutic hypothermia treatment (present or absent), worst EEG background at the study center in the first 24 hours of recording (categorized as normal, mild/moderately abnormal, severely abnormal, status epilepticus at onset of recording, cannot assess), number of calendar days of EEG seizures (integer), and discharge neurologic examination (categorized as normal or abnormal accounting for abnormalities in consciousness, tone, or reflexes). All final model covariates were significant at adjusted $P \leq .1$, except etiology, which was included for face validity.

Validity of the Propensity Model

The propensity model area under the curve was 0.74 (indicating acceptable fit) and improved to 0.92 (indicating outstanding fit) when study site was added. The Hosmer-Lemeshow goodness-of-fit test result ($P = .76$) indicated excellent fit. These results confirm that we adequately accounted for possible confounders.[63] A test of nonlinearity of the single numeric predictor (days of seizure) was not statistically significant ($P = .48$); this supports the assumption of linearity. In addition, we considered and excluded misspecification of the propensity score and unmeasured confounders.

Study site was not included in the propensity adjustment for the primary analyses, as treatment variability by study site was the basis for comparison between otherwise-equivalent clinical scenarios. As a sensitivity analysis, site was used as an instrument in an instrumental variable analysis.

General Analysis

A chi-square or Fisher exact test was used to test for the difference between categorical variables. Analysis of variance or a Kruskal-Wallis test was used to assess the differences

between continuous variables, for normally distributed or not normally distributed, respectively.

Primary Outcome Analysis

For the WIDEA-FS score at corrected age 24 months (aim 1), we conducted a linear mixed-model analysis with random effects for intercepts and time and using restricted maximum likelihood fitting and Kenward-Roger degree-of-freedom adjustments. ASM at study center hospital discharge and propensity for maintenance of medication at discharge, categorized as quintiles, were included as the sole predictors in the regression models. We calculated 90% CIs with noninferiority established if the lower limit of the adjusted CI was above the noninferiority limit (−12 points at 24 months).

Secondary Outcome Analyses

Epilepsy (aim 1). We calculated odds ratios (ORs) with 95% CI for postneonatal epilepsy before age 24 months, plotted Kaplan-Meier curves, and calculated hazard ratios (HRs) with 95% CIs for time to epilepsy diagnosis by ASM at discharge, again adjusted for propensity for ASM at discharge and propensity, categorized as quintiles.

Motor disability (aim 1). We calculated ORs and 95% CI for GMFCS ≥II at age 24 months, and then adjusted for propensity for ASM at discharge and propensity, categorized as quintiles.

LOS (aim 2). Values were log transformed because of skew and to facilitate percentage change interpretations. Log-transformed values were regressed on propensity for ASM at discharge and propensity, categorized as quintiles.

Parent well-being measures (aim 3). Questionnaire results at 12, 18, and 24 months were evaluated by unadjusted linear regression and then adjusted for individual propensity variables and measures of socioeconomic status (race, ethnicity, maternal education, insurance type).

For parent well-being measures, we also conducted a multivariate analysis using validated measures. HADS anxiety, HADS depression, WHOQOL-BREF QOL, and IOF family impact were measured at discharge. At 12, 18, and 24 months, IES PTSS and PTGI posttraumatic growth were added to the measures completed at discharge. To make the outcomes more comparable in the multivariate analysis, we first converted them all to *z* scores and aligned the directionality (so that lower was better). Linear mixed-model analysis similar to that for the primary outcome was used, whereby random intercepts and slopes were used to accommodate the correlations across the 5 parent well-being outcome scales (HADS, IES, IOF, PTGI, and WHO). We included predictors of outcome type (to allow for different mean values across outcomes), ASM at discharge, data collection time point, and the interaction of ASM at discharge and outcome type (to assess similarities of the association across the 5 outcomes).

Prespecified Subgroup Analyses

We designated important subpopulations of interest for prespecified subgroup analyses: (1) levetiracetam treatment, (2) children born preterm (<37 weeks gestation), and (3) children with HIE as the seizure etiology. All of these subpopulations are highly relevant, as they are prevalent among infants with acute symptomatic neonatal seizures and represent issues important to clinicians, parents, and other stakeholders. The analytical methods for these subpopulations were identical to those used for the full cohort.

Sensitivity Analyses

We examined study site as an instrumental variable by fitting a random-effects instrumental variables model (to accommodate the longitudinal repeated measures) on the outcomes for aim 1 (WIDEA-FS score and epilepsy). We used bootstrap SEs to accommodate the use of a linear model for discharge on ASM within the instrumental variables' routine. Study site was associated with the predictor (ASM treatment duration) and was not associated with the outcome after adjusting for the predictor (WIDEA-FS score at 24 months, $P = .48$).

We also examined interaction by recruitment group (inpatient compared with outpatient) with treatment duration for the primary outcome (WIDEA-FS score at 24 months).

Qualitative Analyses

The parent responses to open-ended questions (aim 3) were analyzed using a directed content analysis approach.[64] A codebook was developed and then refined iteratively, in partnership with the parent advisory panel. NVivo V.12 (QSR International) qualitative data analysis software was used to organize and index codes. All responses were coded by 2 team members, and discrepancies were resolved through team consensus. After coding and reviewing all responses, the study team discussed key themes and subthemes characterizing the content, language, and context of parent responses. Themes and subthemes were discussed with the study team until consensus was reached. Parent advisory panel members aided in codebook development, data analysis, and interpretation.

Missing Data

The study database was audited on a regular basis for missing data. When missing data were found, site investigators were asked to review medical records to acquire data or document the reason for missing data. There were virtually no missing data for the following key elements: study site, sex, ethnicity, gestational age at birth, delivery mode, Apgar scores, hypothermia treatment, indication for EEG, seizure type, primary seizure etiology, disposition, and ASM prescribed at the time of discharge. To assess the potential impact of loss to follow-up, we compared those who were and were not lost to follow-up and performed multiple-imputation analysis.

Changes to the Study Protocol

There were no changes to the study protocol during the course of the study.

RESULTS

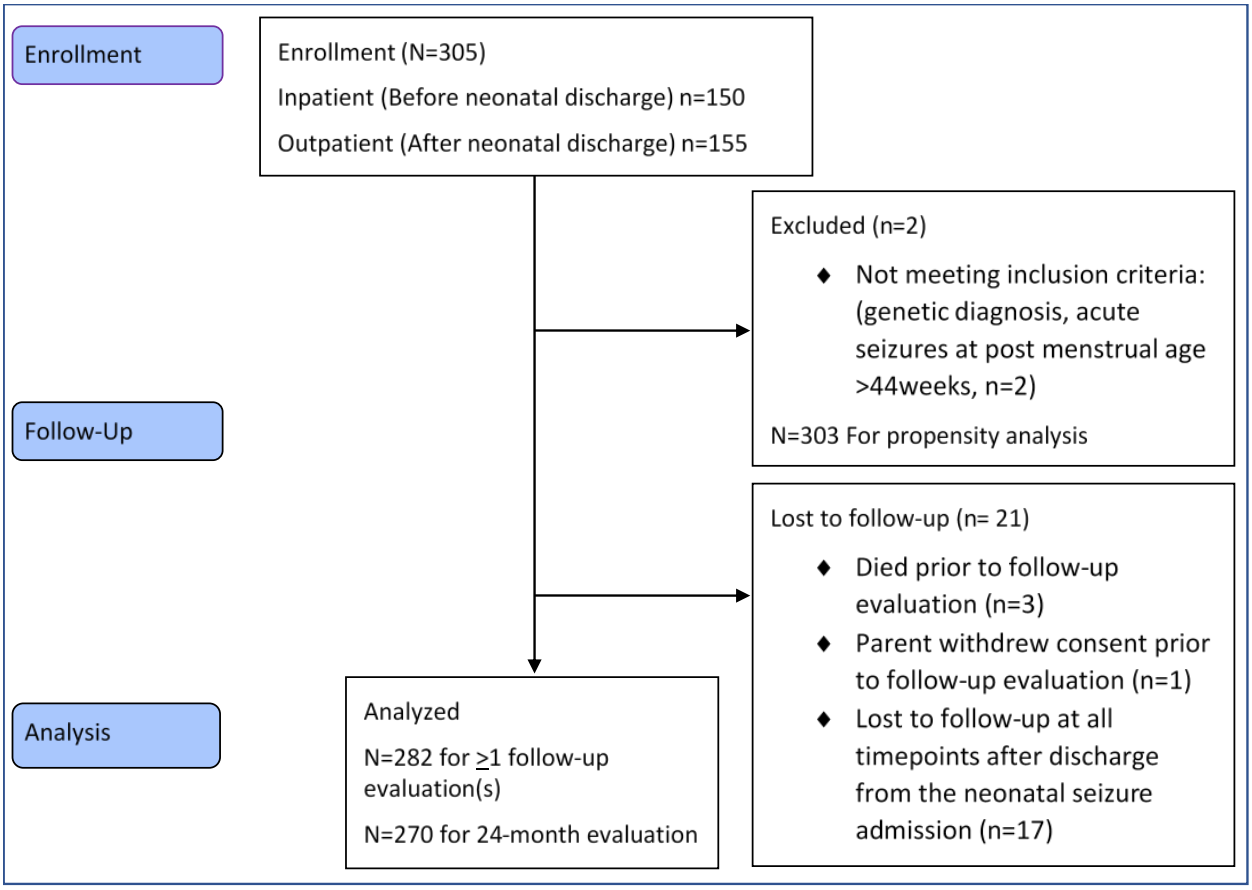
Aim 1

To determine whether ASM discontinued before discharge from the neonatal seizure admission (short duration) compared with ASM maintained at the time of discharge from the neonatal seizure admission (prolonged duration) affects (1) neurodevelopmental outcome and (2) incidence of epilepsy at ages 12, 18, and 24 months.

Study Participants

We enrolled 305 infants from July 2016 to March 2018, with 150 infants from the inpatient setting and 155 infants from the outpatient setting. Two infants were later excluded when exclusion criteria were discovered after enrollment (Figure 2). The remaining 303 infants with neonatal data were used for the analysis of the propensity for ASM maintenance. Twenty-one children did not have any outcome measures: 3 died before the first follow-up time point, 1 family withdrew, and 17 children did not have follow-up at any of the time points. Among the 299 infants eligible for follow-up, 282 (94%) had WIDEA-FS and epilepsy outcomes at 1 or more of the follow-up time points (Figure 2).

Figure 2. Flow Diagram for Aim 1



Study participant loss to follow-up. There were no significant associations between key clinical characteristics and loss to follow-up (Table 4).

Table 4. Characteristics of Children Lost to Follow-up Compared With Survivors With ≥1 Follow-up Evaluation

	Total (N = 299)	Lost to follow-up (n = 17 [6%])	Follow-up data available (n = 282 [94%])	*P* value
Clinical characteristics				
Term gestational age at birth (≥37 wk), No. (%)	251 (84)	13 (76)	238 (84)	.4
Male sex, No. (%)	168 (56)	12 (71)	156 (55)	.2
5-min Apgar score, median (IQR)	8 (5-9)	8 (6-9)	8 (5-9)	.8
NICU at the time of seizure evaluation, No. (%)	267 (89)	15 (88)	252 (89)	.9
Seizure and EEG characteristics				
Seizure etiology, No. (%)				.07
HIE	129 (43)	6 (35)	123 (44)	
Ischemic stroke	78 (26)	2 (12)	76 (27)	
ICH	54 (18)	7 (41)	47 (17)	
Other	38 (13)	2 (12)	36 (13)	
Worst EEG background (first 24 hours at study center), No. (%)				.5
Normal	25 (8)	2 (12)	23 (8)	
Mild/moderately abnormal	197 (66)	10 (59)	187 (66)	
Severely abnormal (burst suppression, depressed/undifferentiated, flat tracing)	51 (17)	5 (29)	46 (16)	
Status epilepticus at onset of recording	24 (8)	0	24 (9)	
Cannot assess	2 (<1)	0	2 (<1)	
High seizure burden (≥7 EEG seizures at the study center), No. (%)	166 (56)	10 (59)	156 (55)	.8
Days of EEG seizures, median (IQR)	1 (1-2)	1 (1-3)	2 (1-2)	.4
PB initial loading ASM, No. (%)	269 (90)	15 (88)	254 (90)	.6
Total inpatient PB exposure, median (IQR), mg/kg	63 (45-105)	48 (29-61)	76 (54-126)	<.0005

	Total (N = 299)	Lost to follow-up (n = 17 [6%])	Follow-up data available (n = 282 [94%])	*P* value
Incomplete response to initial loading dose of ASM, No. (%)	184 (62)	10 (58)	174 (62)	.8
Received ≥2 ASMs to treat acute symptomatic neonatal seizures, No. (%)	159 (53)	9 (52)	150 (53)	.98
Clinical course, No. (%)				
Complex medical diagnosis (congenital heart disease, ECMO, congenital diaphragmatic hernia)	34 (11)	1 (6)	33 (12)	.5
Therapeutic hypothermia	86 (29)	2 (12)	84 (30)	.1
Abnormal neurologic examination at discharge	92 (31)	5 (29)	87 (31)	.9

Abbreviations: ASM, antiseizure medication; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalogram; HIE, hypoxic-ischemic encephalopathy; ICH, intracranial hemorrhage; IQR, interquartile range; NICU, neonatal intensive care unit; PB, phenobarbital.

Neonatal Seizure Characteristics

Seizure etiology was HIE in 130 infants (43%), ischemic stroke in 79 (26%), ICH in 55 (18%), or other acute brain injury in 39 (13%, which included intracranial infection in 24, hypoglycemia in 4, and uncategorized in 11). Phenobarbital was prescribed as the first loading ASM for 90% of infants. More than half (53%) received ≥2 ASMs during the neonatal seizure admission.

ASM at Discharge

ASMs were maintained at the time of discharge from the neonatal seizure admission for 64% of infants (194/303). The range of ASM maintenance at discharge across study sites was 10% to 95% with $P < .0005$ despite significant overlap in key clinical variables (Table 5). Discharge medication regimen was as follows: phenobarbital monotherapy in 131 of 194 (68%) infants, levetiracetam monotherapy in 25 of 194 (13%), and polytherapy in 38 of 194 (20%). All children receiving polytherapy were prescribed phenobarbital as one of their ASMs. Thus, in total, 88% of infants who were maintained on ASMs received phenobarbital at the time of discharge from the neonatal seizure admission.

Table 5. Key Clinical Variables Across Neonatal Seizure Registry Sites

	Site 1 (N = 41)	**Site 2 (N = 55)**	**Site 3 (N = 25)**	**Site 4 (N = 28)**	**Site 5 (N = 47)**	**Site 6 (N = 55)**	**Site 7 (N = 20)**	**Site 8 (N = 17)**	**Site 9 (N = 15)**	***P* value**
Male sex, No. (%)	21 (51)	28 (51)	12 (48)	20 (71)	329(62)	31 (56)	10 (50)	11 (65)	8 (53)	.67
Gestational age at birth, wk, No. (%)										
<28	3 (7)	5 (9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	.28
28 to <32	0 (0)	1 (2)	0 (0)	1 (4)	2 (4)	1 (2)	1 (5)	0 (0)	0 (0)	
32 to <37	4 (10)	6 (11)	3 (12)	7 (25)	4 (8)	7 (13)	1 (5)	2 (12)	1 (7)	
≥37	34 (83)	43 (78)	22 (88)	20 (71)	41 (87)	47 (85)	18 (90)	15 (88)	13 (87)	
Public insurance coverage, No. (%)	16 (39)	31 (56)	8 (32)	16 (57)	25 (53)	10 (18)	11 (55)	7 (41)	4 (27)	.0005
Seizure etiology, No. (%)										
HIE	12 (29)	24 (44)	13 (52)	13 (46)	24 (51)	22 (40)	8 (40)	6 (33)	8 (53)	.83
Ischemic stroke	15 (37)	11 (20)	8 (32)	8 (29)	10 (21)	15 (27)	4 (20)	4 (24)	4 (27)	
ICH	8 (20)	12 (22)	1 (4)	4 (14)	5 (11)	12 (22)	6 (30)	5 (29)	2 (13)	
Other	6 (15)	8 (15)	3 (12)	3 (11)	8 (17)	6 (11)	2 (10)	2 (11)	1 (7)	
Hypothermia treatment, No. (%)	10 (24)	14 (25)	11 (44)	8 (29)	9 (19)	18 (33)	5 (25)	9 (53)	2 (13)	.12
Worst EEG background, No. (%)										
Normal	8 (20)	1 (2)	1 (4)	2 (7)	2 (4)	4 (7)	1 (5)	2 (12)	4 (27)	.002
Mild/moderately abnormal	26 (63)	28 (51)	23 (92)	18 (64)	33 (70)	39 (71)	12 (60)	13 (76)	7 (47)	
Severely abnormal	3 (7)	19 (35)	1 (4)	5 (18)	6 (13)	12 (22)	5 (25)	1 (6)	1 (7)	
Electrographic status epilepticus at the onset of recording	4 (10)	6 (11)	0 (0)	2 (7)	6 (13)	0 (0)	2 (10)	1 (6)	3 (20)	
Days with documented EEG seizure (at study center), median (IQR)	1 (1-2)	1 (1-2)	2 (1-2)	2 (1-3)	1 (1-2)	1 (0-2)	2 (1-2)	1 (1-2)	1 (0-2)	.07
Abnormal examination at discharge, No. (%)	11 (27)	24 (44)	8 (32)	5 (18)	8 (17)	29 (53)	3 (15)	3 (18)	5 (33)	.0008
Maintained on ASM, No. (%)	4 (10)	52 (95)	23 (92)	23 (82)	21 (45)	40 (73)	13 (65)	5 (29)	13 (87)	<.0001

Abbreviations: ASM, antiseizure medication; EEG, electroencephalogram; HIE, hypoxic-ischemic encephalopathy; ICH, intracranial hemorrhage; IQR, interquartile range.

Infants with high seizure burden, complex clinical course, and abnormal discharge neurologic examination had a higher propensity for ASM maintenance at the time of discharge from the neonatal seizure admission than did infants who did not have these clinical features (Table 6). The sex of the infant was not associated with treatment duration. Among neonates in our study whose ASMs were discontinued before discharge, the total *inpatient* exposure to phenobarbital was, on average, 28 mg/kg less than that for infants for whom the medication was maintained at the time of hospital discharge.

Table 6. Characteristics Considered for Propensity Adjustment for 303 Infants With Acute Symptomatic Neonatal Seizures and ASMs Discontinued or Maintained at the Time of Discharge From the Neonatal Seizure Admission

	Total (N = 303)	Discontinued ASM (n = 109 [36%])	Maintained ASM (n = 194 [64%])	*P* value
Clinical characteristics				
Gestational age at birth, wk, No. (%)[a]				.1
<28	9 (3)	5 (5)	4 (2)	
28 to <32	6 (2)	3 (3)	3 (2)	
32 to <37	35 (12)	7 (6)	28 (14)	
≥37	253 (84)	94 (86)	159 (82)	
Male sex, No. (%)	170 (56)	59 (54)	111 (57)	.5
5-min Apgar score, median (IQR)	8 (5-9)	6 (4-9)	8 (6-9)	.002
Infant location at time of seizure evaluation No. (%)				.07
NICU	269 (89)	103 (94)	166 (86)	
PICU	9 (3)	3 (3)	6 (3)	
CICU	24 (8)	3 (3)	21 (11)	
Other	1 (<1)	0	1 (1)	
Seizure and EEG characteristics				
Seizure etiology, No. (%)[a]				.04
HIE	130 (43)	58 (54)	72 (37)	
Ischemic stroke	79 (26)	22 (20)	57 (29)	
ICH	55 (18)	17 (16)	38 (20)	
Other	39 (13)	12 (11)	27 (14)	
Worst EEG background (first 24 hours at study center), No. (%)[a]				.06
Normal	25 (8)	14 (13)	11 (6)	
Mild/moderately abnormal	199 (66)	75 (69)	124 (64)	
Severely abnormal (burst suppression, depressed/undifferentiated, flat tracing)	53 (17)	14 (13)	39 (20)	
Status epilepticus at onset of recording	24 (8)	6 (6)	18 (9)	
Cannot assess	2 (<1)	0	2 (1)	
EEG seizure frequency (at the study center), No. (%)				.02
None	52 (17)	26 (24)	26 (13)	
Few (<7)	83 (27)	35 (32)	48 (25)	
Many isolated (≥7)	58 (19)	20 (18)	38 (19)	
Frequent recurrent	64 (21)	15 (14)	49 (25)	
Status epilepticus	45 (15)	13 (12)	32 (16)	
Documentation inadequate	1 (<1)	0	1 (1)	

	Total (N = 303)	Discontinued ASM (n = 109 [36%])	Maintained ASM (n = 194 [64%])	*P* value
Days of EEG seizures, median (IQR)[a]	1 (1-2)	1 (1-2)	2 (1-2)	.0008
Initial loading ASM, No. (%) PB Levetiracetam Fosphenytoin No loading dose	 273 (90) 17 (6) 3 (1) 10 (3)	 96 (88) 3 (3) 2 (2) 8 (7)	 177 (91) 14 (7) 1 (1) 2 (1)	.007
Incomplete response to initial loading dose of ASM, No. (%)	186 (62)	58 (54)	128 (66)	.06
Received ≥2 ASMs to treat acute symptomatic neonatal seizures, No. (%)	160 (53)	49 (45)	111 (57)	.04
Total inpatient PB exposure, median (IQR), mg/kg	63 (45-105)	48 (29-61)	76 (54-126)	<.0005
Clinical course, No. (%)				
Complex medical diagnosis (congenital heart disease, ECMO, congenital diaphragmatic hernia)	36 (12)	8 (7)	28 (14)	.07
Therapeutic hypothermia[a]	86 (28)	44 (40)	43 (22)	.001
Abnormal neurologic examination at discharge[a]	94 (31)	20 (18)	74 (38)	<.0005

Abbreviations: ASM, antiseizure medication; CICU, cardiac intensive care unit; EEG, electroencephalogram; ECMO, extracorporeal membrane oxygenation; HIE, hypoxic-ischemic encephalopathy; ICH, intracranial hemorrhage; IQR, interquartile range; NICU, neonatal intensive care unit; PB, phenobarbital; PICU, pediatric intensive care unit.
[a]Included in the final propensity model.

There were no missing data in the variables used to construct the propensity score. There was good overlap of participant characteristics between treatment duration groups within the quintiles of the propensity score (Table 7, Figure 3).

Table 7. Balance of Participant Characteristics Between Treatment Duration Groups Within Quintiles of the Propensity Score for All Variables Included in the Propensity Score

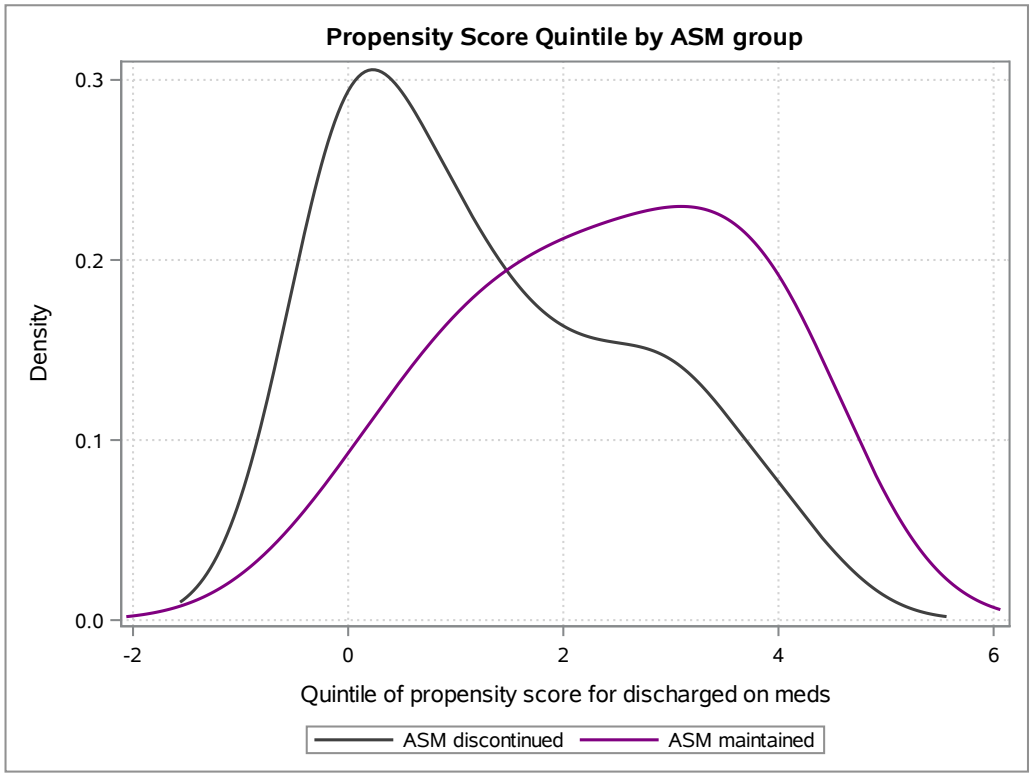
	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	ASM discontinued (n = 43)	ASM maintained (n = 17)	ASM discontinued (n = 25)	ASM maintained (n = 37)	ASM discontinued (n = 16)	ASM maintained (n = 42)	ASM discontinued (n = 18)	ASM maintained (n = 44)	ASM discontinued (n = 8)	ASM maintained (n = 53)
Clinical characteristics										
Gestational age at birth,[a] wk, No. (%)										
<28	4 (9)	2 (12)	1 (4)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
28 to <32	3 (7)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
32 to <37	1(2)	1 (6)	1 (4)	3 (8)	1 (6)	0 (0)	1 (6)	7 (16)	3 (38)	17 (32)
≥37	35 (81)	14 (82)	23 (92)	33 (89)	15 (94)	41 (98)	17 (94)	35 (80)	5 (62)	36 (68)
Male sex, No. (%)	19 (44)	8 (47)	14 (56)	21 (57)	12 (75)	23 (55)	9 (50)	30 (68)	5 (62)	29 (55)
5-min Apgar score, median (IQR)	5 (3-6)	5 (3-6)	8 (5-9)	7 (3-9)	9 (7-9)	9 (7-9)	6 (5-9)	9 (8-9)	7 (5-9)	8 (6-9)
Seizure and EEG characteristics										
Seizure etiology,[a] No. (%)										
HIE	30 (70)	14 (82)	13 (52)	22 (59)	4 (25)	10 (24)	7 (39)	11 (25)	4 (50)	15 (28)
Ischemic stroke	4 (9)	1 (6)	3 (12)	3 (8)	6 (38)	22 (52)	9 (50)	15 (34)	1 (12)	16 (30)
ICH	4 (9)	2 (12)	4 (16)	5 (14)	6 (38)	6 (14)	2 (11)	14 (32)	1 (12)	11 (21)
Other	5 (12)	0 (0)	5 (20)	7 (19)	0 (0)	4 (10)	0 (0)	4 (9)	2 (25)	11 (21)

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	ASM discontinued (n = 43)	**ASM maintained (n = 17)**	**ASM discontinued (n = 25)**	**ASM maintained (n = 37)**	**ASM discontinued (n = 16)**	**ASM maintained (n = 42)**	**ASM discontinued (n = 18)**	**ASM maintained (n = 44)**	**ASM discontinued (n = 8)**	**ASM maintained (n = 53)**
Worst EEG background (first 24 hours at study center), No. (%)										
Normal	11 (26)	2 (12)	3 (12)	4 (11)	0 (0)	3 (7)	0 (0)	1 (2)	0 (0)	1 (2)
Mild/moderately abnormal	29 (67)	11 (65)	20 (80)	26 (70)	14 (89)	31 (74)	10 (56)	29 (66)	3 (38)	27 (51)
Severely abnormal	2 (5)	3 (18)	2 (8)	6 (16)	1 (6)	5 (12)	6 (33)	8 (18)	3 (38)	16 (30)
Status epilepticus	1 (2)	1 (6)	0 (0)	1 (3)	1 (6)	3 (7)	2 (11)	6 (14)	2 (25)	7 (13)
Cannot assess	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4)
EEG seizure frequency (at the study center), No. (%)										
None	16 (37)	3 (18)	6 (24)	4 (11)	3 (19)	12 (29)	0 (0)	3 (7)	1 (12)	4 (8)
Few (<7)	17 (40)	7 (41)	9 (36)	16 (43)	2 (12)	11 (26)	5 (28)	8 (18)	2 (25)	6(11)
Many isolated (≥7)	8 (19)	5 (29)	6 (24)	7 (19)	4 (25)	10 (24)	3 (17)	6 (14)	0 (0)	9 (17)
Frequent recurrent	0 (0)	0 (0)	3 (12)	8 (22)	5 (31)	5 (12)	6 (33)	19 (43)	1 (12)	17 (32)
Status epilepticus	2 (5)	2 (12)	1 (4)	1 (3)	2 (12)	4 (10)	4 (22)	8 (18)	4 (50)	17 (32)
Documentation inadequate	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	ASM discontinued (n = 43)	**ASM maintained (n = 17)**	**ASM discontinued (n = 25)**	**ASM maintained (n = 37)**	**ASM discontinued (n = 16)**	**ASM maintained (n = 42)**	**ASM discontinued (n = 18)**	**ASM maintained (n = 44)**	**ASM discontinued (n = 8)**	**ASM maintained (n = 53)**
Days of EEG seizures, median (IQR)	1 (0-1)	1 (1-2)	1 (1-1)	1 (1-2)	1 (1-2)	1 (0-2)	2 (2-2)	2 (1-3)	1 (1-2)	2 (1-3)
Incomplete response to initial loading dose of ASM, No. (%)	14 (33)	6 (35)	13 (52)	22 (59)	12 (75)	26 (62)	14 (78)	33 (75)	6 (75)	41 (77)
Clinical course										
Therapeutic hypothermia, No. (%)	31 (72)	14 (82)	3 (12)	13 (35)	3 (19)	6 (14)	8 (44)	5 (11)	0 (0)	4 (7)
Abnormal neurologic examination at discharge, No. (%)	2 (5)	0 (0)	2 (8)	6 (16)	3 (19)	12 (29)	7 (38)	13 (30)	6 (75)	44 (83)

Abbreviations: ASM, antiseizure medication; EEG, electroencephalogram; HIE, hypoxic-ischemic encephalopathy; ICH, intracranial hemorrhage; IQR, interquartile range.

Figure 3. Density Plots Show Good Overlap of Propensity Scores Between Infants Whose ASMs Were Maintained vs Discontinued at the Time of Hospital Discharge



Abbreviation: ASM, antiseizure medication.

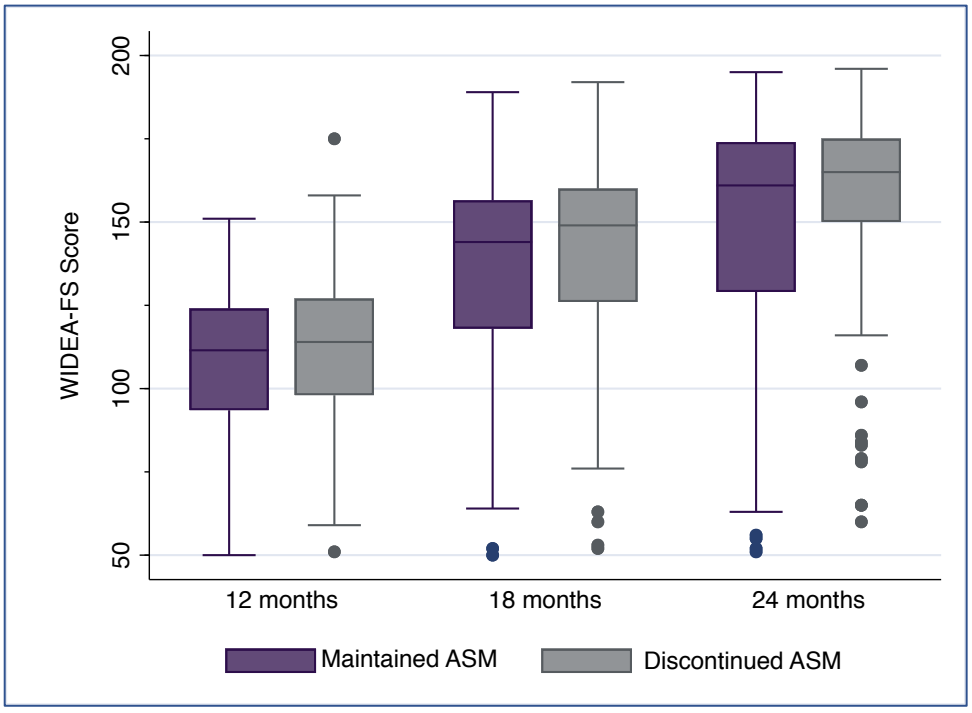
Among infants whose ASMs were discontinued before discharge from the neonatal seizure admission, the duration of therapy was a median of 6 *days* (interquartile range [IQR], 3-11 days), whereas the duration of therapy was a median of 4 *months* (IQR, 3-8 months; $P <$ .0001) among those whose ASMs were maintained at the time of discharge from the neonatal seizure admission.

Compared with the full cohort, for children with HIE as the neonatal seizure etiology (and excluding infants with congenital heart malformations, n = 46), the results for the duration of ASM were similar (ASM duration, 6 *days* [IQR, 3-9 days] when discontinued before discharge from the neonatal seizure admission compared with 4 *months* [IQR, 3-5 months] when maintained at the time of discharge from the neonatal seizure admission, $P <$ .0001).

Primary Outcome (Functional Neurodevelopment)

Unadjusted analyses. The median 24-month WIDEA-FS score was 164 (IQR, 136-175). The total WIDEA-FS score at 24 months was >2 SD below the normal population mean for 93 children (34%). Unadjusted total WIDEA-FS scores were 4 points (2%) higher for children whose ASM was discontinued before discharge from the neonatal seizure admission than for those maintained on ASM at the time of discharge from the neonatal seizure admission (median, 165 [IQR 150-175] vs median, 161 [IQR, 129-174], respectively; *P* =.09; Figure 4, Table 8). The percentages of infants with impaired functional development at 24 months were similar between the 2 ASM treatment groups (28% for children whose ASM was discontinued before discharge compared with 37% for those maintained on ASM at the time of discharge; OR, 0.6; 95% CI, 0.4-1.1; *P* = .11).

Figure 4. Unadjusted (Raw) WIDEA-FS Scores Among 282 Infants With Acute Symptomatic Neonatal Seizures Whose ASMs Were Discontinued vs Maintained at the Time of Discharge[a,b]



Abbreviations: ASM, antiseizure medication; WIDEA-FS, Warner Initial Developmental Evaluation of Adaptive and Functional Skills.

[a]WIDEA-FS scores in typically developing children are 109 ± 17 at 12 months, 152 ± 16 at 18 months, and 172 ± 10 at 24 months.

[b]Top of the box: 75th percentile; bottom of the box: 25th percentile; line in the box: median; whiskers: 1.5 times the IQR. Dots are extreme values.

Table 8. Unadjusted WIDEA-FS Domain Scores by ASM Treatment Duration Group

	Not discharged on ASM, mean (SD)	Discharged on ASM, mean (SD)	All participants, mean (SD)	*P* value for test of difference between ASM groups
12 mo (n = 189 [72/117])				
Self-care: feeding score	17.7 (4.0)	17.5 (4.3)	17.6 (4.2)	.67
Self-care: dressing score	9.7 (2.3)	9.4 (2.1)	9.6 (2.2)	.36
Self-care: diaper awareness score	5.8 (1.9)	5.8 (2.0)	5.8 (2.0)	.90
Mobility score	23.5 (6.3)	22.3 (6.9)	22.8 (6.7)	.25
Communication score	25.9 (7.5)	25.3 (6.3)	25.5 (6.8)	.55
Social cognition score	27.8 (7.1)	26.9 (6.8)	27.2 (6.9)	.35
18 mo (n = 222 [85/137])				
Self-care: feeding score	20.7 (5.0)	20.1 (4.9)	20.3 (4.9)	.35
Self-care: dressing score	12.3 (3.0)	11.5 (3.2)	11.8 (3.1)	.06
Self-care: diaper awareness score	6.6 (2.6)	6.6 (2.5)	6.6 (2.5)	.84
Mobility score	31.0 (7.1)	29.2 (8.1)	29.9 (7.8)	.11
Communication score	36.8 (9.8)	35.3 (9.9)	35.9 (9.8)	.26
Social cognition score	34.0 (7.3)	32.6 (7.6)	33.1 (7.5)	.19
24 mo (n = 272 [102/170])				
Self-care: feeding score	23.1 (5.3)	22.0 (5.9)	22.4 (5.7)	.12
Self-care: dressing score	14.6 (4.0)	13.6 (4.1)	14.0 (4.1)	.04
Self-care: diaper awareness score	7.8 (7.8)	7.8 (2.9)	7.8 (2.8)	.92
Mobility score	32.7 (6.5)	31.1 (8.2)	31.7 (7.6)	.11
Communication score	43.1 (43.1)	40.4 (11.4)	41.4 (10.9)	.05
Social cognition score	35.5 (7.2)	34.3 (7.8)	34.8 (7.6)	.18

Abbreviations: ASM, antiseizure medication; WIDEA-FS, Warner Initial Developmental Evaluation of Adaptive and Functional Skills.

Propensity-adjusted analyses. After propensity adjustment, the difference in WIDEA-FS scores at age 24 months was 4 points (2%) *higher* among infants whose ASM was discontinued before discharge from the neonatal seizure admission than in those maintained on ASM at the time of discharge from the neonatal seizure admission (90% CI, −3 to 11, *P* = .40). This result met our a priori noninferiority limit given that the lower bound of the CI (−3 points) was well above the noninferiority limit of −12 points (Table 9). Similarly, the estimated propensity-adjusted total WIDEA-FS score was within the noninferiority limit at the 12- and 18-month time points (Table 9). The results did not change after multiple-imputation analysis.

Sensitivity analyses. Using site as an instrumental variable and fitting a model comparable to the propensity-adjusted mixed model yielded virtually identical results: the instrumental variables analysis gave an estimated WIDEA-FS score that was 3 points higher (90% CI, 0-7) among those whose ASM was discontinued before discharge from the neonatal seizure admission than that in those maintained on ASM at the time of discharge from the neonatal seizure admission.

None of the outcomes exhibited interactions of the primary predictor (ASM discontinued compared with maintained) with recruitment group (recruitment as an inpatient compared with recruitment as an outpatient). After including inpatient compared with outpatient recruitment as an interaction term, the propensity-adjusted difference in WIDEA-FS scores at age 24 months was 9 points higher among infants whose ASM was discontinued before discharge from the neonatal seizure admission than for those maintained on ASM at the time of discharge from the neonatal seizure admission (90% CI, −1 to 19, *P* = .14).

Table 9. Unadjusted and Propensity-Adjusted Outcomes for 282 Neonates With Acute Symptomatic Seizures and Outcome at ≥1 Time Points[a]

	Discontinued ASM (n = 106)	Maintained ASM (n = 176)	Unadjusted (95% CI)	Unadjusted *P* value	Adjusted (90% or 95% CI)[b]	Adjusted *P* value
WIDEA-FS 12-mo score[c]	114 (98-127)	112 (94-124)	Difference = +5 (95% CI, −1 to 11)	.13	Difference = +1 (90% CI, −4 to 7)	.70
WIDEA-FS 18-mo score[d]	149 (126-160)	144 (118-157)	Difference = +7 (95% CI, 0 to 14)	.04	Difference = +4 (90% CI, −2 to 10)	.31
WIDEA-FS 24-mo score[e]	165 (150-175)	161 (129-174)	Difference = +7 (95% CI, −1 to 15)	.09	Difference = +4 (90% CI, −3 to 11)	.40
Postneonatal epilepsy	12 (11%)	25 (14%)	OR, 0.8 (95% CI, 0.4-1.6)	.49	OR, 1.5 (95% CI, 0.7-3.4)	.32
Motor disability (GMFCS ≥II)	13 (13%)	32 (19%)	OR, 0.6 (95% CI, 0.3-1.3)	.18	OR, 0.9 (95% CI, 0.4-1.9)	.71

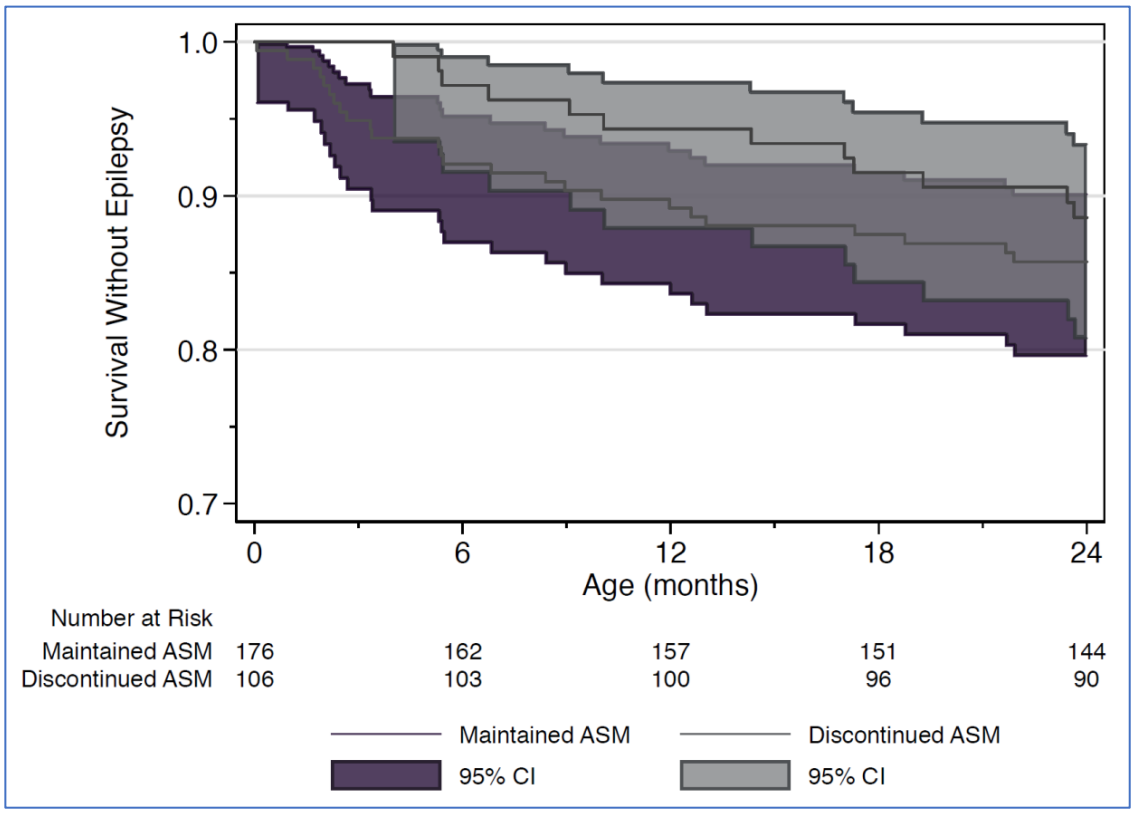
Abbreviations: ASM, antiseizure medication; GMFCS, Gross Motor Function Classification System; IQR, interquartile range; OR, odds ratio; WIDEA-FS, Warner Initial Developmental Evaluation of Adaptive and Functional Skills.
[a]The primary analysis (WIDEA-FS score at 24 months) was powered for a noninferiority limit for the difference of −12 points. Data are presented as No. (%) or median (IQR).
[b]95% CI was used for 2-sided hypotheses and 90% CI for 1-sided hypotheses (noninferiority testing).
[c]n = 187 at 12 months.
[d]n = 220 at 18 months.
[e]n = 270 at 24 months.

Secondary Outcomes

Epilepsy.

Unadjusted analyses. Thirty-seven children (13%) developed postneonatal epilepsy (recurrent unprovoked seizures) after resolution of acute symptomatic neonatal seizures and before age 24 months. Five percent (13/282) had infantile spasms. Epilepsy onset occurred at a median age of 7 months (IQR, 3-14 months). The risk of epilepsy did not differ by ASM treatment duration group (11% for infants whose ASM was discontinued before discharge from the neonatal seizure admission compared with 14% for those maintained on ASM at the time of discharge from the neonatal seizure admission; estimated risk difference of 3%; 90% CI, −10% to 4%; Table 9). There was no significant difference in the timing of epilepsy onset between the groups (HR, 0.8; 95% CI, 0.4-1.5; *P* = .42; Figure 5).

Figure 5. Unadjusted Epilepsy-Free Survival Among 282 Infants With Acute Symptomatic Neonatal Seizures Whose ASMs Were Discontinued vs Maintained at the Time of Discharge[a]



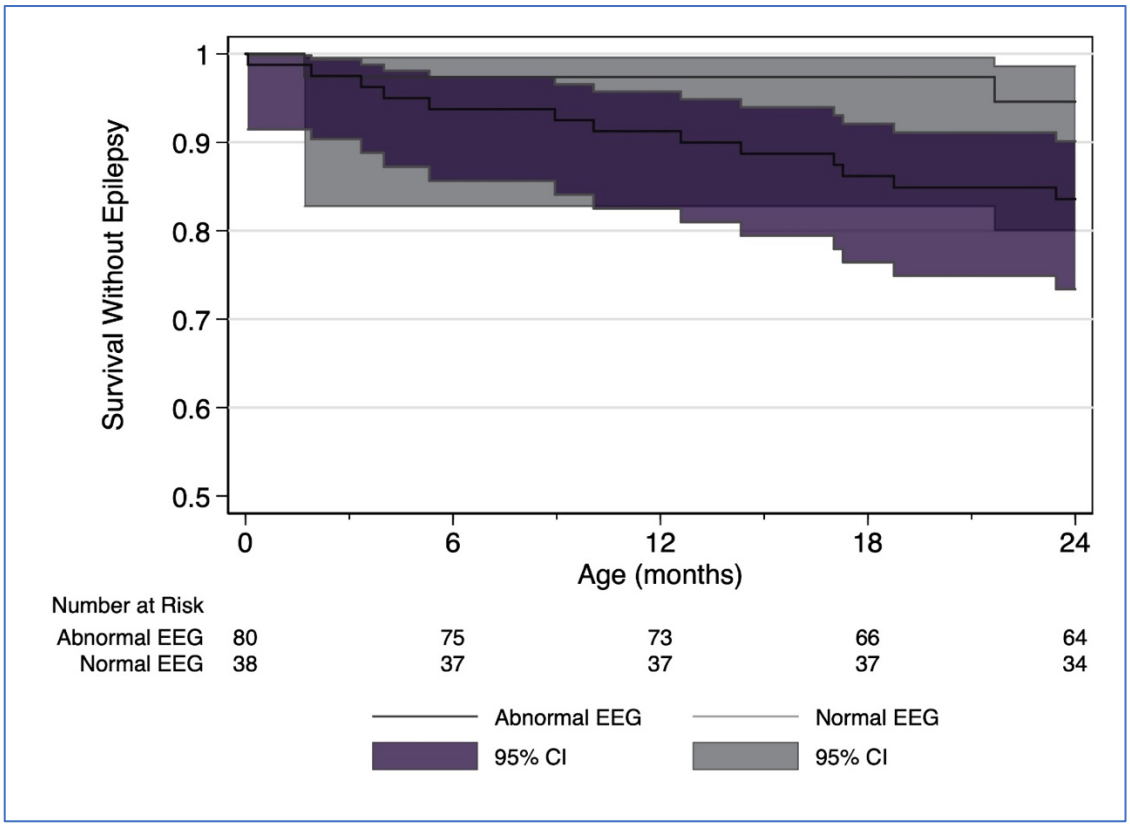
Abbreviation: ASM, antiseizure medication.

[a]HR, 0.8; 95% CI, 0.4-1.5; *P* = .42. Overlapping CIs are indicated by darker gray.

Eleven children had epilepsy onset before 4 months, and among these, 4 of 11 (36%) had infantile spasms. All of these 11 children were maintained on ASM at the time of discharge from the neonatal seizure admission. Epilepsy types were focal epilepsy (20/37 [54%]), mixed epilepsy (both focal and generalized features; 7/37 [19%]), and uncertain epilepsy type (10/37 [27%]). Infantile spasms developed in 13 of 37 (35%) children. At last follow-up, seizure severity (modified Engel classification) was as follows: 20 of 37 (54%) children with epilepsy had been seizure free for ≥6 months, 12 of 37 (32%) had <1 seizure per month, 1 of 37 (3%) had 1-4 seizures per month, and 4 of 37 (11%) had daily seizures. Twelve (32%) had treatment-resistant epilepsy (>2 ASMs prescribed after NICU discharge).

Three-month follow-up EEG. Among 122 infants with 3-month follow-up EEG, 5 already had hypsarrhythmia. Excluding these 5, while infants with abnormal 3-month EEG developed epilepsy somewhat sooner than did those with a normal EEG (HR, 3.3; 95% CI, 0.7-14.5; *P* = .11; Figure 6), the 3-month EEG results were not significantly associated with epilepsy onset by 24 months of age (Table 10).

Figure 6. Epilepsy-Free Survival With 95% CIs Among Children With Acute Symptomatic Neonatal Seizures and Abnormal and Normal 3-Month EEG[a]



Abbreviation: EEG, electroencephalogram.
[a]Overlapping CIs are indicated by darker gray.

Table 10. Association of Epilepsy Diagnosis by 24 Months With 3-Month EEG Characteristics Among 118 Infants With Acute Symptomatic Neonatal Seizures

3-mo EEG characteristics for infants without hypsarrhythmia[a]	Total (N = 118)	Epilepsy (n = 15)	No epilepsy (n = 103)	*P* value
Normal EEG, No. (%)	38 (32)	2 (15)	36 (35)	.06[b]
Abnormal EEG, No. (%)				
Abnormal without epileptiform discharges	50 (42)	6 (40)	44 (43)	
Focal epileptiform discharges	19 (16)	5 (34)	15 (15)	.3[c]
Multifocal epileptiform discharges	10 (9)	2 (13)	8 (8)	

Abbreviation: EEG, electroencephalogram.
[a]Follow-up EEG was available for 122 infants. Five had hypsarrhythmia and are excluded from this table.
[b]Normal compared with abnormal EEG.
[c]Multilevel EEG classification.

Propensity-adjusted analysis. After adjusting for propensity to receive ASMs at discharge, we found no difference in the risk of epilepsy (adjusted OR, 1.5; 95% CI, 0.7-3.4; *P* = .32; Table 9) or age of epilepsy onset (adjusted HR, 1.4; 95% CI, 0.7-2.9; *P* = .37) for infants whose ASM was discontinued before discharge from the neonatal seizure admission compared with those whose ASM was maintained at the time of discharge from the neonatal seizure admission.

Motor function.

Unadjusted analysis. Motor function outcomes were as follows: normal function in 194 children (71%), GMFCS I in 35 (13%), GMFCS II in 17 (6%), GMFCS III in 7 (3%), GMFCS IV in 12 (4%), and GMFCS V in 9 (3%). The overall risk for motor disability (defined as GMFCS ≥II) was not different among children who had ASMs discontinued (13/106 [13%]), compared with those whose ASMs were maintained (32/176 [19%]), at the time of discharge from the neonatal seizure admission (OR, 0.6; 95% CI, 0.3-1.3; *P* = .18; Table 9).

Propensity-adjusted analysis. After adjusting for propensity to receive ASMs at discharge, we found no difference in the risk for motor disability for infants whose ASMs were maintained, compared with discontinued, upon hospital discharge (adjusted OR, 0.9; 95% CI, 0.4-1.9; *P* = .71; Table 9).

Prespecified subgroup analyses.

Prematurity. Among the 50 infants born at <37 weeks gestational age, the propensity-adjusted estimated WIDEA-FS score difference was 14 points higher for children whose ASMs were discontinued before hospital discharge than for those whose ASMs were maintained upon discharge from the neonatal seizure admission (90% CI, −11 to 39; *P* = .34).

HIE. Among the 130 infants with HIE as the neonatal seizure etiology, the propensity-adjusted estimated WIDEA-FS score difference was 10 points higher among children whose ASMs were discontinued before discharge from the neonatal seizure admission than for those

who were maintained on ASMs at the time of discharge from the neonatal seizure admission (90% CI, 0-20 points; *P* = .09).

Levetiracetam monotherapy was used in only 12 participants; thus, it was not possible to perform a meaningful analysis of this subpopulation.

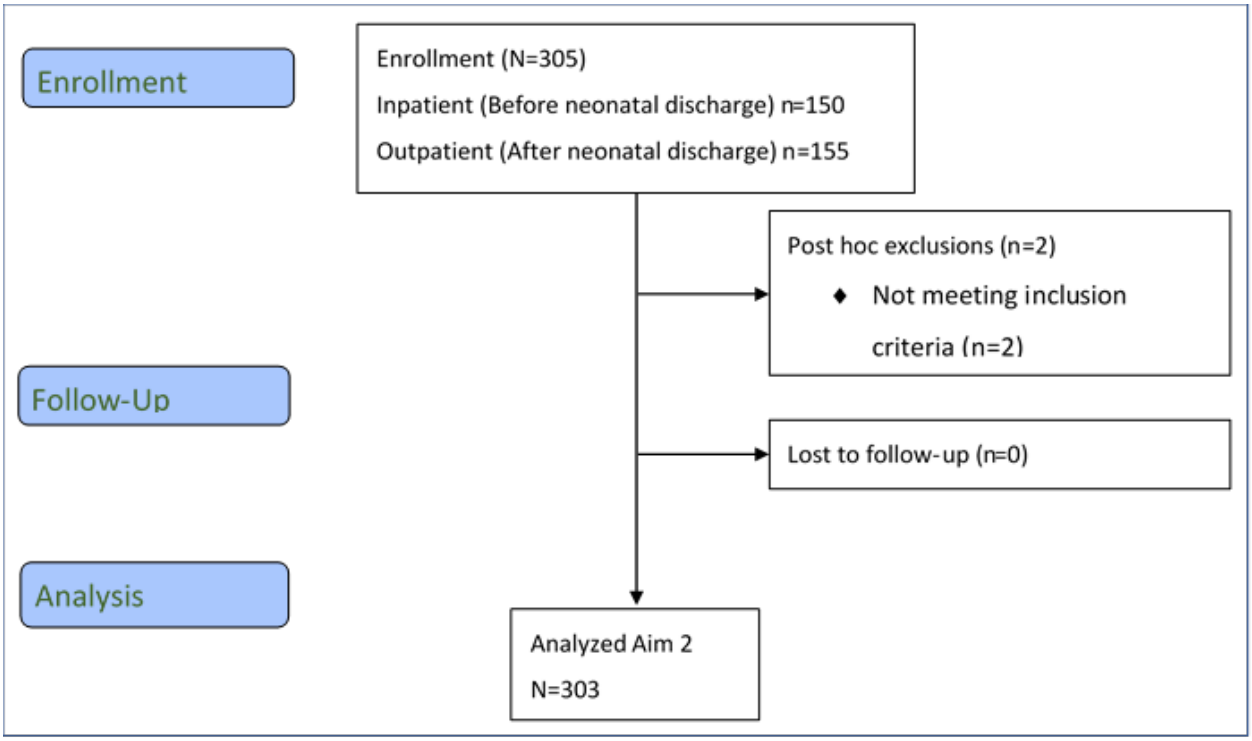
Aim 2

To determine whether duration of antiseizure treatment during NICU admission affects hospital LOS among neonates with acute symptomatic seizures, a factor highlighted by stakeholders as important for family well-being.

Study Participants

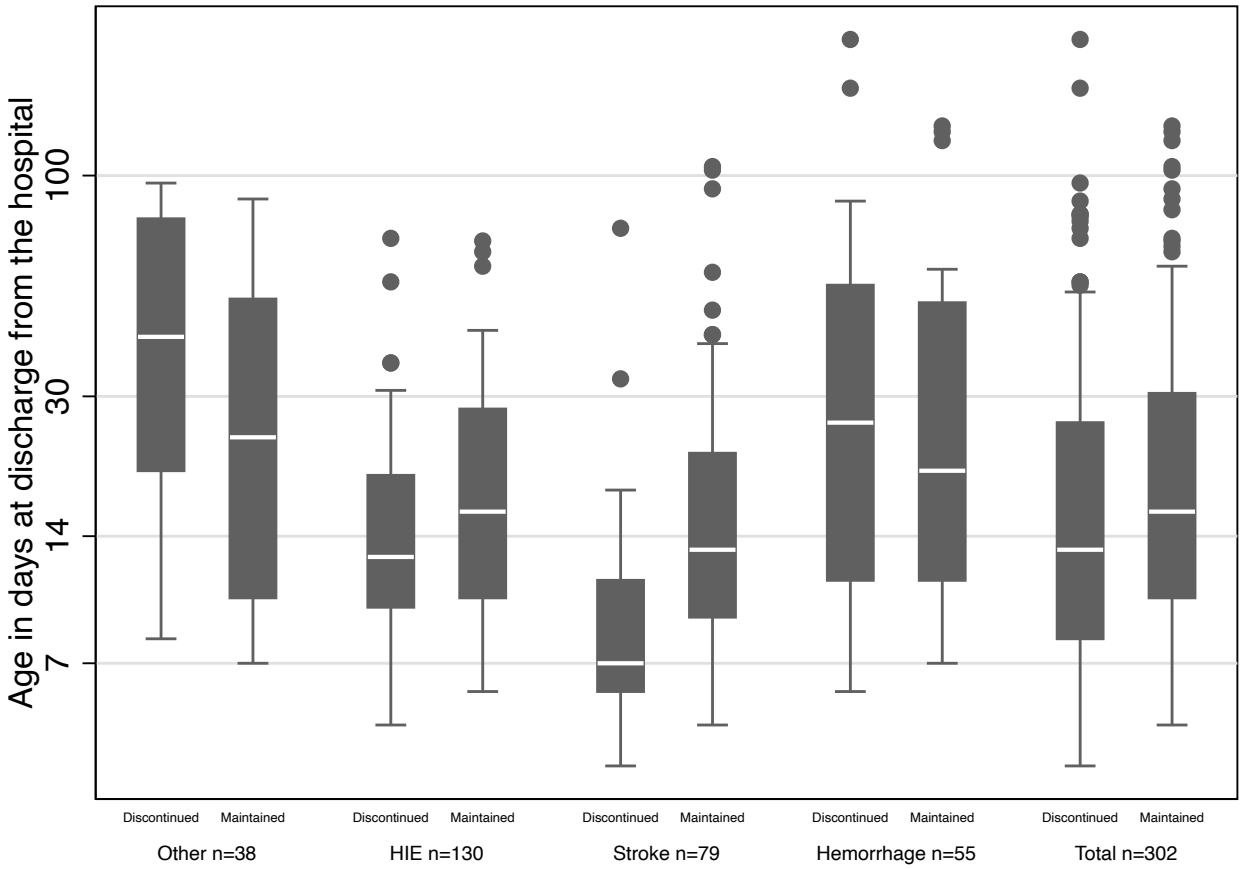
Among the 305 infants, 150 were enrolled from the inpatient setting and 155 from the outpatient setting. Two infants were later excluded due to criteria determined after enrollment (Figure 7). The remaining 303 infants with neonatal data were included in the LOS analysis.

Figure 7. Flow Diagram for Aim 2



Unadjusted analyses. The median LOS was 15 (IQR, 9-29) days. In the unadjusted analysis, the point estimate for LOS was shorter for children whose ASMs were discontinued before discharge from the neonatal seizure admission than for those whose ASMs were maintained at the time of discharge from the neonatal seizure admission (median, 13 [IQR, 8-25] days compared with a median of 17 [IQR, 10-32] days, respectively; *P* = .07; Figure 8].

Figure 8. LOS by Neonatal Seizure Etiology and ASM at Hospital Discharge[a]



Abbreviations: ASM, antiseizure medication; HIE, hypoxic-ischemic encephalopathy; LOS, length of stay.
[a]Top of the box: 75th percentile; bottom of the box: 25th percentile; line in the box: median; whiskers: 1.5 times the IQR. Dots are extreme values.

Propensity-adjusted analysis. After propensity adjustment, we found that the LOS did not differ between treatment duration groups (8% shorter; 95% CI, 26% shorter to 14% longer; *P* = .5) for children whose ASM was discontinued before discharge from the neonatal seizure admission.

In a propensity-adjusted stratified analysis, the effect was strongest for children with ischemic stroke as the neonatal seizure etiology (36% shorter; 95% CI, 59% shorter to 2% longer; *P* = .06), compared with children with HIE (7% shorter; 95% CI, 25% shorter to 17% longer; *P* = .6) or ICH (14% longer; 95% CI, 35% shorter to twice as long; *P* = .6). When added to the model for LOS, the interaction term between discharge on ASM and seizure etiology (4-level category) had a *P* value of .07, suggesting a trend toward interaction by seizure etiology and helping justify the stratified analysis.

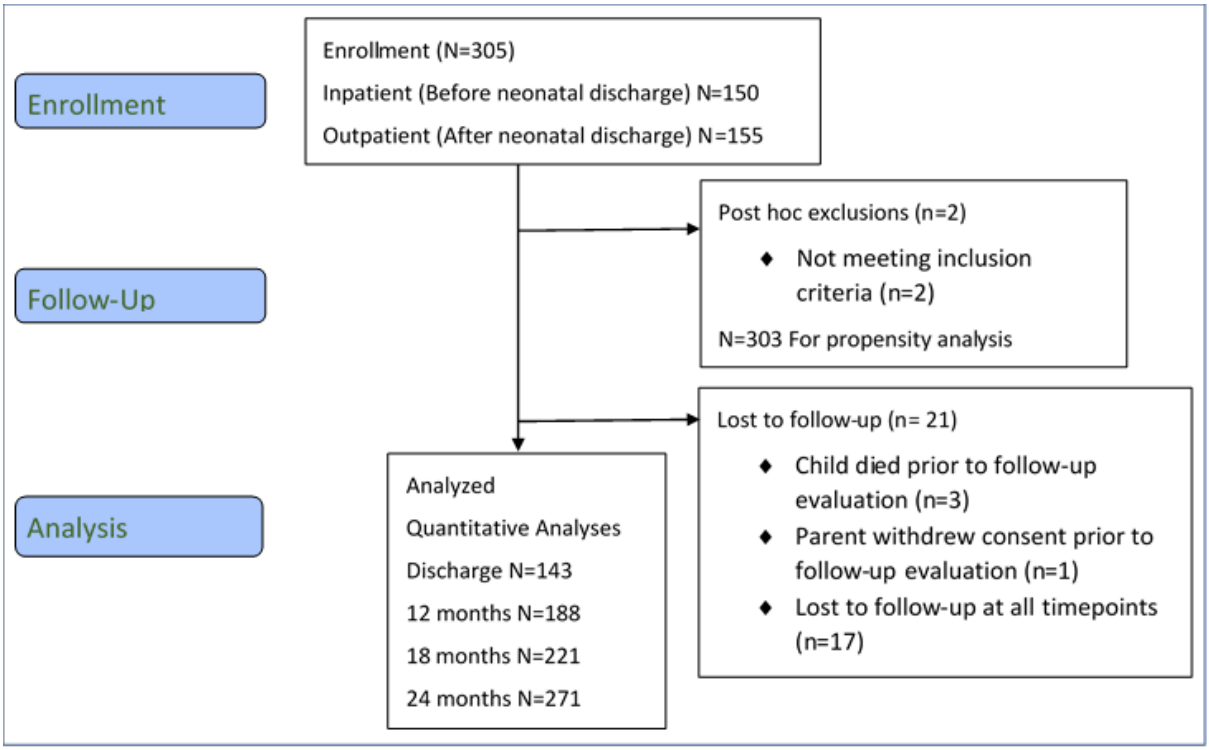
Aim 3

To determine how ASM discontinued before discharge from the neonatal seizure admission (short duration) compared with ASM maintained at the time of discharge from the neonatal seizure admission (prolonged duration) affects parent well-being.

Study Participants

Of the 305 parents, 150 were enrolled from the inpatient setting and 155 from the outpatient setting. Two were later excluded due to criteria determined after enrollment (Figure 9). The 303 infants with neonatal data were used for propensity analysis, as described for aims 1 and 2. The number of parent responses at each time point is indicated in Figure 9. The available number of parent responses varied based on the child's age at the time of enrollment.

Figure 9. Flow Diagram for Participants Enrolled in Aim 3 (Parent Well-being)



Quantitative measures.

Baseline parent well-being at hospital discharge. At the time of hospital discharge, among 144 parents, 54% had anxiety scores in the borderline (24%) or clinical (30%) range, and 32% had depression scores in the borderline (19%) or clinical (13%) range. QOL scores on the WHOQOL-BREF were in the upper tertile of the scale range (indicating better QOL), and mean IOF scores were in the lower tertile of the scale range (indicating less impact). The measures at each time point are presented in Table 11.

Seizure etiology was associated with both depression and QOL, with parents of infants with seizures due to HIE reporting more depression (HADS mean depression score difference, 2.8 [95% CI, 0.8-4.7]; effect size Cohen *d* = 0.73) and lower QOL (mean QOL score difference, 10.5 [95% CI, 0.5-20.5]; effect size Cohen *d* = 0.52) than did parents of infants with ICH. The rates of abnormal depression scores (cases) were 15% for parents of infants with HIE, 7% for those with infants with ICH, and 5% for other seizure etiologies. The rates of abnormal HADS

anxiety scores (cases) were 33% for parents of infants with HIE, 15% for those with infants with ICH, and 29% for other seizure etiologies. Parent QOL was also lower with greater infant age at discharge, with each additional week of hospitalization decreasing the QOL score by 1.3 (95% CI, 0.01-2.6). Only a maternal education of college or more (compared with less than college graduation) was associated with greater impact on the IOF scale (mean difference, 5.4 [95% CI, 1.4-9.4]; effect size Cohen *d* = 0.60).

Unadjusted analyses. Anxiety and depression scores were higher (worse) among parents of children whose ASMs were discontinued before discharge from the neonatal seizure admission at the 18-month time point than those of parents of children whose ASMs were maintained at the time of discharge from the neonatal seizure admission, although the difference was not significant. For all other time points and parent well-being measures, there were no significant differences between the groups (Table 11).

Table 11. Parent Well-being Measures at Each Time Point, by ASM Status at Discharge

Score measure[a]	ASM discontinued, mean (SD)	ASM maintained, mean (SD)	Total, mean (SD)	*P* value
Discharge (n = 142)				
HADS depression (higher = more depressed)	5.8 (4.3)	5.5 (3.9)	5.6 (4.0)	.78
HADS anxiety (higher = more anxious)	8.3 (4.5)	8.3 (4.2)	8.3 (4.3)	.81
WHOQOL-BREF (higher = better)	73.1 (22.2)	73.6 (19.7)	73.4 (20.6)	.96
IOF (higher = more impact)	34.8 (9.2)	34.8 (10.0)	34.8 (9.7)	.95
12 mo (n = 172)				
HADS depression (higher = more depressed)	4.0 (3.8)	3.2 (2.8)	3.5 (3.2)	.19
HADS anxiety (higher = more anxious)	6.6 (4.9)	5.8 (3.9)	6.1 (4.3)	.42
WHOQOL-BREF (higher = better)	70.8 (20.6)	77.2 (17.5)	74.8 (18.9)	.09
IOF (higher = more impact)	27.5 (11.4)	29.3 (10.2)	28.7 (10.7)	.17
PTGI (higher = more growth)	64.1 (24.9)	62.8 (24.9)	63.3 (24.8)	.74
IES (higher = worse)	17.3 (15.7)	16.9 (15.0)	17.2 (15.2)	.89
18 mo (n = 209)				
HADS depression (higher = more depressed)	3.9 (3.7)	2.8 (2.7)	3.2 (3.2)	.05
HADS anxiety (higher = more anxious)	6.3 (4.1)	5.2 (3.7)	5.6 (3.9)	.06
WHOQOL-BREF (higher = better)	73.4 (19.8)	75.7 (18.2)	74.8 (18.9)	.68
IOF (higher = more impact)	28.2 (10.8)	29.0 (10.0)	28.7 (10.3)	.49
PTGI (higher = more growth)	61.9 (28.6)	60.6 (26.3)	61.2 (27.2)	.73
IES (higher = worse)	17.9 (15.8)	14.2 (13.9)	15.7 (14.7)	.09
24 mo (n = 246)				
HADS depression (higher = more depressed)	3.3 (3.4)	3.3 (3.0)	3.3 (3.1)	.43
HADS anxiety (higher = more anxious)	6.0 (4.4)	6.0 (4.0)	6.0 (4.1)	.55
WHOQOL-BREF (higher = better)	76.8 (18.6)	76.5 (18.0)	76.6 (18.2)	.61
IOF (higher = more impact)	27.1 (10.4)	28.6 (10.3)	28.0 (10.4)	.18
PTGI (higher = more growth)	62.3 (25.0)	60.4 (25.9)	61.2 (25.5)	.57

Score measure[a]	ASM discontinued, mean (SD)	ASM maintained, mean (SD)	Total, mean (SD)	*P* value
IES (higher = worse)	15.4 (14.2)	14.5 (14.5)	14.9 (14.3)	.50

Abbreviations: ASM, antiseizure medication; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale; IOF, Impact on Family Scale; PGTI, Posttraumatic Growth Inventory Growth Inventory; WHOQOL-BREF, World Health Organization Quality of Life Brief Assessment.

[a]Reported n is the largest sample at that time point with well-being data. Within a given time point, n varies slightly based on the well-being measure in question.

Propensity-adjusted analyses. After adjustment for the variables that were incorporated in the propensity score, we found no differences in any of the parent mental health measures. The same was true after additionally adjusting for parent socioeconomic factors (Table 12).

When examining interactions in the multivariate model, we found that HADS anxiety, HADS depression, and IES scores compared with IOF scores had significantly different outcomes in parents of children whose ASMs were discontinued before discharge from the neonatal seizure admission from those of parents of children whose ASMs were maintained (*P* = .01 for interaction term; Figure 10). Parents of children whose ASMs were discontinued had higher (worse) scores for anxiety, depression, and IES, although the difference was not significant, whereas they had better scores for IOF (*P* = .01). The scores for WHOQOL-BREF and PTGI were similar. Differences and 95% CIs can be found in Table 13.

Table 12. Parent Well-being Measures at 24 Months by ASM Discontinued at the Time of Hospital Discharge Compared With ASM Maintained at the Time of Hospital Discharge, Adjusting for Variables That Were Incorporated in the Propensity Score and for Race/Ethnicity, Maternal Education, and Insurance Type

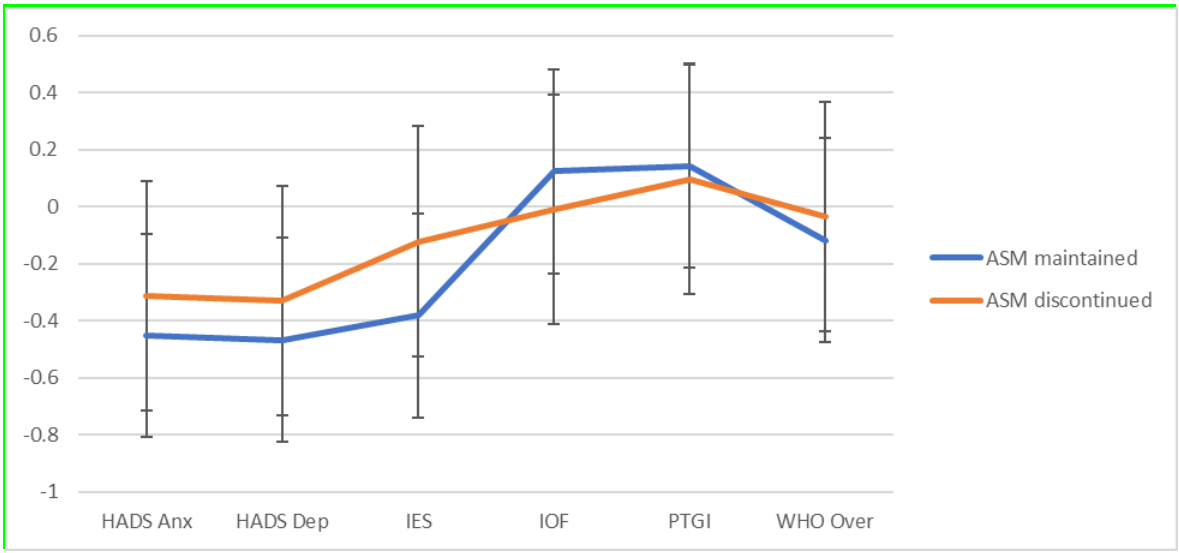
Measure[a]	β (95% CI) for discharged on medication term (maintained ASM compared with discontinued ASM)	
	Controlling for individual variables[b] that contribute to propensity score	Controlling for individual variables that contribute to propensity score plus race/ethnicity, maternal education, and insurance type
HADS depression at 24 mo (n = 246, 240)	.0 (−.9 to .9)	.2 (−.7 to 1.1)
HADS anxiety at 24 mo (n = 246, 240)	.1 (−1.1 to 1.3)	.0 (−1.2 to 1.3)
WHOQOL-BREF overall at 24 mo (n = 230, 224)	−.1 (−5.4 to 5.3)	−.1 (−5.6 to 5.5)
IOF overall at 24 mo (n = 245, 239)	.7 (−2.2 to 3.6)	1.8 (−1.3 to 4.8)
PTGI at 24 mo (n = 245, 239)	−3.4 (−1.7 to 3.8)	−3.6 (−11.0 to 3.8)
IES at 24 mo (n = 245, 239)	−.4 (−4.6 to 3.7)	.5 (−3.8 to 4.8)

Abbreviations: ASM, antiseizure medication; EEG, electroencephalogram; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale; IOF, Impact on the Family Scale; PTGI, Posttraumatic Growth Inventory Growth Inventory; WHOQOL-BREF, World Health Organization Quality of Life Brief Assessment.

[a]The n values refer to the total number of participants in each model; the number of participants included for each is slightly variable depending on responses to parent well-being surveys and available data for race/ethnicity, maternal education, and insurance type.

[b]Seizure etiology, hypothermia treatment, preterm category, worst EEG background, abnormal neurologic examination at discharge.

Figure 10. Predicted Mean Values and 95% CIs for Each Parent Well-being Measure (Expressed as *z* Scores) and by ASM Status at Discharge Across All Time Points[a]



Abbreviations: ASM, antiseizure medication; HADS, Hospital Anxiety (Anx) and Depression (Dep) Scale; IES, Impact of Events Scale; IOF, Impact on the Family Scale; PTGI, Posttraumatic Growth Inventory; WHO Over (WHOQOL-BREF), World Health Organization Quality of Life Brief Assessment

[a]Means for parents whose children's ASMs were maintained (or discontinued) are connected with a line for visual emphasis and to allow assessment of effect modification. Parallel lines indicate no effect modification, while lines that cross indicate a reversal of the discharge effect across outcomes.

Table 13. Difference and 95% CIs for Figure 10

Outcome	Difference (95% CI) for ASM maintained and ASM discontinued groups
HADS anxiety	0.14 (−0.12 to 0.40)
HADS depression	0.13 (−0.12 to 0.40)
IES	0.26 (0.00-0.52)
IOF	−0.13 (−0.39 to 0.13)
PTGI	−0.05 (−0.31 to 0.21)
WHOQOL-BREF	0.08 (−0.18 to 0.34)

Abbreviations: ASM, antiseizure medication; HADS, Hospital Anxiety and Depression Scale; IES, Impact of Events Scale; IOF, Impact on the Family Scale; PTGI, Posttraumatic Growth Inventory Growth Inventory; WHOQOL-BREF, World Health Organization Quality of Life Brief Assessment

Qualitative analyses from open-ended questions. Of the 150 parents who completed the NICU discharge survey, 144 provided responses to the open-ended questions (732 total comments). Four themes were identified.

Sources of strength. Families valued medical team consensus, opportunities to contribute to their child's care, and bonding with their infant.

Uncertainty. Parents reported 3 primary types of uncertainty, all of which caused distress: (1) the daily uncertainty of the intensive care experience, (2) concerns about their child's uncertain future, and (3) lack of consensus between members of the medical team.

Adapting family life. Parents described the many ways in which they anticipated their infant's condition would lead to adaptations in their family life, including adjusting their family's lifestyle, parenting approach, and routine. Many parents described financial and work challenges due to caring for a child with medical needs.

Emotional and physical toll. Parents reported experiencing anxiety, fear, stress, helplessness, and loss of sleep.

A total of 310 parents completed surveys across the 12-, 18-, and 24-month time points; 118 parents (38%) of 115 infants provided recommendations to the clinical team at 1 or more survey time points. For 3 infants, 2 parents participated. Most responses were from mothers (n = 103 [87%]).

Key recommendations for clinicians to improve family-centered communication were as follows: (1) offer transparent, balanced information in an accessible way; (2) understand and validate parent experience through empathy, compassion, and a commitment to parent-partnered clinical care; and (3) provide support and resources, including emotional support, education, connection with peers, and help navigating the health care system. Close to 60% of parents endorsed the first 2 themes, and approximately a third endorsed the third theme. The research team and parent advisory panel developed an infographic to raise awareness among clinicians, educators, and advocacy organizations and to guide initiatives to improve parent-

clinician communication. Table 14 provides the frequencies of codes across time points, and Figure 11 displays the key points as an infographic.

Table 14. Frequency of Parent Participant Response Codes to Open-Ended Questions Related to Clinician Advice at 12-, 18-, and 24-Month Survey Time Points

	Total (N = 118)		12-mo survey (n = 50)		18-mo survey (n = 58)		24-mo survey (n = 77)	
Participant response	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Communicate information effectively	69	58	25	50	30	52	34	44
Tell us everything	38	32	13	26	15	26	15	19
Choose words carefully	18	15	6	12	7	12	10	13
Communicate as a team	15	13	8	16	3	5	5	6
Repeat information as many times as we need	14	12	3	6	8	14	4	5
Give us balanced information	11	9	4	8	4	7	4	5
It's okay to say, "I don't know"	6	5	2	4	2	3	3	4
Understand and validate our experience	65	55	27	54	21	36	41	53
Be compassionate	31	26	11	22	10	17	18	23
Meet us where we are	25	21	9	18	11	19	12	16
Take our concerns seriously	20	17	10	20	3	5	9	12
Empower us to participate in our child's care	15	13	5	10	5	9	6	8
Provide support and resources	37	31	16	32	14	24	14	18
We need care, too	15	13	5	10	5	9	8	10
Educate us	13	11	5	10	3	5	5	6
Connect us with peers	10	8	5	10	2	3	3	4
Help us navigate care	10	8	6	12	4	7	1	1

Figure 11. Best Communication Practices

This work was funded by the Patient Centered Outcomes Research Institute (CER-1507-31187).

This infographic was designed by our study team in collaboration with parent advisory panel members and includes advice from parents for clinicians when communicating with families impacted by acute symptomatic neonatal seizures. These strategies were identified using parent responses to open-ended survey questions when infants reached ages 12, 18, and 24 months. Parents offered a range of advice to clinicians, which was indexed, categorized, and organized into themes using a conventional content-analysis approach. Throughout the analysis, parent advisory panel members were engaged in codebook development, theme generation, and manuscript preparation. Clinicians, educators, and advocacy organizations can use this information to guide initiatives to improve parent-clinician communication.

DISCUSSION

Through this prospective, observational comparative effectiveness study of treatment duration for acute symptomatic neonatal seizures, we demonstrate a clinically important result: discontinuation of ASM before hospital discharge is safe. After adjustment for propensity to maintain ASM, we found no increase in the risk of abnormal functional neurodevelopment or epilepsy among children whose ASM was discontinued before hospital discharge (aim 1). Discharge home without ASM did not alter the LOS for the entire cohort (aim 2). Importantly, there was no harmful impact on the family when ASM was discontinued before discharge (aim 3).

Importantly, this study question, design, and implementation, as well as data analysis and interpretation of results, were informed by deliberate and consistent involvement of our parent advisory panel and leaders of relevant parent support organizations. Our strategy of deliberate inclusion of parent partners was integral to the success of the project. The data collection period came to a close at the time when the COVID-19 pandemic resulted in widespread stay-at-home orders and cancellation of all in-person professional conferences. We continue to engage our parent advisory panel to reinvent plans for dissemination of the practice-changing results we present in this report.

Aim 1

To determine whether ASM discontinued before discharge from the neonatal seizure admission (short duration) compared with ASM maintained at the time of discharge from the neonatal seizure admission (prolonged duration) affects (1) neurodevelopmental outcome and (2) incidence of epilepsy at ages 12, 18, and 24 months.

In this rigorous, prospective, multicenter comparative effectiveness study of neonates with acute symptomatic seizures, we found that with discontinuation of ASM before hospital discharge there was an estimated small (but statistically nonsignificant) improvement in functional neurodevelopment at age 24 months as measured using the WIDEA-FS; the CIs met our a priori noninferiority limit of 0.5 SD, indicating no harm to neurodevelopment for

discontinuation. Similarly, there was no significant effect of early ASM discontinuation on the risk of epilepsy or of abnormal gross motor function by age 24 months. The robust analytic approach suggests that these findings are not due to differences in neonatal clinical characteristics, as propensity analyses adjusted for the important clinical variables that influence treatment duration decisions (eg, seizure etiology and severity).

Our findings strengthen the preliminary conclusions from earlier single-center and retrospective studies suggesting that early discontinuation of phenobarbital was not associated with increased seizure recurrence or risk for neurodevelopmental abnormalities.[6,10-12] Guillet and Kwon[6] retrospectively evaluated 146 children with neonatal seizures and found that phenobarbital prophylaxis (ie, ASM maintained at hospital discharge) was not associated with improved neurological outcomes with respect to seizure recurrence or neurodevelopment. Fitzgerald et al[10] evaluated 59 survivors of HIE at a median of 19 months and found that half of the children had their ASM discontinued before hospital discharge. The rate of seizure recurrence was 11%; none of the children whose ASM was discontinued developed epilepsy. Glass et al[11] evaluated 144 children with acute symptomatic neonatal seizures who developed epilepsy at a cumulative incidence rate of 7%. Epilepsy was more common among children who were maintained on ASM, although the difference was not significant in the adjusted analysis. Hellström-Westas[12] et al examined a small cohort of 31 survivors of neonatal seizures and found a low rate of seizure recurrence (8%) that was similar among children discontinued and those maintained on ASMs.

By definition, there is a seizure-free (or latent) period between the resolution of acute seizures and the onset of epilepsy. The median age of epilepsy onset in our full cohort was 7 months, which was months after the median age at which ASMs were stopped. Thus, there was no indication in our study that continuing ASM altered epileptogenesis. Indeed, every infant who developed epilepsy before age 4 months had been maintained on ASM after hospital discharge. In addition, 4 of 11 children (36%) with epilepsy onset before age 4 months had infantile spasms. The standard ASMs used for neonates (namely, phenobarbital and levetiracetam) are not effective for infantile spasms.[65,66] These results support reports from

smaller studies that the ASMs used as maintenance dosing after acute symptomatic neonatal seizures do not appear to change the latent-period duration of overall risk of epilepsy.[6,10,67]

Continuing ASM for months after resolution of acute symptomatic neonatal seizures was common practice[68] before the standard use of EEG monitoring for seizure diagnosis or brain magnetic resonance imaging (MRI) for etiologic evaluation. The contemporary approach to neonatal neurocritical care includes EEG to characterize clinical events and to evaluate for subclinical seizures. Infants whose events do not have an EEG correlate do not require ASMs; these infants were thus excluded from our study but may have been included in previous studies that did not employ EEG.[69] Similarly, most previous studies did not distinguish infants with neonatal-onset epilepsies from those with acute symptomatic neonatal seizures; yet, the treatment approach differs dramatically.[70,71]

Subpopulation Considerations

Levetiracetam. Most participants in our study, and neonates with seizures worldwide,[7,20,72-75] were treated with phenobarbital. However, there has been an increasing trend toward the prescription of levetiracetam for neonatal seizures.[7] In our study, infants treated with levetiracetam almost always also received phenobarbital (only 12 infants were maintained on levetiracetam monotherapy after hospital discharge). Our study was not powered for a separate analysis of levetiracetam treatment duration. However, a recently published clinical trial (ClinicalTrials.gov identifier NCT01720667; https://clinicaltrials.gov/ct2/show/NCT01720667?term=NCT01720667&draw=2&rank=1) suggested that levetiracetam was less effective than phenobarbital for initial neonatal seizure treatment.[76] Thus, phenobarbital remains the first-line treatment for neonatal seizures. We are not able to assess whether long-term prescription of levetiracetam alters the outcome after acute symptomatic neonatal seizures.

Prematurity. Among preterm infants, there was no adverse effect on neurodevelopmental outcome associated with discontinuation of ASM compared with maintenance of ASM after discharge.

Hypoxic-ischemic encephalopathy. About half of neonates who receive therapeutic hypothermia with HIE have seizures, and HIE is the most common etiology of acute symptomatic seizures in neonates.[77,78] In contrast to preterm infants, who often require a months-long neonatal admission, neonates with HIE typically are admitted for much shorter periods. We suspect that some clinicians may be reluctant to discontinue ASMs shortly before discharge from a brief hospital admission. Yet, our data show there is no harm to neurodevelopment among children with HIE whose ASMs were discontinued, compared with those whose ASMs were maintained, at the time of discharge from the neonatal seizure admission.

Limitations

Several limitations to our study merit specific discussion:

1. Although the study was adequately powered to assess noninferiority for the primary outcome (WIDEA-FS scores at 24 months), the power for postneonatal epilepsy was less robust. Epilepsy was a relatively rare outcome (just 13% in our cohort compared with >20% in other reports).[2,3,71,79] Therefore, although there was no significant difference in epilepsy risk based on treatment duration groups, we could not exclude a risk of up to 3.4 times the odds of developing epilepsy by age 24 months among the children whose ASMs were discontinued compared with those whose ASMs were maintained. We further note that, for the epilepsy outcome, adjusting for the propensity score reverses the direction of effect. A larger sample size will be needed to better understand the relationship between duration of ASM therapy and epilepsy.

2. Follow-up was limited to 24 months. It is possible that additional functional developmental abnormalities may emerge over time, and it is likely that some children will develop epilepsy later in life. However, we do not expect that ASM treatment duration in the neonatal period would modulate the risk for these later outcomes.

3. We were not able to quantify brain injury through a central review of neuroimaging for the full cohort; however, seizure severity and EEG background reflect the severity of overall brain injury.[80,81] Thus, our analyses do account for the extent of injury.

4. We do not have specific data on adherence to ASM regimens after NICU discharge nor documentation of adverse drug effects.

Aim 2

To determine whether duration of ASM treatment during NICU admission affects hospital LOS among neonates with acute symptomatic seizures, a factor highlighted by stakeholders as important for family well-being.

In doses commonly used for seizure treatment, phenobarbital leads to varied central nervous system alterations ranging from mild sedation to coma and respiratory depression.[82] Behavioral-state control is an important prerequisite for feeding in neonates; sedation can be associated with poor oral feeding in infants exposed to phenobarbital and other ASMs.[83,84] Given that achieving safe provision of nutrition (most commonly oral feeding) is a prerequisite to hospital discharge, we hypothesized that longer phenobarbital use would be associated with a longer hospital stay. In our study, increased days of phenobarbital exposure was associated with longer neonatal hospital LOS. After adjustment for propensity to maintain ASMs upon hospital discharge, we found a trend toward shorter hospital LOS among neonates with seizures caused by ischemic stroke when ASM was discontinued before discharge (95% CI, 59% shorter to 2% longer; $P = .06$).

Decreasing LOS is a priority for parents and hospitals. Our results suggest that future work that assesses the effects of implementing shorter ASM duration, particularly for neonates with seizures due to ischemic stroke, could have clinically important impact.

Limitations

Acute symptomatic neonatal seizures often occur in infants with complex medical problems. For infants with prematurity, congenital heart disease, or other significant medical or surgical issues, LOS is likely not dependent simply on the duration of ASM. The stratified analysis, which aimed to address the variable complexity among the different etiologies, was not prespecified; rather, it was a hypothesis we developed during the analysis phase. Of note, it is standard of care at our sites for a newborn who is treated with therapeutic hypothermia for HIE to have a brain MRI after rewarming. Some sites schedule the MRI when the infant is aged 7

to 10 days, and it is possible that this resulted in longer hospital LOS for some infants and may have masked an effect of shorter ASM duration on LOS.

Aim 3

To determine how ASM discontinued before discharge from the neonatal seizure admission (short duration) compared with ASM maintained at the time of discharge from the neonatal seizure admission (prolonged duration) affects parent well-being.

Parent-Reported Results From Validated Instruments

One of the unique aspects of this study is its focus on parent well-being for newborns with acute symptomatic seizures. Aim 3 was designed with direct input from our parent advisory panel and offers valuable insights into potential impacts of deliberate family supports.

At the time of their infant's neonatal seizure hospital discharge, more than half of parents reported clinically important symptoms of anxiety, and nearly a third experienced clinically important symptoms of depression. In a separate published manuscript, we reported important associations between demographic and clinical characteristics and parent QOL and depression, as well as family impact.[23] Although parent anxiety was prevalent, it was not associated with any of the infant characteristics measured in this study. This may suggest that all parents of infants with acute symptomatic neonatal seizures would benefit from preventative anxiety reduction interventions, and that those with risk factors should be screened and offered services to prevent depression.

Combined with the results for aim 1 that suggest that early discontinuation of ASM is safe for the infant, the results for aim 3 provide an additional rationale for a call to action for changes in practice. In a comparison of parent well-being over time for children whose ASMs were discontinued with parents of children whose ASMs were maintained at discharge from the neonatal seizure admission, the impact of being discharged on ASMs differed based upon the specific dimension of parent well-being. Parents express high rates of depression, anxiety, and impact on the family in caring for a child with acute symptomatic neonatal seizures. It is not clear whether discontinuing ASMs significantly influences parent well-being; these findings

require additional research to understand these relationships and investigate interventions to support optimal parent well-being because of their important influence on child health and development.

Results From Analysis of Open-Ended Questions

Parents of neonates with seizures face challenges as they adapt to and find meaning in their role as a parent of a child with medical needs. Our findings support and extend research into the well-being of parents with children who have other neonatal conditions. Clinicians and researchers can use these findings to develop interventions tailored to the needs of parents whose children have newborn seizures and other neurological conditions.

The parent participants in our study also provided key advice to clinicians that fell into 3 important themes: (1) effective communication, (2) understanding and validation of parent experiences, and (3) provision of support and resources (Figure 11). The results from this aim translate directly to actionable guidance for clinical providers who care for newborns with seizures.

Other researchers have reported parents' value of clear, understandable, and transparent communication, particularly in terms of coordination of this communication among members of the clinical team.[85-87] Specific to our study and its patient populations, parents expressed clear appreciation of clinicians' balancing prognostic information to include the range of potential neurodevelopmental outcomes. Provision of best, worst, and most-likely outcomes ensures that families have the information they need to make decisions for their children.[86] Importantly, parents did not wish for "false hope" but did appreciate receiving honest communication about their children's possible future abilities. Parents also clearly appreciated honest communication regarding prognostic uncertainty.

Most parents underscored their need for clinical care team members to recognize and validate their experiences. They appreciated clinicians' compassion, empathy, and patience. Nonetheless, burnout is common for NICU clinicians,[88] and clinician fatigue, moral distress, and burnout can decrease clinicians' ability to sustain these key features of communication and care

for patients and their families. Thus, clinician well-being is a key component of any intervention designed to improve parent support.

Parents also consistently reported that being involved in the clinical care of their newborn was of key importance. Promoting parent engagement in basic newborn care and encouraging opportunities for holding are valuable for families.[89-91]

The rates of parent-reported symptoms of anxiety and depression on the validated instruments were reflected in parents' highlighted need for emotional support and access to mental health resources. Peer support was also identified as a key element of ideal comprehensive care.

Limitations

Although the participants in our study were geographically diverse, most of the parents were mothers. We did not gather extensive sociodemographic information about parent participants, which limited our ability to assess the relationships between race, ethnicity, family income, or other factors and the responses to open-ended questions. Additionally, for the study to be feasible, we restricted enrollment to parents who spoke English or Spanish, which limits our ability to generalize our findings to families who speak other languages. We were able to adjust for maternal education and race for the responses to validated questionnaires. Programs to support and communicate with families may have varied by study site or over the course of the study period.

Generalizability

Aim 1

Strengths of this study include the rigorous diagnosis of acute symptomatic neonatal seizures with conventional neonatal EEG monitoring in level IV NICUs in the United States. We recognize that many newborns do not receive this level of intensive care, and this may limit generalizability for neonates whose seizures are diagnosed clinically or by amplitude-integrated EEG. To further enhance generalizability, we included neonates with a range of acute

symptomatic seizure etiologies and did not exclude infants with prematurity or complex medical courses. We also allowed for clinical teams to make the decisions regarding treatment of acute symptomatic neonatal seizures (including medication selection, dosing, and duration).

Aim 2

There is practice variability with regard to criteria for NICU discharge, and this was certainly true for the sites in this study. For centers with large geographic catchment areas, transfer from the level IV NICU back to a local hospital for convalescence is common practice. Discharge home with nasogastric tube feedings also varies across institutions. This range of clinical practices, represented among our study sites, enhances the generalizability of the results.

Aim 3

We aimed to be as inclusive as possible of infant and parent participants in this study. Although we did not specifically collect data on parent race, the profile of the infants was fairly diverse (63% White, 12% Black or African American, 7% Asian, 3% more than 1 race, and missing information for the remainder). Still, most parents who completed the well-being instruments were mothers. Whether mothers' results are generalizable to all parents is a reasonable question. The fact that we included parents with a range of socioeconomic status indicators whose infants had seizures caused by a range of etiologies and had a range of neurodevelopmental outcomes improves the generalizability of the results.

A minor limitation to the generalizability of the data is the lack of study sites in the southern United States. For this reason, there may be particular geographic or cultural issues that are not captured in our work.

Dissemination of Results

The results of this work are presented (or under review) in the traditional peer-reviewed literature, with open access whenever feasible. Although restrictions related to the COVID-19 pandemic limited the authors' ability to present the results at in-person national and

international meetings, the abstracts were presented via electronic posters, webinars, and recorded platform presentations. We have also worked to present detailed results at grand rounds presentations across academic centers.

Importantly, we continue to work with our parent advisory panel to create opportunities to disseminate the results through newsletters to participants, posts to parent advocacy group websites, and co-presentations at institutional grand rounds. We are committed to the pursuit of additional dissemination opportunities.

Future Directions

Our parent advisory panel was clear that while the 24-month outcomes are good, school-aged outcomes are a priority. Thus, we have embarked on long-term follow-up of the present cohort of enrolled children to determine predictors of neurodevelopment (eg, full-scale intelligence quotient, executive functioning, and school readiness), epilepsy, and family well-being at ages 4 to 8 years. This long-term follow-up is now funded by NIH grant NS111166.

Additional high-priority future directions include an evaluation of genetic susceptibility to postneonatal epilepsy among children who survive acute symptomatic neonatal seizures, as well as quantitative EEG markers of epileptogenesis.

CONCLUSIONS

We conclude that discontinuation of ASM before discharge from the neonatal seizure admission is safe: after adjusting for propensity to prescribe ASM after discharge, we found that the 24-month functional developmental outcomes and risks of epilepsy were similar between the treatment duration groups. Importantly, longer treatment duration had measurable negative effects on family well-being. Taken together, our data support routine discontinuation of ASM after resolution of acute symptomatic seizures and before hospital discharge regardless of seizure etiology and gestational age. This will necessitate a change in practice at many centers.

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RELATED PUBLICATIONS

Published manuscripts:

Franck LS, Shellhaas RA, Lemmon M, et al; Neonatal Seizure Registry study group. Associations between infant and parent characteristics and measures of family well-being in neonates with seizures: a cohort study. *J Pediatr*. 2020;221:64-71.e4. doi:10.1016/j.jpeds.2020.02.024

Lemmon ME, Glass HC, Shellhaas RS, et al; Neonatal Seizure Registry. Parent experience of caring for neonates with seizures. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(6):634-539.

Glass HG, Grinspan ZM, Li Y, et al; Neonatal Seizure Registry study group. Risk for infantile spasms after acute symptomatic neonatal seizures. *Epilepsia*. 2020;61(12):2774-2784.

Glass HC, Soul JS, Chang T, et al. Safety of early discontinuation of anti-seizure medication after acute symptomatic neonatal seizures *JAMA Neurol.* 2021;May 24:e211437. doi:10.1001/jamaneurol.2021.1437

Shellhaas RA, Wusthoff CJ, Numis AL, et al. Early-life epilepsy after acute symptomatic neonatal seizures: a prospective multicenter study. *Epilepsia.* Epub ahead of print. 2 July 2021. doi: 10.1111/epi.16978

Submitted manuscripts (under review):

Lemmon ME, Glass HC, Shellhaas RA, et al; Neonatal Seizure Registry. Communicating about neonatal seizures: advice from parents.

ACKNOWLEDGMENTS

The study investigators would like to thank the Neonatal Seizure Registry advisors, Drs Donna Ferriero, Faye Silverstein, and Kevin Staley, as well as the clinical research coordinators at each site for their tireless work enrolling and following study participants.

APPENDICES

Appendix A. WIDEA-FS (Aim 1a; Primary Outcome Measure)

Appendix A: WIDEA-FS (Aim 1a; primary outcome measure)

The Warner Initial Developmental Evaluation of Adaptive and Functional Skills

(Warner IDEA-FS TM) ▪ Version 11 ▪ March 1, 2005

Michael E. Msall, Nancy Lyon, Melissa Gray, Kathleen DiGaudio

➤➤➤ How often can your child do the following without help? **Subject #:_____**

1 = Never 2 = Sometimes, infrequent 3 = Most of the time 4 = All of the time

I. Self-Care: Feeding	
1. Easily drinks formula or breast milk	
2. Easily swallows baby food	
3. Chews solid food	
4. Finger feeds	
5. Eats using a spoon	
6. Drinks from cup without a lid	
7. Eats using a fork	
II. Self-Care: Dressing	
1. Holds arms up so you can put shirt on	
2. Removes socks	
3. Pulls pants down	
4. Pulls up a zipper once it is started	
5. Puts on t-shirt	
6. Removes all clothes	
III. Self-Care: Diaper Awareness	
1. Indicates a wet diaper	
2. Indicates a soiled diaper	
3. Voids into potty chair or toilet	
4. Sits on potty chair and has bowel movement	
Subtotal Self-Care Domain (max=68)	

IV. Mobility	
1. Rolls both ways	
2. Maintains sitting without support	
3. Crawls short distance	
4. Walks few feet with assistance (cruises)	
5. Scoots or moves in wheelchair 10 feet	
6. Walks 10 feet independently	
7. Crawls up stairs	
8. Gets on and off a chair	
9. Walks up stairs *with hand held*	
Subtotal Mobility Domain (max=36)	

V. Communication	
1. Understands words for people in immediate family (mommy, daddy) (R)	
2. Demonstrates 2 syllable babbling (E)	
3. Understands words for some common objects (R)	
4. Gestures a social greeting (wave, blow a kiss) (E)	
5. Carries out a 1 step oral request with gesture (pick up toy, cup) (R)	
6. Uses single words or signs to request or communicate (E)	
7. Carries out a 1 step oral request without gesture (R)	
8. Identifies one body part (R)	
9. Identifies three or more body parts (R)	
10. Points at pictures (R)	
11. Has at least 10 words or 10 signs (E)	
12. Combines words or signs to make needs known (E)	
13. Names pictures (E)	
Subtotal Communication Domain (max=52)	

VI. Social Cognition	
1. Plays "peek-a-boo", "patty cake", or "so big"	
2. Looks for object dropped out of sight	
3. Initiates social contacts with peers	
4. Takes turns rolling a ball	
5. Imitates another child	
6. Recognizes familiar song	
7. Starts mechanical toy or VCR/DVD/computer	
8. Can pretend play with doll or toy	
9. Turns pages in a book	
10. Points at pictures when you read a story	
11. Helps with simple household tasks	
Subtotal Social Cognition Domain (max=44)	

TOTAL SCORE

Total Items: 50 ▪ Maximum Score: 200

Appendix B. Seizure/Epilepsy Follow-up Telephone Questionnaire (Aim 1b)

Appendix B: Seizure/Epilepsy Follow-Up Telephone Questionnaire (Aim 1b)

Date_____
Subject # _____ Subject age_____
Person completing questionnaire _____

1. Did your child have seizures as a newborn (at any time during the first 28 days of life)?
    a. Yes
    b. No
    c. Don't know
2. If your child was treated with medicine for neonatal seizures, did he/she ever stop taking this medicine?
    a. Yes, before we left the hospital
    b. Yes, after we left the hospital
    c. No
    d. Don't know
3. Your child was treated in the hospital for his or her seizures. After you went home from that admission, did your child ever have more seizures?
    a. Yes
    b. No
    c. Don't know

[If answer to 3. Is "No", then indicate answer "a" for question 5 and end telephone survey. If yes, then continue.]

4. Let's talk about the seizure that happened after you went home from the hospital. When did your child start having seizures?
    a. Age_____ months
    b. Don't know
5. How often does your child have a seizure now?
    a. No seizures since he/she was a newborn
    b. Seizure-free for at least 6 months (# of months seizure-free _____)
    c. 1 – 12 seizures per year (Fewer than 1 seizure per month)
    d. 1 – 4 seizures per month
    e. 5-30 seizures per month
    f. >30 seizures per month (daily seizures)
    g. Multiple seizures a day (2 or more seizures per day)
    h. Don't know
6. Has your child ever been diagnosed with infantile spasms (a particular kind of epilepsy)?
    a. Yes
    b. No
    c. Don't know
7. Is your child taking medication for seizures now?

a. Yes (Name of medication(s), if known _____)
b. No
c. Don't know

Epilepsy questions for medical record review:

1. Did the child remain seizure-free after discharge from the admission during which neonatal seizures were diagnosed?
    a. Yes.
    b. No. Acute symptomatic neonatal seizures stopped, but unprovoked seizures began later.
        i. Date of first unprovoked seizure:_____
    c. No. Seizures persisted without a convalescent period.
    d. Don't know.

2. Postneonatal seizure semiology:
    a. No seizures
    b. Seizure semiology:

	no	Yes, not specified	Bilateral, symmetric	Bilateral, asymmetric	Unilateral, focal	Unilateral, Hemi
Epileptic spasms	☐	☐	☐	☐	☐	☐
Tonic	☐	☐	☐	☐	☐	☐
Clonic	☐	☐	☐	☐	☐	☐
Tonic Clonic	☐	☐	☐	☐	☐	☐
Myoclonic-Tonic	☐	☐	☐	☐	☐	☐
Myoclonic	☐	☐	☐	☐	☐	☐
Myoclonic-Atonic	☐	☐	☐	☐	☐	☐
Absence	☐	☐	☐	☐	☐	☐
Atonic/Drop-attack	☐	☐	☐	☐	☐	☐
Arrest/Staring/Blinking seizures	☐	☐	☐	☐	☐	☐
Other Focal Motor	☐	☐	☐	☐	☐	☐
Sensory/Autonomic	☐	☐	☐	☐	☐	☐

3. Date of postneonatal epilepsy diagnosis:_____
4. Postneonatal epilepsy diagnosis:
    a. No postneonatal epilepsy
    b. Infantile spasms
    c. Focal epilepsy related to structural brain injury
    d. Focal epilepsy, cause unknown
    e. Generalized epilepsy related to structural brain injury
    f. Generalized epilepsy, cause unknown
5. Epilepsy treatments prescribed (list all that apply):_____

Appendix C. Parent Well-being Scales (Aim 3)

Appendix C: Parent Well-being scales (Aim 3)

Domains of well-being	Questionnaire	Timepoints	Rationale
Parent quality of life	WHO-Brief QOL	NICU Discharge & 12, 18, & 24 months	The most comprehensive and yet brief; well-validated
Parent anxiety and depression	HADS	NICU Discharge & 12, 18, & 24 months	The most comprehensive and yet brief of the surveys reviewed; well-validated
Family coping	Impact on Family; *Understanding the medical situation* subscale of Coping Health Inventory for Parents	NICU Discharge & 12, 18, & 24 months	Have been used with families of children with epilepsy as well as many other conditions
Parent post-traumatic stress	Impact of events	12, 18, & 24 months	One of the most well-known measures of post-traumatic stress symptoms in relation to a specific event
Parent post-traumatic growth	Post-traumatic growth	12, 18, & 24 months	Allows us to examine positive *and* negative outcomes after a stressful event
Parent/infant/family socio-demographics	Study specific instrument with standard items (education, employment, etc.) and parent report of infant condition and treatment	NICU Discharge & 12, 18, & 24 months	These variables are needed to describe the sample and may be adjusted for if they have an independent effect on the outcomes of interest
Open-ended questions	Study specific instrument to explore in more depth the effects of the seizures and treatment on parent, child and family well-being	NICU Discharge & 12, 18, & 24 months	These questions will be asked as part of the surveys, and will also be used as a question guide to engage a subset of parents in a more in-depth interview to describe their experiences and perceptions

Open-ended questions to be answered by a parent at the time of <u>hospital discharge</u>:

Date_____ Subject # _____

Race: _____ Ethnicity: _____

1. What level of agreement or doubt was there among the medical care team about the duration of anti-seizure medication treatment? How did that make you feel? How did it impact your family?

2. On a scale of 1 to 5, with 1 being not confident at all and 5 being very confident, how confident do you feel about taking care of your baby's medical condition?

3. Will your child's treatment affect your usual family routines (Yes or No)? If so, how?

4. In what other ways might your child's treatment impact you and your family?

5. The most positive part of caring for my child is:

6. The most difficult part of caring for my child is:

7. Do you have any worries/concerns/fears about your child's seizure condition or treatment (Yes or No)? If yes, please describe.

Open-ended questions to be answered by a parent at the <u>12-month follow-up</u>:

Date_____ Subject # _____

Race: _____ Ethnicity: _____

1. Looking back, what if any, impact did your child's seizure medication during the NICU stay have on you or your family? If your child continued to receive medication for seizures in the past year, what if any impact did this treatment have on you or your family? How did affect your usual family routines?

2. Looking back at the time of discharge from the NICU, what questions did you have about your baby's condition at the time of discharge? What recommendations do you have for other parents in the same situation? What recommendations do you have for the clinical staff?

3. Looking back over the past year of caring for your baby, what questions did you have about your baby's condition at the time of discharge? What recommendations do you have for other parents in the same situation? What recommendations do you have for the clinical staff?

4. Looking back, what level of agreement or doubt was there among the medical care team about the duration of anti-seizure medication treatment? How did that make you feel? How did it impact your family?

5. The most positive part of caring for my child is:

6. The most difficult part of caring for my child is:

7. Do you have any worries/concerns/fears about your child's seizure condition or treatment? (Yes/No) If yes, please describe:

Appendix D. Parent Newsletters

NSR NEONATAL SEIZURE REGISTRY

Volume 1 | Issue 1

Spring 2017

Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study

- funded by Patient Centered Outcomes Research Insititute (PCORI) -*

Welcome to our first newsletter for the ***Neonatal Seizure Registry (NSR)***. Our goal is to provide you with updates about our research and new developments in the field of newborn seizure treatment.

Our Work

We are working with the Patient Centered Outcomes Research Institute (PCORI) to carry out a large, multi-site observational study to better understand how to treat seizures in newborns. Our seven participating hospital sites and Parent Partners span from coast to coast:

PARTICIPATING HOSPITALS

UCSF Benioff Children's Hospital
Hannah Glass, MD
Mott Children's Hospital
Renée Shellhaas, MD
Lucille Packard Children's Hospital
Courtney Wusthoff, MD
Children's Hospital of Philadelphia
Nicholas Abend, MD
Children's National Medical Center
Taeun Chang, MD
Massachusetts General Hospital
Catherine Chu, MD
Boston Children's Hospital
Janet Soul, MD

There is not enough high quality research to tell doctors the best way to treat seizures in babies. Different doctors have different approaches. Our goal is to figure out the safest and most effective way to treat newborns with seizures. We also want to understand how the medical treatments for newborn seizures can impact families as their children grow.

We began recruitment efforts for this study in July 2016. We are on target to enroll 300 babies and their families in this study by March 2018.

Families are invited to participate if:

- Their baby is born at or transferred to one of our 7 study centers
- Their baby's seizures began less than 4 weeks after the baby's full term due date and needed medication to treat the seizures

If your child is enrolled in the study:
Follow-up is in person for an EEG at 3 months and by telephone at 12, 18, and 24-months.

Meet Our Parent Partners

Our Parent Partner Panel is a unique and valuable part of our study. This group is made up of nine wonderful parents, who have experienced caring for a child with neonatal seizures. They have been deeply involved in the study and continue to be very important to our work and its progress. **They keep us focused on what is important to families, help us ensure that the study procedures are reasonable for families to participate, and will work with us to share our findings with families and care providers.**

Here is what our Parent Partners have to say about why they chose to participate in the NSRII Parent Panel:

"I am happy to participate in studies related to seizures… The more we know, the better we can fight for our babies."

– Marty Barnes (Casey's Circle)

"My role in this study is to guide [the investigators] on how best to relate to and communicate with families who have a child with neonatal seizures. Participation… is vital to a valuable outcome, but it is also a very overwhelming and emotional time to be asked to volunteer [to take part in research], especially when [families] are just learning how to cope with an unexpected reality."

– Dana Annis (Children's National Medical Center)

Advances in Neonatal Health

This will be a regular feature of the newsletter, featuring the latest research from the field. This first highlight is from our team!

One of our very own Parent Partners, Elizabeth Hill MD, from the University of Michigan, co-authored the article **"Seizures and Antiseizure Medications are Important to Parents of Newborns with Seizures" in the journal, *Pediatric Neurology*** in October 2016 along with members of the study team (Hannah Glass MD, MAS, Linda Franck RN, PhD, Renee Shellhaas MD, MS, Stephanie Rau BS, CCRP) and Parent Partners Marty Barnes, Casey's Circle and Kelli Kelley, HandtoHold.org.

The article reports what we learned about parental experiences and concerns regarding newborn seizure treatment. We conducted an online survey of what parents thought about seizures and gathered their suggestions for high priority research topics.

We found that **newborn seizures and the medications used to treat them worry parents and have a long-term impact on families**. Parents feel unsure about the immediate and long-term effects of the medications. According to our results, **research should focus on the information that will help lower risk and increase benefits of anti-seizure medications for newborns, infants and children**. Parents also wanted research to **better understand how families to cope with newborn seizures and treatments**.[1].

If you are interested in learning more about the study or have any questions, please contact Isheeta Madeka at (415) 476-3785.

*Research reported in this newsletter was funded through a Patient-Centered Outcomes Research Institute (PCORI) Award CER-1507-31187.

[1] Hill E, Glass HC, Kelley K, Barnes M, Rau S, Franck LS, Shellhaas RA. Seizures and Antiseizure Medications are Important to Parents of Newborns With Seizures. Pediatric Neurology. 2017 Feb; 67: 40-44.

NSR NEONATAL SEIZURE REGISTRY

Volume 1 | Issue 2

Fall 2017

Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study

- funded by Patient Centered Outcomes Research Institute (PCORI) -

Welcome to our second newsletter for the ***Neonatal Seizure Registry (NSR)***. We have recruited 217 families and are on target to enroll 300 babies and their families in this study by March 2018.

Our Work

We are working with the Patient Centered Outcomes Research Institute (PCORI) to carry out a large, multi-site observational study to better understand how to treat seizures in newborns. Our nine participating hospital sites and Parent Partners span from coast to coast:

We would like to welcome our two new sites, Duke University and Cincinnati Children's Hospital Medical Center!

PARTICIPATING HOSPITALS

UCSF Benioff Children's Hospital
Hannah Glass, MD, MS
Mott Children's Hospital
Renée Shellhaas, MD, MS
Lucille Packard Children's Hospital
Courtney Wusthoff, MD, MS
Children's Hospital of Philadelphia
Nicholas Abend, MD, MS
Children's National Medical Center
Taeun Chang, MD
Massachusetts General Hospital
Catherine Chu, MD, MS
Boston Children's Hospital
Janet Soul, MD
Duke University
Monica Lemmon, MD
Cincinnati Children's Hospital Medical Center
Cameron Thomas, MD

There is not enough high quality research to tell doctors the best way to treat seizure in babies. Different doctors have different approaches. Our goal is to figure out the safest and most effective way to treat | newborns with seizures. We also want to understand how the medical treatments for newborn seizures can impact families as their children grow.

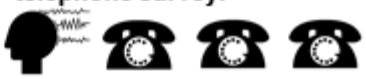
Families are invited to participate if:

- ☐ Their baby is born at or transferred to one of our 9 study centers
- ☐ Their baby's seizures began less than 4 weeks after the baby's full term due date and needed medication to treat the seizures
- ☐ The family speaks and reads English or Spanish

What happens in the study:

At 3 months: A clinic visit for children to receive an EEG and parents to complete a survey.

At 12, 18, and 24 months: parents complete a telephone survey.



Meet Our Parent Partners and New Site Investigators

"Understanding how long to continue seizure medications after neonatal seizures, and how neonatal seizures and their treatments impact parent well-being, are pressing questions for our field. We are delighted to join as a site for this important study, and look forward to working with all of you."

–Monica Lemmon, MD (Duke University)

"As a parent of an adult son suffering from an uncontrolled seizure disorder, I feel blessed to be given the opportunity to support neonatal seizure research which will help guide younger parents as they begin caring for their child. As Always for My Christopher…"

–Lisa Grossbauer (Children's Hospital of Philadelphia NSR Parent Partner)

Education Corner

Epilepsy and Infantile Spasms after Neonatal Seizures

Most children with neonatal seizures will never have another seizure. Studies estimate that 75% (3 in 4 children) do not develop epilepsy. Unfortunately, we don't know how to accurately tell which babies will go on to have more seizures. This is why more research is needed.

Epilepsy is tendency toward "out of the blue" (unprovoked), recurrent seizures. These seizures usually begin months or years after the initial newborn seizures subside. Epilepsy may be diagnosed via an EEG test, descriptions of the seizures, or videos of the episodes.

Infantile Spasms is a rare type of epilepsy that occurs in less than 10% (1 out of 10) of children with neonatal seizures. Spasms usually have their onset before 1 year of age (average age is 4 months, range 1 month to 2 years). Spasms can have a subtle appearance (for example head drops or body "crunches" that occur in clusters), so it may be difficult for parents to recognize that it is a serious problem. Spasms are sometimes mistaken for startle reflex, colic or reflux. It is very important to recognize that a child has infantile spasms as soon as they begin because specific medications can control the spasms and the longer the spasms last before they are controlled, the higher the chance of developmental disability. An EEG is always used to help diagnose infantile spasms. Most children with spasms will have a very abnormal EEG pattern called hypsarhythmia. Infantile spasms may come before other types of seizures or may come after a child has other seizures.

References: http://www.childneurologyfoundation.org/disorders/epilepsy/ ***and*** http://www.childneurologyfoundation.org/disorders/infantile-spasms/

Funding update! The *Neonatal Seizure Registry* recently received funding from the Pediatric Epilepsy Research Foundation (PERF) to study risk factors for infantile spasms in children who had neonatal seizures. We hope to predict which children are at highest risk so that we can diagnose and treat spasms rapidly and eventually start trials of new medications to prevent this type of epilepsy.

NSR NEONATAL SEIZURE REGISTRY

Volume 1 | Issue 3

Spring 2018

Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study

~ *funded by Patient Centered Outcomes Research Insititute (PCORI)* ~

Welcome to our third newsletter for the ***Neonatal Seizure Registry (NSR)***. We are pleased to announce that we have met and exceeded our recruitment target and have 305 babies and their families enrolled in the study! We will continue to follow participants to the 24-month time-point and are in the preliminary stages of baseline data analysis. We will continue to update you as our analyses uncover new findings.

Our Work

There is not enough high quality research to tell doctors the best way to treat seizures in babies. Different doctors have different approaches. Our goal is to figure out the safest and most effective way to treat newborns with seizures. We also want to understand how the medical treatments for newborn seizures can impact families as their children grow. We are working with the Patient Centered Outcomes Research Institute (PCORI) to carry out a large, multi-site observational study to better understand how to treat seizures in newborns. Our nine participating hospital sites and Parent Partners span from coast to coast:

PARTICIPATING HOSPITALS

UCSF Benioff Children's Hospital
Hannah Glass, MD, MS
Parent Partner: Kamil Pawlowski
Mott Children's Hospital
Renée Shellhaas, MD, MS
Parent Partner: Libby Hill
Lucille Packard Children's Hospital
Courtney Wusthoff, MD, MS
Parent Partner: Gwen Ma
Children's Hospital of Philadelphia
Nicholas Abend, MD, MS
Parent Partner: Lisa Grossbauer
Children's National Medical Center
Taeun Chang, MD
Parent Partner: Dana Annis
Massachusetts General Hospital
Catherine Chu, MD, MS
Parent Partner: Tristan Baraka
Boston Children's Hospital
Janet Soul, MD
Parent Partner: Jennifer Guerriero
Duke University
Monica Lemmon, MD
Parent Partner: Terri Long
Cincinnati Children's Hospital Medical Center
Cameron Thomas, MD, MS
Parent Partner: Katie Grant

AFFILIATE ORGANIZATIONS

Hand to Hold
Parent Partners: Claire Brown
Parent Partner: Karla Contreras
Casey Circle
Parent Partner: Marty Barnes

What happens in the study:
At 3 months: A clinic visit for children to receive an EEG and parents to complete a survey.
At 12, 18, and 24 months: parents complete a telephone survey.

MOVING?

Don't forget to contact your local study coordinator to update your contact information.

Your Participation Matters

"It is a privilege being a part of this multi-site study in which we are able to communicate so directly with our parent partners. What we learn is so much more useful when we keep the patient and family perspective front and center. It is exciting to already be seeing results and we look forward to learning even more as the data continues to be gathered and analyzed. What we have learned so far will be shared at national meetings in the coming months and is certain to generate a lot of excitement and discussion in this field. Among our study investigators, we are already discussing the impact of what we are learning and how this can provide the best and most accurate information to families and guide future research. We appreciate the patience and consistency that our families show in their continued participation with the study over time. We are hopeful that we can continue to learn from the wonderful patients and families enrolled in this study as this phase is completed and for many years to come."

– Cameron Thomas, MD, MS (Cinncinatti Children's Hospital Medical Center)

"When our newborn daughter, Tosca, had a stroke followed by seizures, my wife and I were stunned, scared, and totally bewildered. Having access to the resources being developed by the Neonatal Seizure Registry would have made an enormous difference, which is why I'm thrilled to be a member of its Parent Stakeholder Advisory Panel. Being involved with the NSR has also shown me the critical importance of collecting longitudinal data, as well as the great value of regular communication between clinical researchers and the parents of children suffering from seizures."

– Tristan Barako (Massachusetts General Hospital NSR Parent Partner)

Next Phase

A Message from the Lead Investigators:

"As we follow these infants and their families through the first two years of their lives, we will learn about how the neonatal seizures and their treatment influence child development, later seizures, and family well-being. We hope the results of this work will help doctors and families of newborns with seizures as they make treatment decisions and will provide clear information about what to expect for the future."

– Renée Shellhaas, MD, MS and Hannah Glass, MD, MS (Co-Principal Investigators)

Future Applications:

We are in the process of writing grant applications to receive funding to extend the follow up period within this cohort. Parents have told us they are keenly interested in identifying predictors for early school age development outcomes at 4-6 years old. We are excited to partner with you to answer these questions and will keep you updated in the coming months!

Contact for Future Research: This research is only possible because of the willingness of our families. We are grateful for your ongoing participation and hope that you continue with the same enthusiasm moving forward.

For more information about the study, please visit our website:

https://www.pcori.org/research-results/2016/continued-anticonvulsants-after-resolution-neonatal-seizures-patient-centered

NSR NEONATAL SEIZURE REGISTRY

Volume 1 | Issue 4

Fall 2018

Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study

~ funded by Patient Centered Outcomes Research Insititute (PCORI) ~

Welcome to our fourth newsletter for the ***Neonatal Seizure Registry (NSR)***. As many of you already know, we exceeded our enrollment target in March and have now completed all 3-month EEGs! We will continue to follow participants at 12, 18, and 24-month time-points and are in the preliminary stages of baseline data analysis. We will update you as our analyses uncover new findings.

PARTICIPATING HOSPITALS

UCSF Benioff Children's Hospital
Hannah Glass, MD, MS
Parent Partner: Kandi Pawlowski

Mott Children's Hospital
Renée Shellhaas, MD, MS
Parent Partner: Libby Hill

Lucile Packard Children's Hospital
Courtney Wusthoff, MD, MS
Parent Partner: Gwen Ma

Children's Hospital of Philadelphia
Nicholas Abend, MD, MS
Parent Partner: Lisa Grossbauer

Children's National Medical Center
Tarun Chong, MD
Parent Partner: Dana Annis

Massachusetts General Hospital
Catherine Chu, MD, MS
Parent Partner: Tristan Barsko

Boston Children's Hospital
Janet Soul, MD
Parent Partner: Jennifer Guerrero

Duke University
Monica Lemmon, MD
Parent Partner: Terri Long

Cincinnati Children's Hospital Medical Center
Cameron Thomas, MD, MS
Parent Partner: Katie Grant

AFFILIATE ORGANIZATIONS

Hand to Hold
Parent Partners: Claire Brown
Parent Partner: Karla Contreras

Casey's Circle
Parent Partner: Marty Barnes

Our Work

What is a comparative effectiveness study?

Comparative effectiveness studies are research projects designed to tell us whether one treatment is better than another. Our goal is to figure out the safest and most effective way to treat newborns with seizures. We also want to understand how the medical treatments for newborn seizures can impact families as their children grow.

What types of data are being analyzed?

- Demographics (age, sex, race, mother's education, etc.)
- Imaging (EEGs and MRIs)
- Treatment of seizures (past and/or current medications and how long they were given)
- Cause of seizures (hypoxic-ischemic encephalopathy, stroke, hemorrhage, infection, etc.)
- Parent mental health (depression and anxiety scores)

Our nine participating hospital sites and Parent Partners span from coast to coast:

Partnering Site	Number of Participating Families
UCSF Benioff Children's Hospital	41
University of Michigan C.S. Mott Children's Hospital	54
Lucile Packard Children's Hospital	28
Children's Hospital of Philadelphia	20
Children's National Medical Center	48
Massachusetts General Hospital	25
Boston Children's Hospital	55
Duke University	18
Cincinnati Children's Hospital Medical Center	16

Study Timeline:

At 3 months: A clinic visit for children to receive an EEG and parents to complete a survey.
At 12, 18, and 24 months: parents complete a telephone survey.

Your Participation Matters

"Family well-being is necessary for children to grow and thrive. That is why it is so important to learn more about parent and family well-being during the early years after a child has had neonatal seizures."

– Linda Franck, RN, PhD, FAAN (UCSF Core Study Team)

"As a parent of a child who had a fetal maternal hemorrhage and had a stroke and related seizures, it was very scary and difficult to think about having another child. My husband and I feel so blessed to announce the birth of our new baby, who is loved so much by the older sibling. I am honored to play a role as an NSR parent partner, and I hope other families going through what we went through can benefit from our experience.

–Jennifer Guerrriero, PhD (Boston Children's Hospital Parent Partner)

Upcoming Conferences

The *Neonatal Seizure Registry* team will be presenting two abstracts at the Child Neurology Society annual meeting in Chicago this October. The first presentation will be about our research findings showing that children who continue anti-seizure medication (like phenobarbital) after they go home from the newborn stay receive higher doses of medication and may have slightly longer hospital stays. The second presentation will highlight our findings that many newborns continue to have seizures after the first dose of anti-seizure medication unrelated to whether the baby is born early or not, or type of medication. However, we did find that children who receive cooling therapy and have low seizure burden may be more likely to respond to the first dose of medicine. These are very exciting preliminary results and we are pleased to share them with other child neurology specialists at the conference. We hope to have more results that will improve young children's anti-seizure treatment as the study continues – and we will share those findings with you.

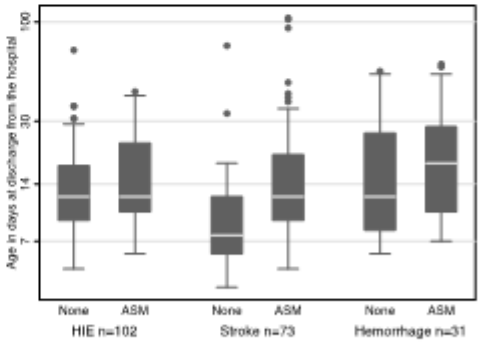


Figure: Newborns who stay on anti-seizure medication (ASM) after the newborn stay may be more likely to have a longer length of stay.

For more information about the study, please visit our website:

https://www.pcori.org/research-results/2016/continued-anticonvulsants-after-resolution-neonatal-seizures-patient-centered

NSR NEONATAL SEIZURE REGISTRY

Volume 1 | Issue 5

Spring 2019

Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study

~ funded by Patient Centered Outcomes Research Insititute (PCORI) ~

PARTICIPATING HOSPITALS

UCSF Benioff Children's Hospital
Hannah Glass, MDCM, MAS
Parent Partner: Kamil Pawlowski

Mott Children's Hospital
Renée Shellhaas, MD, MS
Parent Partner: Libby Hill

Lucille Packard Children's Hospital
Courtney Wusthoff, MD, MS
Parent Partner: Gwen Ma

Children's Hospital of Philadelphia
Nicholas Abend, MD, MS
Parent Partner: Lisa Grossbauer

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Taeun Chang, MD
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Massachusetts General Hospital
Catherine Chu, MD, MS
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Boston Children's Hospital
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Parent Partner: Jennifer Guerriero

Duke University
Monica Lemmon, MD
Parent Partner: Terri Long

Cincinnati Children's Hospital Medical Center
Cameron Thomas, MD, MS
Parent Partner: Katie Grant

AFFILIATE ORGANIZATIONS

Hand to Hold
Parent Partners: Claire Brown
Parent Partner: Karla Contreras

Casey's Circle
Parent Partner: Marty Barnes

Study Progress:

3-mo EEG ✓

12-mo ✓

18-mo Pending...

24-mo Pending...

Welcome to our fifth newsletter for the ***Neonatal Seizure Registry (NSR)***. This time last year we welcomed the last family into the study and in April 2019 all participants will have completed their 1-year follow-up! We will continue to follow participants at 18 and 24-month time-points. While we are working toward those milestones, we are in the early stages of analyzing the data from the first time points, sharing those findings, and writing new proposals for funding to continue learning more about neonatal seizures and their effect on child development and family well-being. We will update you about what we learn as we go.

Our Work

Pictured from left to right: Dr. Shavonne Massey (Children's Hospital of Philadelphia), Dr. Nicholas Abend (Children's Hospital of Philadelphia), Dr. Janet Soul (Boston Children's Hospital), Dr. Renée Shellhaas (Mott Children's Hospital), Dr. Hannah Glass (UCSF Benioff Children's Hospital), Dr. Taeun Chang (Children's National Medical Center), Dr. Adam Numis (UCSF Benioff Children's Hospital).

This past October, hundreds of child neurologists and other professionals gathered in Chicago, IL for the 47th annual Child Neurology and Society (CNS) Conference. The *Neonatal Seizure Registry* team presented three abstracts: "**EEG Monitoring and Seizure Characteristics of the Neonatal Seizure Registry Cohort of Neonates with Severe Cardiopulmonary Disease,**" "**Seizure Management and Medication Efficacy in the Neonatal Seizure Registry Cohort of Neonates with Severe Cardiopulmonary Disease**" and "**Response to Anti-Seizure Medication in Neonates with Acute Symptomatic Seizures.**" Our study team is dedicated to advancing knowledge about the safety and effectiveness of treating seizures in newborns and understanding how the medical treatment impacts families.

Data Analysis – What is it like for parents of babies who have neonatal seizures?

We are learning a lot from our first look at the data collected so far. At discharge from the hospital, parents answered questions about their views and experiences of caring for their baby and its impact on their baby and family. Four themes were identified from the 144 parents who participated in the first survey:

- ***Sources of strength*** (91% of parents): Families highly valued medical team consensus and opportunities to contribute to their child's care. Parents shared that bonding with their baby, and witnessing their developmental and medical progress, brought them joy and hope.
- ***Uncertainty*** (72% of parents): Parents described three primary types of uncertainty, all of which caused distress: 1) the daily uncertainty of the intensive care experience, 2) concerns about their child's uncertain future, and 3) lack of consensus between members of the medical team.
- ***Adapting family life*** (67% of parents): Parents described the many ways in which their baby's condition led to adaptations in their family life, including adjusting their family's lifestyle, parenting approach, and routine. Many parents described financial and work challenges due to caring for a child with medical complexity.
- ***Emotional and physical toll*** (62% of parents): Parents shared their worries, concerns, and fears. Many felt helpless in the face of their child's complex early medical course.

In conclusion, parents of babies with seizures face challenges as they adapt to and find meaning in their role as a parent of a child with medical complexity. Despite these challenges, nearly all parents identified sources of strength. Our next steps are to widely share these findings with healthcare professionals caring for babies with seizures and their families and work with them to develop and test new ways to support parents and promote resilience.

THANK YOU

"Program officers from our sponsor (PCORI) are very pleased with the overall progress and high retention rates of our cohort. These achievements are only possible through the willingness and participation of our families. We cannot do this work without your involvement and support. Thank you for your continued participation and for joining the NSR Family!"

-Renée Shellhaas, MD, MS and Hannah Glass, MDCM, MAS (Co-Principal Investigators)

For more information about the study, please visit our website:
https://www.pcori.org/research-results/2016/continued-anticonvulsants-after-resolution-neonatal-seizures-patient-centered

NSR NEONATAL SEIZURE REGISTRY

Volume 1 | Issue 6

Fall 2019

Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study

~ funded by Patient Centered Outcomes Research Insititute (PCORI) ~

PARTICIPATING HOSPITALS

UCSF Benioff Children's Hospital
Hannah Glass, MDCM, MAS
Parent Partner: Kamil Pawlowski

Mott Children's Hospital
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Parent Partner: Libby Hill

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Parent Partner: Terri Long

Cincinnati Children's Hospital Medical Center
Cameron Thomas, MD, MS
Parent Partner: Katie Grant

AFFILIATE ORGANIZATIONS

Hand to Hold
Parent Partners: Katrina Moline

Casey's Circle
Parent Partner: Marty Barnes

Study Progress:

3-mo EEG ✓

12-mo ✓

18-mo ✓

24-mo Pending...

Welcome to our sixth newsletter for the ***Neonatal Seizure Registry (NSR)***. We have now completed all 12 and 18-month follow up! While we continue to follow participants to the final 24-month time-point, we are analyzing data and applying for grant funding to continue learning more about neonatal seizures and their effect on child development and family well-being. We are grateful for our team of investigators, parents, and families that have made this work possible and are excited for the future of this project.

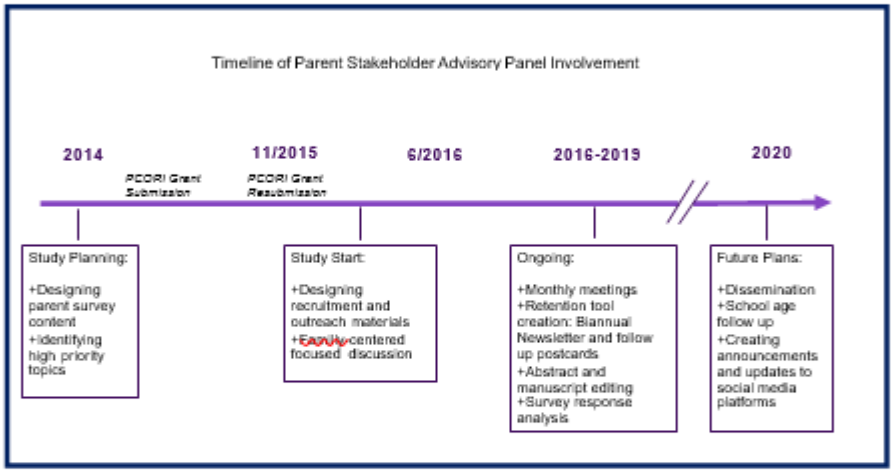
Our Work

Pictured from left to right: Dr. Cameron Thomas (Cincinnati Children's Hospital Medical Center), Dr. Hannah Glass (UCSF Benioff Children's Hospital), Dr. Linda Franck (UCSF Benioff Children's Hospital), Dr. Taeun Chang (Children's National Medical Center), Dr. Adam Numis (UCSF Benioff Children's Hospital), Dr. Monica Lemmon (Duke University), Dr. Janet Soul (Boston Children's Hospital), Dr. Nicholas Abend (Children's Hospital of Philadelphia), Dr. Renée Shellhaas (Mott Children's Hospital), Dr. Shavonne Massey (Children's Hospital of Philadelphia).

In April of 2019, the annual Pediatric Academic Societies Meeting (PAS) meeting in Baltimore MD united thousands of pediatricians, researchers, and academics from across the USA and abroad in a shared mission to enhance childhood health. Ten investigators from the *Neonatal Seizure Registry* met for a working dinner to discuss preliminary results, ancillary studies, and grant proposals.

Parent and Stakeholder Involvement

Our Parent Partner Panel has been a unique and invaluable component of our team since the study's inception. Each of our eleven parent advisors has personally experienced caring for a child with neonatal seizures. Their authentic input keeps us focused on family priorities and helps us relate and communicate with participants. Parent Partners work with us to share our findings with families and care providers. As the study evolves, Parent Partners are actively involved in data analysis and interpretation of parent survey responses. As a result of their important contribution, members from the Panel will present a poster detailing their engagement and how this involvement has contributed to the success of the study at our sponsor's (PCORI) Annual Meeting in Washington DC in September 2019. With the help of the Parent Panel, the overall retention rate has been 86% or higher throughout the study.



Upcoming Conferences and NSR Presentations

Child Neurology Society (CNS) *Charlotte, NC – October 2019*

+ Parent Experience of Caring for Neonates with Seizures
+ Characteristics of Neonatal Seizures Related to Intracranial Hemorrhage in Term Neonates: A Study of the *Neonatal Seizure Registry*

American Epilepsy Society (AES) *Baltimore, MD - December 2019*

+ Seizure characteristics of neonates with severe cardiopulmonary diseases in the *Neonatal Seizure Registry*
+ Neonatal EEG Monitoring Strategy is Associated with Better Seizure Control
+ A New Risk Prediction Tool for Infantile Spasms after Acute Symptomatic Neonatal Seizures

Our study team has remained devoted to our initial goal – to figure out the safest and most effective way to treat newborns with seizures and understand how the medical treatments for newborn seizures can impact families as their children grow. We will continue to update you as we learn more!

For more information about the study, please visit our website:

https://www.pcori.org/research-results/2016/continued-anticonvulsants-after-resolution-neonatal-seizures-patient-centered

Volume 1 | Issue 7

Spring 2020

PARTICIPATING HOSPITALS

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Parent Partner: Libby Hill

Lucile Packard Children's Hospital
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Cameron Thomas, MD, MS
Parent Partner: Katie Grant

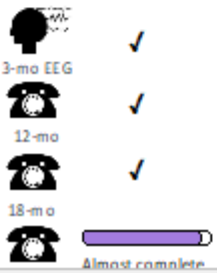
AFFILIATE ORGANIZATIONS

Hand to Hold
Parent Partners: Claire Brown

Casey's Circle
Parent Partner: Marty Barnes

Hope for HIE
Parent Partner: Betsy Pilon

Study Progress



Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study

~ *funded by Patient Centered Outcomes Research Insititute (PCORI©)* ~

Welcome to our seventh newsletter for the ***Neonatal Seizure Registry (NSR)***. As we wrap up our final follow-ups and plan our data analyses, we have exciting news to share! We have learned that the National Institutes of Health has funded our early childhood follow-up study, which we are calling "*Neonatal Seizure Registry – Developmental Functional Evaluation*" or *NSR-DEV*. This means that we will have four more years of funding to answer your important questions about early childhood outcomes after neonatal seizures.

NSR-DEV Details

Our Parent Partners helped us identify 3 key research priorities for this study:

1. Neonatal or infant predictors of developmental and learning challenges in childhood
2. Characteristics of parent well-being that help or hinder success in childhood
3. Early, easily applied, accurate methods to predict childhood impairment

NSR-DEV will work to address these priorities by conducting 3 or 4 additional follow ups over the next four years. These will occur in person and through electronic surveys when children reach the ages of 3 to 8 years.

	NSR-DEV Follow Up Time Points					
Study Measurement	Enrollment	3 years	4 years	5.5 years	7 years	8 years
Medical history review	X	X	X	X	X	X
Parent well-being surveys	X	X	X	X	X	X
Developmental surveys	X	X	X	X	X	X
In-person assessment				X		
Teacher rating forms				X		

Your local teams will be in contact with more information soon!

Featured Work

At the 2019 meeting of the Child Neurology Society, *NSR* Investigator Monica Lemmon presented the four major themes from the analysis of the neonatal discharge survey.

"Thank you for providing such important information about the parent experience of caring for newborns with seizures. It was a privilege to share these experiences with the child neurology community." – Monica Lemmon

1. ***Sources of strength***
- Medical team consensus
- Opportunities to contribute to child's care
- Watching child's progress

2. ***Uncertainty***
- Daily uncertainty of the NICU experience
- Uncertain future
- Lack of consensus between team members

3. ***Adapting family life***
- Adjusting the family's lifestyle
- Adjusting parenting approach and routine
- Anticipated financial and work challenges

4. ***Emotional and physical toll***
- Parents reported worry, fear, stress, and helplessness

Parent and Stakeholder Engagement

NSR welcomes Hope for HIE president Betsy Pilon. Hope for HIE is deeply committed to providing comprehensive, personalized support for each family's journey. We are fortunate to have Betsy on our team!

"*So many of our families in the HIE community struggle with the experience they have in the NICU, with neonatal seizures as one of the most stressful complications from HIE. This research is vital to helping our community, and those that will join in the future, get the best treatment and resources for their journey ahead.*"-Betsy Pilon

Parent Partner Lisa Grossbauer will join the *NSR* team in Philadelphia at the Pediatric Academic Societies annual meeting, where we will engage participants in a discussion on "*Studying what matters: How to engage parents in research.*" Lisa will join *NSR* investigators and representatives from PCORI and NIH for this workshop.

"I am very proud and humbled to represent such a devoted team of family stakeholders at the Pediatric Academic Societies annual meeting in Philadelphia. As Children's Hospital of Philadelphia's family partner representative, it will be "extra special" to share our story with dedicated physicians, and researchers in hopes of planting a seed of thought with regards to family contributions to valued research in pediatrics." -Lisa Grossbauer

Our study team has remained devoted to our initial goal – to figure out the safest and most effective way to treat newborns with seizures and understand how the medical treatments for newborn seizures can impact families as their children grow. We will continue to update you as we learn more!

For more information about the study, please visit our website:

https://www.pcori.org/research-results/2016/continued-anticonvulsants-after-resolution-neonatal-seizures-patient-centered

NSR NEONATAL SEIZURE REGISTRY

Volume 1 | Issue 8

Summer 2020

Continued Anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study

~ funded by Patient Centered Outcomes Research Institute (PCORI©) ~

Welcome to our eighth newsletter for the ***Neonatal Seizure Registry (NSR)***. This is the final newsletter for the *"Continued anticonvulsants After Resolution of Neonatal Seizures: A Patient-Centered Comparative Effectiveness Study"* (*NSR-II*). We are excited to share the preliminary *NSR-II* study results with you!

We are grateful for your participation in this study and look forward to working with you on our follow-up study "*Neonatal Seizure Registry – | Developmental Functional EValuation" (NSR-DEV).*

Main Findings about Treatment Duration (preliminary)

1. Anti-Seizure medications (usually phenobarbital) were stopped during the hospital stay after about 6 days for 36% of children ("short duration") and continued for about 4 months in 64% of children ("long duration").
2. Newborns who had a lot of seizures, complex clinical course, and abnormal neurological exam at hospital discharge were more likely to receive long duration phenobarbital.
3. The risk for abnormal development or epilepsy was the same in the short and long treatment duration groups. *This suggests that short treatment duration is safe.*

Based on these findings, we will encourage all centers to adopt a "short duration" approach for most newborns with acute neonatal seizures.

Want to know more? Register now to see these results presented by video link to the 2020 Pediatric Academic Societies annual meeting on July 28, 2020: https://2020.pas-meeting.org/webinar-events-calendar/

View the talk, which will be posted online at the same website after the live presentation.

Other opportunities: All study investigators plan to present the work at their local centers during the upcoming academic year.

PARTICIPATING HOSPITALS

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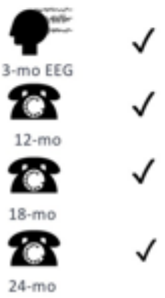
Hope for HIE

Study Progress



Findings about Parent Well-Being

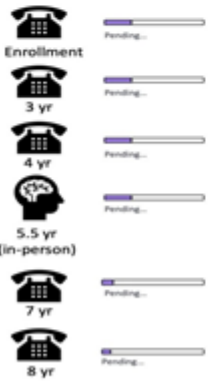
1. *Parent and family well-being can suffer when newborns have seizures:* Symptoms of anxiety and depression are common and several parent and infant characteristics are associated with poorer parental quality of life and family well-being. *These findings are a call to action to improve mental health screening and services for parents of infants with neonatal seizures.*
2. *Parent experience of caring for neonates with seizures*: Parents shared key challenges at the time of NICU discharge, including navigating uncertainty, adapting family life, and the processing the emotional and physical toll of the NICU experience. Parents also emphasized sources of strength, including agreement among team members, developing a parent-child bond, and participating in their child's medical care.
3. *Advice for clinicians*: Parents offered advice for members of the health care team in 3 key areas: 1) Understand and validate the parent experience, 2) Communicate information effectively, and 3) Provide support and resources.

Next Steps: Working with our Parent Partner Advisory Panel, we are looking at how parent and family well-being changed over the 2-year study period. We will report those results soon, and them propose new interventions to support parents and families.

NSR-DEV: Let's now work together to learn more about longer term outcomes

Our Parent Partner Advisory Panel helped us identify 3 key priorities for this study:

1. Early predictors of developmental and learning challenges in childhood
2. Features of parent well-being that help or hinder success in childhood
3. Early, easily applied and accurate methods to predict childhood impairment after neonatal seizures



	NSR-DEV Follow Up Time Points					
Study Measurement	**Enrollment**	**3 years**	**4 years**	**5.5 years**	**7 years**	**8 years**
Medical history review	X	X	X	X	X	X
Parent well-being surveys	X	X	X	X	X	X
Online neurodevelopmental assessments	X	X	X	X	X	X
In-person neurodevelopmental assessments				X		

Your local team will be in contact with more information soon!

NSR-DEV Enrollment begins

Families are already enrolling in NSR-DEV! **Join us today**

For more information about the study, please visit our website: http://neonatalseizureregistry.ucsf.edu/

Disclaimer:

The [views, statements, opinions] presented in this report are solely the responsibility of the author(s) and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute® (PCORI®), its Board of Governors or Methodology Committee.

Acknowledgment:

Research reported in this report was funded through a Patient-Centered Outcomes Research Institute® (PCORI®) Award (CER-1507-31187). Further information available at: https://www.pcori.org/research-results/2016/looking-effect-treatment-duration-newborn-infants-who-have-seizures