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

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RESEARCH STRATEGY

A. Background

Seizures affect ~16,000 newborns/year in the United States and have lasting adverse impacts on affected children and their families. About 15% of newborns with seizures die, and at least 50% of survivors have one or more long-term disability, 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 12-18 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 non-remittance (lack of complete response to medications)[4]. As such, neonatal seizures have a major impact, not only on the health of newborn infants, but also on their long-term neurological morbidity and chronic epilepsy [Criterion 1].

Despite the wide-ranging impacts of seizures in the newborn, alarmingly significant knowledge gaps persist [RQ-1]. The current management paradigm for neonatal seizures is to treat clinical events, with or without confirmation of EEG seizures, which can lead to both under- and over-treatment. Phenobarbital, the most commonly prescribed anticonvulsant, is often maintained for several months because of clinicians' and parents' concern that early discontinuation of medicine might cause seizures to recur[5]. 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[6,7]. Preliminary evidence suggests that early discontinuation of medication is not harmful,[5,6,8] but the optimal duration of therapy remains unknown.

Parents of infants with neonatal seizures, including those involved in this proposal, highlight the lack of certainty regarding treatment duration as a major concern. The proposed PCORI-funded research will provide critical data, where very little currently exist, to guide key decision-making for clinicians and families of these highly vulnerably 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.

> *"The question of… how long to continue phenobarbital after neonatal seizures is one that weighs heavily on families."*
>
> - Libby Hill, MD, Parent Partner and Pediatrics Resident

No published studies examine the impact of anticonvulsant treatment on parent/family well-being. A few studies have focused on parents' experience after their infant's discharge home from the NICU[9]. Parents of preterm and term infants may experience apprehension, 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 over time gain perspective about their experience. However, approximately one-third of parents will experience post-traumatic stress (PTSD) related to their child's hospitalization, and this has a negative impact on the family[10,11]. It is unknown whether ongoing anticonvulsant treatment contributes to difficulties in parent and family functioning.

According to the FDA and NINDS, understanding the best management for neonatal seizures is a priority. In 2005 and 2007, the FDA and NINDS sponsored workshops on improving treatment of neonatal seizures. There was a consensus that "*high priorities for research included investigations to understand adverse effects of [anti-seizure medications] and… to determine the relationship between efficacy for seizure suppression and long-term outcome*"[12]. Nearly 10 years later, the neonatal neurology community has failed to address either priority.

Although the NIH is interested in neonatal seizure management, traditional research approaches have failed to answer important questions. In 2009, the NICHD funded a multi-center, randomized, double blind, placebo-controlled trial *to examine the very question we pose* by randomizing neonates with seizures that resolved within 7 days to receive phenobarbital or placebo for four months (PROPHENO, NCT01089504). Although adequate numbers of potential subjects 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 conclude that another randomized trial is not feasible. Yet, a well-conceived, large-scale observational study with a

propensity score analysis strategy can provide the needed data and causal inference to answer the question of the optimal duration of medical treatment for neonatal seizures. Dr. Guillet (PROPHENO's PI) is a consultant for our proposal and has endorsed the present study's scientific design. *The clinical question, family centered design, and comparative effectiveness methods that we now propose are well aligned with PCORI priorities.*

The *Neonatal Seizure Registry* (PI Glass) is an established, multi-center collaborative of top pediatric hospitals from across the United States that is poised to answer the question of optimal duration of seizure medication through a comparative effectiveness study. The *Neonatal Seizure Registry* was established in 2012 with seed funding from the Pediatric Epilepsy Research Foundation. Unique among neonatal seizure studies, the *Neonatal Seizure Registry* is enrolling newborns at 7 American Children's Hospitals, *all of which* have the capability to perform long-term neonatal EEG monitoring and world-class pediatric neurology follow-up. The *Neonatal Seizure Registry* has collected data on more than 480 consecutive newborns to examine etiology and management of seizures in the immediate, neonatal period. The registry is currently not funded or structured to collect personal health information (PHI), or to follow patients prospectively for neurodevelopmental outcomes. With funding from PCORI, we will prospectively gather consent from families to allow collection of important PHI, and to initiate standardized follow up including EEG studies, neurodevelopmental evaluations, assessments for epilepsy, and measures of parent and family well-being.

Due to the dearth of evidence, substantial practice variability continues for neonatal seizures. Among 488 newborns enrolled in the *Neonatal Seizure Registry*, 364 had seizures due to an acute symptomatic cause and survived until the time of discharge. The registry data regarding phenobarbital treatment duration reflect two main clinical practices: 1) short duration (whereby medication is discontinued prior to discharge from hospital); *versus* 2) prolonged duration (whereby medication is continued 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 medication discontinued prior to discharge (range by site: 3-75%), while 77% continued on seizure medication. Phenobarbital was the most commonly prescribed anticonvulsant (89% of those maintained on medications). Although the *Neonatal Seizure Registry* sites are similar in patient acuity and conditions treated, the approach to neonatal seizures differs across sites and between providers at each site. In adjusted analyses that include seizure etiology, seizure burden, and maximum phenobarbital levels, *the study site was the only independent predictor of discharge to home with continued seizure medication* after resolution of acute symptomatic neonatal seizures ($p<0.001$). The present proposal will take advantage of this heterogeneity in practice to fill critical knowledge gaps regarding appropriate treatment duration for neonatal seizures.

B. Significance

Seizures affect ~16,000 newborns/year in the United States. Neonatal seizures can have substantial, lasting adverse impacts, not only for the affected children, but also for their parents and siblings. Seizures in neonates carry a high mortality rate, and at least 50% of survivors have one or more long-term disability, such as cerebral palsy, intellectual disability, and/or epilepsy[1] [Criterion 1]. For any major health condition, understanding the correct treatment choice and the ideal length of treatment is critical. Phenobarbital has been the mainstay of neonatal seizure treatment for decades, even though it is incompletely effective and has substantial side effects. How long to treat a baby with phenobarbital remains an open question [RQ-1], and this leads to significant practice variability[5]. This variability is clearly reflected in preliminary data from the *Neonatal Seizure Registry* – odds of discharge without medication vary substantially by study site ($p<0.001$). Animal models and observational studies of human neonates raise concern that ongoing seizures harm the developing brain[13]. Yet, prolonged treatment with phenobarbital may have neurodevelopmental consequences[6,7]. Our proposal is designed to determine whether the duration of treatment has an impact on long-term neurodevelopment and the incidence of post-neonatal epilepsy for newborns with seizures. The results are expected to bring about substantial changes in clinical care, and will lead to meaningful improvements in healthcare and outcomes for newborns with acute symptomatic seizures. [Criterion 2; RQ-3]

The questions we seek to address through this proposal are highly relevant to parents [Criterion 4]. With our collaborators at *HandtoHold.org*, our Parent Partner Libby Hill posted a survey requesting parent input regarding the impact of neonatal seizures, the effect of seizures and their treatment on families, and research

priorities for neonatal seizures. Within 7 days, 153 parents responded. On a scale of 0 to 10 (0= no impact, 10= very significant impact), parents responded that neonatal seizures had a major effect on their families (mean 7.8±3.2 out of 10) and, importantly, that medications to treat seizures were almost as impactful as the seizures themselves (rated 6.7±3.0). Of 81 parents who typed in their infants' treatments, 73 indicated their infant received phenobarbital. Parents indicated major concerns about medication side effects and worries about long term effects of medications on neurodevelopment. In free text responses, 72 provided feedback on priorities for research. Many highlighted the duration of therapy as a top priority research topic – "*Does the child need to continue on meds and for how long?" "Do transient seizures… warrant the same preventative treatment?" "Are we over medicating these babies to prevent something that might never even happen?" "How fast should medicine be weaned?"*

Furthermore, respondents wrote that sedating medications have an impact on the whole family. From one mother: "*Luckily they took pictures before the seizure so that I was able to see her eyes, but I did not see them in person until she reopened them around 1 month…*" Dr. Libby Hill, a Parent Partner who is both a pediatrician in training and the mother of an infant with neonatal seizures, wrote: "*getting home and trying to get into a routine of what will become the new normal for our family was definitely important. It's hard to bond with your baby (and probably therefore hard to foster his/her development) in a NICU [neonatal intensive care unit].*"

We presented the proposed study to the Patient and Family Research Council at the University of Michigan's Child Health Evaluation and Research Unit (CHEAR, www.chear.org). The council consists of patients and parents of patients with a variety of childhood conditions who review research proposals and provide feedback to investigators so that they may incorporate patient and family perspectives into their research design.

> *"[The proposed study] allows individual doctors and families to make individual decisions, and still lets the researchers learn the information we need."*
>
> - Patient and Family Research Council, University of Michigan

Parents and patients were unanimous in their support of the proposed study question, design, and outcome measures. [Criterion 4]

C. Study Design or Approach

Specific Aims

Neonatal seizures that are due to brain injury (acute symptomatic seizures) are difficult to treat, harm the developing brain, and are associated with long-term neurodevelopmental disabilities, including intellectual disabilities, autism, epilepsy, and cerebral palsy[1]. Although acute symptomatic seizures are self-limited in the neonatal period, ≥20% of patients will go on to develop epilepsy (the neonatal seizures resolve, but the infant develops recurrent, unprovoked seizures later in life) and the highest risk is in the first year of life. Recommendations for immediate treatment of neonatal seizures are based largely on pre-clinical studies which show that seizures are injurious to the developing brain through alterations in neurogenesis, neuronal loss, and excitability[13-16]. However, traditional and commonly used anticonvulsant medications, such as phenobarbital, are potentially neurotoxic[17] and are associated with lower cognitive scores when used long-term[6,7]. Despite this, phenobarbital, the most commonly prescribed first line medication[18], is often administered for up to several months, even without electrographic confirmation of seizures[5]. A randomized, controlled trial to examine the risks and benefits of continued treatment with phenobarbital following resolution of acute symptomatic seizures (PROPHENO - NCT01089504) failed due to lack of enrollment. The fundamental management question of how long to treat seizures in the neonatal period remains unanswered. Thus, *a large-scale observational study is urgently needed, to inform the critical decision regarding duration of treatment for acute symptomatic neonatal seizures*[19].

Our *long-term goal* is to improve neurodevelopmental outcomes following acute symptomatic seizures in newborns. The *objective of this application* is to examine whether the duration of treatment with phenobarbital has an impact on neurodevelopmental and epilepsy outcomes, as well as parent and family well-being, after neonatal seizures. Our collaborative research team has established the *Neonatal Seizure Registry* - a multi-center association of institutions across the United States - and has partnered with Parent Partners and

NICU Patient & Parent Advocacy groups to develop the patient centered questions and outcomes outlined in this application.

We will take advantage of heterogeneity of treatment duration for acute symptomatic seizures within our *Registry* to *determine the comparative effectiveness* of two common approaches to phenobarbital prescription for treatment of neonatal seizures for 300 enrolled neonates: (1) short duration of treatment (discontinuation of medication prior to discharge from hospital), and (2) prolonged duration of treatment (discontinuation of medication at the time of outpatient follow-up, after discharge from hospital). Importantly, based on specific stakeholder feedback, we will also examine parental and family well-being in both treatment plans. The *central hypothesis* of this application is that the duration of medical management has no impact on neurodevelopmental outcome or the development of post-neonatal epilepsy after acute symptomatic neonatal seizures (Aim 1) but is associated with NICU length of stay (Aim 2) and parent and family well-being (Aim 3).

Aim 1: To determine whether short *versus* prolonged phenobarbital treatment affects (a) neurodevelopmental outcome, and (b) incidence of epilepsy at age 24-months.
Hypothesis: There will be no differences in (a) functional developmental outcome, or (b) incidence of epilepsy between short duration phenobarbital treatment (*i.e.,* seizure medication discontinued prior to discharge home) and prolonged phenobarbital treatment (*i.e.,* medication continued until the time of the first clinical follow up appointment), and results of an electroencephalogram (EEG) during convalescence can be used to predict the risk of epilepsy.
Approach: Cohort study of 300 neonates with seizures due to acute symptomatic causes (*e.g.* hypoxic-ischemic encephalopathy [HIE], stroke, etc.), 150 who are newly enrolled and 150 who were previously enrolled into the *Neonatal Seizure Registry* at one of the established sites across the United States. We propose a propensity adjusted, non-inferiority, *comparative effectiveness study* of the longitudinal cohort enrolled using (a) the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA FS) - a simple, free, one-page assessment to determine functional outcome[20] - and (b) a simple questionnaire[3] to define incidence and modified Engel classification[21] to determine severity of epilepsy; all assessments at 12 , 18, & 24 months of age. *Functional developmental outcome will be the primary outcome for this proposal.*

Aim 2: To determine whether duration of phenobarbital treatment during the NICU admission affects length of hospital stay among neonates with acute symptomatic seizures – a factor highlighted by stakeholders as important for family well-being.
Hypothesis: Longer duration of inpatient phenobarbital treatment is associated with a longer length of stay.
Approach: Adjusted linear regression analysis of the cohort enrolled in Aim 1.

Aim 3: To determine whether short *versus* prolonged treatment affects parent and family well-being.
Hypothesis: Shorter treatment duration is associated with improved parent and family well-being.
Approach: For this exploratory *parent stakeholder-initiated* aim, we will use a parallel convergent mixed methods approach to compare quantitative and qualitative data on parent and family well-being between groups and over time. With our Parent Partners, we selected a set of validated instruments to measure parent and family psychosocial dimensions, including measures of parent quality of life, anxiety and depression, family coping, parent post-traumatic stress and post-traumatic growth. Our Parent Partners also helped us to design a set of open-ended free-text questions to explore the scientific impact of seizure medication on parent and family well-being. Data will be collected at four time points: at discharge, 12 months, 18 months, and 24 months after discharge.

We anticipate that this proposal will yield the following *expected outcomes*: Outstanding data with which to develop evidence-based, rapidly-disseminated management guidelines that address the questions that matter most to parents regarding treatment duration of neonatal seizures. These results will have an important *positive impact* on infants with neonatal seizures, their families, and providers who care for these patients. If giving more phenobarbital does not change the risk of developmental delay or epilepsy, and is acceptable to families, then this study will provide key evidence that shorter treatment duration is safe. In that case, a practice change to shorter treatment duration will eliminate unnecessary exposure to medication. The data generated from this study will, for the first time, allow clinicians and parents to make evidence-based decisions regarding duration of treatment.

Research Strategy [Criterion 3]

Overview of study design. This is a prospective, observational cohort study to examine the comparative effectiveness of short *versus* prolonged treatment of neonatal seizures due to an acute symptomatic cause. To permit causal inference with an observational study design, we will use a propensity score analysis approach. This will account for baseline patient characteristics that influence treatment duration recommendations. For infants with comparable propensity scores, the distribution of observed baseline covariates will be similar between the treatment groups.[22,23]

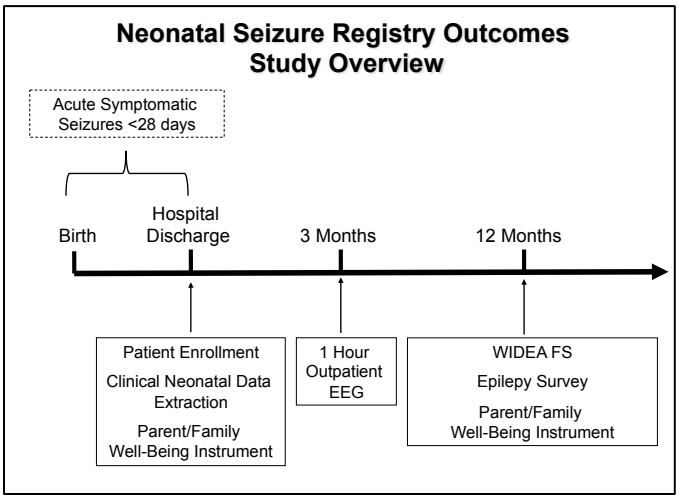

Figure 1: Study overview

Newborns and their families will be enrolled at the seven tertiary children's hospitals that make up the *Neonatal Seizure Registry*. Preliminary data from the *Neonatal Seizure Registry* indicate that there is substantial heterogeneity in treatment, such that some neonates with acute symptomatic seizures are treated for a short duration (seizure medication discontinued prior to discharge home) and some neonates are treated for prolonged duration (medication continued until follow up evaluation at 2-4 months of age or longer), and that this is largely independent of the seizure etiology and severity and most related to study center ($p<0.001$). Through this proposal, we will obtain consent to study outcomes for 150 infants already enrolled in the *Neonatal Seizure Registry* who are still young enough to permit prospective 24-month outcome assessment, and will prospectively enroll an additional 150 newborns with acute symptomatic neonatal seizures. These infants will be enrolled prior to discharge from hospital and evaluated with EEG at age 2-4 months and by telephone and follow-up questionnaires at age 12, 18, and 24months. Validated parent and family well-being instruments will be administered at the time of hospital discharge and again at 12-month, 18-month, and 24-month follow-ups (**Figure 1**).

The study team is uniquely qualified to conduct cutting-edge comparative effectiveness research for neonatal seizures. The co-PIs are highly respected neonatal neurologists with active research programs that are directly relevant to the present proposal and a track record of high quality multidisciplinary research. They have enlisted experienced parent partners and stakeholder collaborators who have both personal and professional experience with research and with neonatal seizures. The team of co-investigators completes this multidisciplinary team, to insure that the work proposed is conducted with the highest level of patient-centeredness, robust study design, and valid statistical analyses.

"[Y]our proposal of a comparative effectiveness study is currently the best opportunity to gain robust data regarding this important question… We anticipate that the data generated through this ground-breaking research could lead to a change in clinical practice."
- American Academy of Pediatrics, Section on Neurology Letter of Support

Subject identification, selection and recruitment [PC-2]. Study personnel at each site will review daily admissions to the Intensive Care Nursery, Pediatric and Cardiac Intensive Care Units, as well as records of patients monitored with long-term EEG, to identify eligible infants. Neonatal seizures affect newborns of both genders and all races and ethnicities. Therefore, no patient will be excluded on the basis of gender, race or ethnicity. A study investigator will contact the parents/legal guardians of eligible patients and, using a consent form approved by the local Institutional Review Board, describe the known risks and benefits of the study. The consent teams will include only experienced study personnel who are sensitive to the vulnerable nature of this population and who will emphasize the voluntary nature of research. All site PIs have extensive experience with patient recruitment for clinical trials and cohort studies. *We expect high rates of enrolment based on feedback from our Parent Partners regarding the importance of the question and the low risk observational nature of the study*. A representative sample of 150previously enrolled infants who are young enough allow for

prospective 24-month follow-up assessments will be contacted by the study sites to request consent for participation in this study. Once a family agrees to participate, study personnel will begin data collection. For prospectively enrolled infants, plans for follow-up appointments will be initiated prior to the family's discharge home from the hospital. Infants at each site are eligible for clinical follow up as outpatients through their respective Pediatric Neurology Clinics and High-Risk Newborn Follow-up Programs, which will help with participant retention.

Plan for developing a formal study protocol [RQ-2]. The co-PIs will finalize the draft of the Manual of Operations, clinical research forms, and consent forms during the first month of the study period. Site investigators from participating centers and our Parent Partners will be invited to provide feedback in writing and/or during a teleconference, and the PIs will incorporate this feedback prior to finalizing the documents. For the parent and family well-being aim (Aim 3), our co-investigator Dr. Franck will work with our Parent Partners to refine the co-developed protocol for measuring parent and family psychosocial dimensions, including administering the validated instruments at the time of initial hospital discharge and at the 12-month, 18-month, and 24-month follow-ups.

Study Procedures (Table 1). (1) Neonatal Clinical Data. Clinical and demographic data will be collected from the hospital charts during the neonatal admission (**Appendix 1**). (2) Follow-up Outpatient EEG. A 1-hour EEG will be obtained at 2-4 months corrected age, and two investigators who are blinded to treatment duration and outcome will score the studies according to published criteria[24,25] (**Appendix 2**). (3) Follow Up. A trained member of the study team, who is blinded to treatment duration, will contact families to administer a validated follow-up instrument to measure functional developmental outcome (The Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA FS)) and follow-up questionnaires to determine the rates and types of epilepsy at 12, 18, & 24 months old(**Appendices 3 & 4**). (4) Parent and family well-being. Validated instruments to measure selected dimensions of well-being and open-ended free-text questions specific to the impact of anticonvulsant treatment impact on parents and families will be administered at the time of hospital discharge and concurrent with the other assessments (**Appendix 5)**.

Table 1: Study Procedures and Measurements.

Study Measurements	**Examples**
Neonatal Clinical Data (Appendix 1)	
- Demographics	Sex, birth weight, gestational age at birth, mode of delivery, etc.
- Seizure etiology	HIE/ischemic stroke/intracranial hemorrhage/intracranial infection/other (based on chart review and neuroimaging findings)
- Seizure characteristics	Presence and frequency of electrographic seizures, including presence of status epilepticus
- Medications administered	Type, dose and timing of each seizure medication during the admission and at the time of discharge home Medication duration measured as short (discontinued prior to or at discharge) vs. prolonged (discontinued after discharge)
3-Month Follow Up (Appendix 2)	
- 1 hr outpatient EEG	Scored by 2 independent EEG reviewers, blinded to patient history
12-18- & 24-Month Follow Ups (Appendices 3 & 4)	
- Functional neurological score	Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA FS) administered by telephone
- Epilepsy evaluation	Epilepsy assessment instrument and modified Engel classification (administered by telephone); epilepsy syndrome characteristics and treatment confirmed through medical record review
Parent Surveys (Appendix 5)	
- Parent and family well-being measurement	A suite of validated instruments and open-ended free-text questions were selected in partnership with our Parent Partners. These will be administered at the time of hospital discharge and at the 12-month, 18-month, and 24-month follow-up.

Selection of comparators [RQ-5]. The primary comparator will be duration of medication use for the treatment of acute symptomatic seizures.

- As described in our analysis below, we will examine duration of phenobarbital as follows:
  - Treatment as a dichotomous predictor (short *versus* prolonged, Aims 1 & 3)
  - Treatment as a continuous predictor (Aim 2)

Preliminary data from the *Neonatal Seizure Registry* support two main patterns of treatment, which will be our comparators:

1. Short duration phenobarbital: Discontinuation of phenobarbital for acute symptomatic neonatal seizures prior to discharge home.
2. Prolonged duration phenobarbital: Continuation of phenobarbital for acute symptomatic neonatal seizures until outpatient follow-up (age 2-4 months).

The selected comparators are relevant to clinicians. The current management paradigm is typically to maintain anticonvulsants 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, which suggests that early discontinuation of medication is not harmful. 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[5,6,8]. Since 85% of term neonates with acute symptomatic seizures are discharged home by 1 month of age (*Neonatal Seizure Registry* unpublished data), and follow up is typically at age 2-4 months, *we expect minimal overlap between the two exposure groups*.

The selected comparators are highly relevant to parents and stakeholders. According to Marty Barnes, mother of a child with seizures since birth, and Kelli Kelley our collaborative stakeholder partner at Hand to Hold, sedating anticonvulsant medications have an impact on the whole family. From a parent whose child had neonatal seizures: *"The decision about continuing phenobarbital weighed heavily on [our family]… was the medicine I was giving my child really for the best?"* The 153 respondents to our online parent survey overwhelmingly indicated concerns regarding immediate side effects (especially sedation) and long-term outcomes (epilepsy and development) for their children who had been treated for neonatal seizures. This was confirmed during focus group discussions with our Parent Partners.

Preliminary data suggest adequate heterogeneity in clinical practice to examine short *versus* prolonged phenobarbital duration within our established multi-center registry. Unpublished data from our *Neonatal Seizure Registry* indicate heterogeneity for neonatal seizure treatment. Among 306 consecutive newborns enrolled in the *Neonatal Seizure Registry* for acute symptomatic seizures who survived to discharge, 23% had medication discontinued prior to discharge (range by site 3 to 75%), while 77% continued on anticonvulsants. In multivariate analyses, *treating institution was the only independent predictor of continued medication after discharge to hom*e ($p<0.001$); neither seizure burden nor etiology of acute symptomatic seizures predicted this treatment decision ($p>0.1$). Phenobarbital was the most commonly prescribed anticonvulsant (89% of those maintained on medication).

Outcome selection [RQ-6]. Our proposed outcome measures are all highly relevant to parent stakeholders. *Primary outcome.* After discussion with Parent Partners, we selected the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA FS), a simple, free, one-page assessment that will be administered by telephone at age 12, 18, and 24 months to determine functional developmental outcome (Aim 1a).[20] In order to administer the WIDEA FS, the examiner (who is blinded to the treatment group) asks the parent a series of questions to determine which specific developmental milestones have been gained in the following domains: Feeding, Dressing, Diaper Awareness, Mobility, Communication, and Social Cognition. The results are tabulated and scored against norms for age for children ages 0-36 months. The WIDEA FS takes about 20-30 minutes to administer, and requires minimal training for the research team. Dr. Rogers (Co-

Investigator) – a neonatologist and developmental pediatrician with extensive experience establishing neurodevelopmental outcomes from clinical trials – will oversee all aspects of the developmental outcome aim. She is trained to use and teach the WIDEA FS, and will train a research coordinator from each site to perform the measure.

We have chosen functional developmental outcome as a primary outcome measure because our Parent Partners, stakeholders, and survey respondents have *all* told us that neurodevelopment and milestones are what matter most to parents in the first year of life: *"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 heart break."* Furthermore, parents value outcome measures that are simple and can be rapidly administered.

We hypothesize no difference in developmental milestones, as measured by the WIDEA FS, between infants who were prescribed short *versus* prolonged duration of phenobarbital. As discussed below, the study is powered as a *non-inferiority analysis* to detect a clinically relevant difference (<7%) on the WIDEA FS. This difference is both clinically meaningful and relevant to parents and stakeholders: in the county of San Francisco, which includes one of the study centers, patients must be at least 33% delayed prior to age 24 months to merit referral for developmental services[26] (e.g. functioning at the level of a 12-month-old when the child is 18-months of age). Therefore a difference of, at most, 7% would fall well below a clinically relevant threshold.

Secondary outcomes.
a) *Epilepsy* (Aim 1b) is one of the most dreaded complications after neonatal seizures. The seizures of newborns with acute symptomatic seizures resolve, but up to 20% will later develop recurrent unprovoked seizures (epilepsy). This pattern is distinct from newborns whose seizures are caused by neonatal-onset epilepsy (those infants are excluded from this study). A history of seizures in the newborn is a major risk factor for non-remittance of post-neonatal epilepsy[4] and many affected children have very difficult-to-treat epilepsy, such as infantile spasms[27]. *Parent survey respondents indicated major concerns about the risk of epilepsy*. If prolonged treatment of acute symptomatic neonatal seizures was shown to decrease the risk of epilepsy, then subtle associated cognitive consequences of the medication might be acceptable to parents, according to our Parent Partners. The members of the University of Michigan Patient and Family Research Council also highlighted the development of early, accurate predictors of unfavorable outcomes as priorities for research.

Therefore, assessment of the incidence of epilepsy, and potential predictors of epilepsy, are priorities for this application. As part of the 12-month, 18-month, and 24-month assessments, parents of enrolled infants will be asked a series of questions designed to discern if the child has developed epilepsy, and if so, what type of epilepsy. Medical records will be reviewed in order to extract detailed data regarding epilepsy syndromes and treatments. All infants will undergo a follow-up 1-hour EEG when they are 2-4 months old. Two board-certified clinical neurophysiologists (Drs. Shellhaas and Wusthoff) who are blinded to the neonatal seizure treatment duration will score the EEG recordings using well-defined, standardized variables (**Appendix 2**), with differences resolved by consensus. The EEG results will be included in the statistical modeling of potential predictors of epilepsy. The study investigators who ascertain the epilepsy and EEG outcomes will be blinded to the treatment group.

b) *Length of stay* (Aim 2) is an important outcome for parents, clinicians and insurance providers. Said one parent: *"Every additional minute in the hospital… feels like an eternity… The sooner you get home, the better."* Preliminary data from the *Neonatal Seizure Registry* suggest a trend toward longer length of stay among newborns who were discharged home with medication (p=0.1).

c) *Parent and family well-being* (Aim 3, **PC-3**). Our Parent Partners selected the hospital discharge and 12, 18, and 24-month instruments during focus groups co-led by a study co-investigator who has extensive experience in parent engagement in research (Dr. Franck) and a lead Parent Partner (Libby Hill). The Parent Partners discussed the most relevant domains of family well-being, reviewed the pertinent validated instruments (*e.g.* measures of quality of life, anxiety and depression, family coping, parent post-traumatic stress and post-traumatic growth, parenting confidence and competence, and family functioning), and then selected the most

relevant and valid measures (see **Appendix 5**). Questions specific to the impact of seizure medication on family well-being were developed together by the Parent Partners and investigators (see **Appendix 5**).

Participants at the Patient and Family Research Council felt strongly that *"all of these are important outcomes."* Libby Hill, Parent Partner, re-iterated this point: *"the developmental outcome matters only in the context of epilepsy and quality of life outcomes; they are all related and all important."*

Data Analysis [IR-3]. The centers from the *Neonatal Seizure Registry* enrolled 306 consecutive newborns with seizures due to acute symptomatic cause, and who survived hospital discharge, over our initial 12-27 months of collaboration (variable timing of initiation of enrollment by site). We conservatively estimate that we can enroll 150 of these infants to collect personal health information and follow up data, as well as 150 additional newborns over the 18 months proposed, for a total of 300 subjects with outcome measures for all three aims. This will require that we enroll ~50% of eligible newborns, a very achievable recruitment goal for an observational study.

Sample Size Calculations

Aim 1a: Our hypothesis is that short duration treatment with phenobarbital will be inferior to long duration by no more than a non-inferiority margin of 7% in our primary outcome (functional developmental outcome, measured by the WIDEA FS) adjusted for propensity for maintenance of phenobarbital. This margin is well below the clinically-significant threshold since a developmental delay of more than 33% is needed before a child may access developmental services26. If there is truly no difference in neurodevelopmental outcome among children who had short versus prolonged treatment with phenobarbital (Aim 1a), and using a 12 month WIDEA FS mean of 109 with standard deviation of 16.5 (Appendix 3), we calculate that 192 subjects are required to be 80% sure that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority limit of -7. The WIDEA (our primary outcome measure) is also validated for age 24-months. At age 24-months, the standard deviation of the WIDEA is lower than at 12 months, which will improve our power to detect differences between the groups and, using a similar sample size, lower our non-inferiority margin from 7% to 4.25% for the primary outcome while also increasing accountability for loss to follow-up from 15 to 20%. . Therefore our proposed N=300 newborns, divided into N1 (short duration: phenobarbital discontinued prior to discharge) = 90, and N2 (prolonged duration: phenobarbital continued at discharge) = 210, allows 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 requires that we inflate the sample size by 9%[28].

Aim 1b: We hypothesize that there is no clinically significant difference in epilepsy frequency between the groups. If there is truly no difference between short versus prolonged treatment, with epilepsy incidence conservatively estimated at 20%[27], then we will have sufficient subjects to be 80% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference of more than 13% between groups[29]. The clinical importance of a potential difference of 13% in epilepsy incidence between the groups depends, according to our stakeholders and parent partners, on the results of the primary neurodevelopmental outcome analysis. If developmental outcomes are not different between the short- and prolonged- treatment groups, then a difference of 13% in epilepsy incidence is meaningful and parents would be willing to accept prolonged medication treatment in hopes of reducing the risk for epilepsy. If developmental outcomes are disparate between the two groups, then parents say that the epilepsy risk is less important and they would prefer the treatment regimen that is least likely to produce developmental disabilities.

Aim 2: We hypothesize that length of stay is shorter among neonates who receive a shorter duration of phenobarbital during their initial admission, adjusted for clinical risk factors. Our sample size is based on our total enrollment for the proposal (N=300). Preliminary data from the *Neonatal Seizure Registry* show that the distribution of length of stay is approximately normal after log transformation, so it will be transformed prior to analysis. The standard deviation of the log-transformed length of stay in our preliminary data is 0.71, which gives a detectable difference (with 80% power) of 0.28 on the log scale, corresponding to a 32% difference in length of stay. The median length of stay is 14 days, so our sample will permit detection a difference >4.5 days, a duration that is clinically meaningful to families and important for health resource utilization considerations.

Aim 3: Family well-being measures will be available for the N=150 prospectively enrolled families at the time of hospital discharge and when the child reaches 12-months, 18-months, and 24-months of age. The N=150 families who have already been enrolled in the *Registry* will provide 12-month, 18-months, and 24-month well-being data. Summary scores for standardized questionnaires will be compared between the short and prolonged treatment duration groups. Answers to free-text questions will be analyzed separately using inductive thematic analysis[32] and then compared to determine how they inform, expand on, or challenge each other to form an integrated understanding of the data[30-33]. Using the sample sizes of N_1=36 and N_2=84 (accounting for expected dropout among the prospectively recruited N=150) for families with both hospital discharge and 24-month outcome data, we will have 80% power to detect a standardized difference of 0.56. We will thus have adequate power to detect moderate sized differences in standardized survey scores between groups[34].

Pilot outcome data suggest feasibility and no harmful effect of discontinuation of early discontinuation of phenobarbital. Among newborns from the co-PIs' two study centers who had acute symptomatic seizures and survived to discharge, 39 were evaluated in follow-up clinics at age ≥6 months (31 of the 39 were evaluated at age ≥12-18 months). These infants met the enrollment criteria for the proposed study. There was no association between short vs. prolonged phenobarbital prescription and outcomes (Table 2).

Table 2: Outcomes of children with neonatal seizures who were evaluated in clinical follow-up at age ≥6 months.

	Home on phenobarbital N= 30	Home off phenobarbital N=9	Unadjusted Relative Risk (95% CI)	P-Value
Abnormal examination	10 (33.3 %)	6 (66.6 %)	0.7 (0.5-1.1)	0.07
Abnormal development	12 (40.0 %)	3 (33.3 %)	1.1 (0.8-1.5)	0.7
Epilepsy (any type)	6 (20.0 %)	0 (0.0 %)	1.3 (1.1-1.6)	0.2
Infantile Spasms	2 (6.7 %)	0 (0.0 %)	1.3 (1.1-1.6)	0.4

Statistical analysis and addressing causal inference [CI-1 to 6]. We will follow PCORI guidelines for addressing causal inference using *propensity score adjustment* as a strategy for addressing confounding by indication for Aims 1a and 1b[22,23]. Using propensity scores, we will estimate the unbiased effect of short *versus* prolonged treatment with phenobarbital by accounting for all covariates that predict treatment duration.

Guillet, *et al,* examined duration of neonatal seizure treatment by surveying neonatologists and neurologists across the United States. They concluded that "*the coefficients of variation… were >0.2, which supports the notion that there is wide variability in thinking about actual practices*[5]," however no measured variables (including work setting, training, or geographic location) could account for the inconsistencies. Preliminary, unpublished data from the *Neonatal Seizure Registry* also suggest sufficient heterogeneity within our established group to adequately address the primary hypothesis using propensity scores. Although the centers care for similar patient populations (for example the primary cause of seizures at all centers is hypoxic-ischemic encephalopathy) and have similar initial management strategies (phenobarbital is, by far, the most common initial medication in all centers), management decisions regarding whether or not to maintain seizure medication until the time of outpatient follow-up are very discrepant. Among newborns enrolled in the *Neonatal Seizure Registry*, 23% had medication discontinued prior to discharge (range by site 3-75%), while 77% continued on anticonvulsants. Phenobarbital was the most commonly prescribed anticonvulsant (prescribed to 89% of those maintained on medication).

We will derive propensity scores by developing a regression analysis that includes the major potential reasons that treating physicians may decide to continue phenobarbital after resolution of acute symptomatic seizures and until the time of outpatient follow-up (see list, below). These reasons represent possible sources of confounding by indication. All variables are currently collected in the *Neonatal Seizure Registry* database.

Propensity score co-variables (potential confounders) for Aim 1:

- Confirmation of electrographic seizures *versus* seizure diagnosis on clinical grounds alone
- Severity of seizures (seizure burden)
- Etiology of seizures

- Number of seizure medications prescribed during the inpatient hospitalization
- Gestational age at birth
- Abnormal neurological examination (consciousness, tone, or reflexes) at the time of discharge
- Length of hospital stay
- Highest measured phenobarbital level during NICU admission
- Institution

Using a propensity score analysis, we will examine the association between short *versus* prolonged treatment with phenobarbital, and the WIDEA FS developmental outcome (Aim 1a), as well as the incidence of epilepsy (Aim 1b). Propensity scoring will allow adjustment for differences in treatment response to phenobarbital and will assure lack of exposure overlap between groups. Ability of the propensity score to balance covariates will be checked by standard means[23]. Analyses will be repeated and stratified by term vs. preterm birth to examine differences in treatment response by gestational age. If the confidence interval for the propensity adjusted association is greater than our non-inferiority limit, then we will reject the null hypothesis that short duration of treatment is non-inferior to long duration with respect to neurodevelopmental outcome or rates of epilepsy.

For Aim 2, standard linear regression methods will be employed to examine duration of inpatient phenobarbital treatment and length of stay as a log-transformed continuous variable and adjusted for the potential confounding co-variables listed above as propensity score co-variables (except length of stay).

For Aim 3, standardized survey results will be compared between the short and prolonged treatment duration groups using parametric and non-parametric bivariate comparison tests as appropriate. Answers to free-text questions will be analyzed using inductive thematic analysis[32]. This data analysis occurs iteratively and simultaneously with data collection[33]. Dr. Franck will train the research assistants to undertake coding, and will supervise them through this process. They will engage in repeated close readings of the responses, searching for units of meaning or 'codes' that describe the underlying social processes and interactions. Codes will be organized into categories that are both highly represented in the data and account for the greatest variation in the data[35]. Open, focused and theoretical codes will then be developed to describe aspects (dimensions) of participants' experiences. Rigor will be maintained through reflexivity, attention to response quality, member reflection and systematic analysis. We will discuss emerging themes with our Parent Partners, to engage in ongoing validation of interpretations and to avoid making assumptions about meaning.

Sensitivity analyses [IR-5]. In order to strengthen causal inference, we will perform a sensitivity analysis using institution as an instrumental variable. Institution is a good instrumental variable: preliminary data from the *Neonatal Seizure* Registry indicate that it is associated with the use of short *versus* prolonged duration of phenobarbital in spite of the fact that patient characteristics (including etiology and seizure frequency) are similar. We have not yet collected data with respect to developmental outcomes for the *Neonatal Seizure Registry*, and so we cannot preclude the impact of institution on outcome; however all important procedures of care that might actually impact outcomes (*e.g.,* therapeutic hypothermia for hypoxic-ischemic encephalopathy) are standardized across the centers for excellence that comprise the *Neonatal Seizure Registry*. As such, we expect the entire effect of institution to be mediated through short versus prolonged treatment with phenobarbital (after adjustment for potential confounders). Since the use of an instrumental variable analysis does not depend on the assumption unmeasured confounders, this instrument will be a good complement to the propensity score matching, which depends on identification of all potential confounders.

Propensity score and instrumental variable analyses may not estimate exactly the same quantity[36]. A discrepancy between the analyses may point to differences in the average effect of duration of therapy overall (average cause effect or ACE) versus only those who would comply with assignment to short versus long duration (local average treatment effect or LATE). In the situation of a discrepancy between the two analyses, the LATE interpretation of the instrumental variable analysis will still be valuable.

Scales and tests [IR-4].

Primary outcome: The WIDEA FS, a simple, free, one-page assessment to determine functional developmental outcome in children. It will be administered by telephone at age 12-months, 18-months, and 24-months.[20] (see **Appendix 3**).

Secondary Outcomes:

1) The epilepsy survey to be administered at age 12-months, 18-months, and 24-month has been used in our previous work[3]. The survey comprises standardized questions and chart review to derive a modified Engel Classification, which is a validated way to describe the severity of epilepsy (see **Appendix 4**).
2) The parent and family well-being assessment will be conducted in conjunction with the hospital discharge and 12-month, 18-month, and 24-month evaluations. Our Parent Partners arrived at consensus on the pertinent domains and selected a suite of validated questionnaires (see **Appendix 5**). They also helped us to design a set of open-ended free-text questions to explore the specific impact of seizure medication on family well-being. These instruments will be available in English and in Spanish.

The NICU discharge survey will have 63 items (answered on a 4 to 5 point scale), a 10 item socio-demographic form, 3 items about the newborn's seizures and treatment plan, and 7 open-ended free text questions. The 12-month survey will have 106 items (answered on a 4 to 5 point scale), a 10 item socio-demographic form and 7 open-ended free text questions to specifically probe the impact of seizure medications on family well-being. The Parent Partners emphasized having choices to complete the surveys online or by mail and so these different options will be made available. They were also mindful that the time to complete the survey packet be no longer than one hour total, with the option to complete the survey packet in several shorter intervals.

Data source adequacy [IR-1]. Data will be collected and entered into a REDCap database according to policies established for the *Neonatal Seizure Registry* discussed below.
Data Accuracy and Editing: The database limits range values for numerical data and will utilize radio buttons or drop down lists rather than free text for qualitative data.
Updating: REDCap automatically creates a historical record of past saved data for each field so that errors can be traced.
Data and Form Checks: Database quality is maintained through analyses that target anomalies, delinquent data, and data entry errors. Along with built-in data validation, the Study Coordinator performs a quarterly check for discrepancies in data that includes: incorrect data types, out-of-range or erroneous data, inconsistent and illogical over-time dates, fields on a "completed form" actually not completed; or no reason for missing data is provided. Sites are notified of data discrepancies and are asked to verify and correct discrepancies within 2 weeks of notification.

Missing data [MD-1 to 5]. The study coordinator will audit the database every 3 months for missing data. In case of missing data, site investigators will be asked to review charts to acquire data and in the case that the data are not available, carefully document in the comments field the reason for missing data.

Based on audits of our *Registry* data, we expect <1% missing data for the following key elements: institution, sex, ethnicity, gestational age at birth, delivery mode, Apgar scores, hypothermia treatment, indication for EEG, seizure type, primary seizure etiology, disposition and seizure medication prescribed at the time of discharge. For Aims 1 and 3, in our study design we have conservatively accounted for 15% loss to follow-up (the anticipated main source of missing data) and have adjusted our enrollment target accordingly. We will perform sensitivity analyses to assess the potential impact of loss to follow-up: we have extensive information about our participants and will compare those that are and are not lost to follow-up. We will compare our primary analysis (a complete case analysis) with an analysis using multiple imputation using the "multiple imputation with chained equations" methodology. This approach allows us to specify realistic models for each variable, such as the ordered categorical for the Engel scale. For Aim 2, we expect little to no missing data. Also, for Aim 3, we will audit the amount of missing data for the open-ended free-text questions to determine if there are patterns and will consult with our Parent Partners about ways to improve response rates if needed.

Heterogeneity of treatment effects [HT-1 to 4]. As suggested by PCORI methodological guidelines, all assessments of heterogeneity of the effect of short versus prolonged phenobarbital treatment have been preplanned and have been justified (see *Potential participant subgroups* section below). Analysis will be by entering subgroup by intervention interaction effects in the analyses described above to test for moderation.

Reporting plan [IR-6]. Data will be reported according to STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines, as is recommended for observational studies.

Patient-centered outcomes research (PCOR) data registry details are presented in **Appendix 6.**

D. Project Milestones and Timeline

Table 3: Project Timeline

	Months					
	1-6	**7-12**	**13-18**	**19-24**	**25-30**	**31-36**
Planning						
- Finalize protocol	✓					
- IRB approval	✓					
- Clinicaltrials.gov registration & results reporting	✓					✓
Patient Enrollment						
- Start recruitment		✓				
- Complete 25% recruitment		✓				
- Complete 50% recruitment			✓			
- Complete 75% recruitment			✓			
- Complete enrollment				✓		
Patient Evaluation						
- Follow-up EEG (age 2-4 months) (Aim 1)		✓	✓	✓	✓	
- 24-month follow up (Aim 1) - previous NSR subjects		✓	✓	✓		
- 24-month follow up (Aims 1&3) - newly enrolled subjects			✓	✓	✓	✓
Analysis						
- Interim analysis				✓	✓	
- Final analysis						✓
Progress reports						
- Interim progress reports	✓	✓	✓	✓	✓	
- Final progress report						✓
Engagement Updates	✓	✓	✓	✓	✓	✓
Dissemination						
- Write manuscripts					✓	✓
- Submit copies of published manuscripts					✓	✓
- Presentations by PIs/stakeholders at national meetings					✓	✓
- Write management guidelines						✓
- Apply for additional funding					✓	✓
- Newsletters to participating families to report results					✓	✓
- Partner with *Hand to Hold* to disseminate results online					✓	✓

E. Patient Population

Table 4: Quarterly *Neonatal Seizure Registry* enrollment (6/2013 to 9/2015)

Site	**Median (min, max)**	**Total Newborns Enrolled in *NSR***
UCSF	6 (2, 13)	59
University of Michigan	12 (5, 16)	102
MGH	3 (0, 10)	29

Stanford	6 (0, 29)	72
CNMC	10 (0, 37)	86
CHB	11 (5, 17)	79
CHOP	2 (0, 19)	40

Recruitment Plan. We aim to collect follow-up information for 150 infants that have already been enrolled in the *Neonatal Seizure Registry* (from among >300 eligible newborns; a representative sample of the youngest infants at the time of study initiation will be approached for consent, to allow for prospective collection of 24-month outcome data). An additional prospective sample of 150 newborns will also be enrolled. We have had stable enrollment of 20-30 newborns/month, >70% of whom have acute symptomatic seizures and would meet enrollment criteria for the proposed study. Thus, we expect 250-375 eligible infants over the 18 month enrollment period. We, therefore, will need to enroll 40-60% of eligible newborns, which is very conservative for a non-intervention study with non-invasive follow-up. We will monitor enrollment monthly and address lagging rates on a site-specific basis, as necessary. Given that PCORI requests data within nine months of the end of the final year of funding, even if recruitment is slower than anticipated, there is an additional six months of recruitment time available to us to meet this deadline.

Table 5: Recruitment Goals

	Previously-enrolled infants	**Prospectively-enrolled newborns**
Total number of study participants expected to be screened:	300	375
Total number of study participants expected to be eligible of those screened:	300	300
Target sample size (use same number stated in milestones):	150	150

Table 6: Estimated Final Racial/Ethnic and Gender Enrollment Table [RQ-3]

Race	**Male (N) 55%**	**Female (N) 45%**	**Total (N)**
American Indian/Alaska Native	1	0	1
Asian	10	8	18
Black/African-American	21	17	38
Hawaiian/Pacific Islander	1	0	1
White	88	73	161
Multirace	7	6	13
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)	25	21	46
Non-Hispanic	112	92	204

The study population will be newborns with seizures who are admitted at one of the participating children's hospitals, and their parents. Study sites were selected based on their enrollment of patients in the *Neonatal Seizure Registry* and their ability to confirm neonatal seizure diagnoses with video EEG monitoring, according to the American Clinical Neurophysiology Society (ACNS) guidelines[37].

Inclusion criteria [RQ-3]

- Neonates <44 weeks postmenstrual age at seizure onset
- Seizures due to an acute symptomatic cause (including, but not limited to hypoxic ischemic encephalopathy, stroke, or cerebral hemorrhage)
- Parent(s) who are English or Spanish literate (with assistance of interpreter)

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 (*e.g.*, mild hypoglycemia, hyponatremia, hypocalcemia)
- Newborns with neonatal-onset epilepsy syndromes

- Neonates who do not survive the initial hospital admission
- Neonates will not be excluded based on race, ethnicity, gender or gestational age

Study population [RQ-3]. We will recruit 300 newborn infants with acute symptomatic seizures (including 150 who were previously enrolled in the *Neonatal Seizure Registry*). No infant will be excluded based on gender, race, or ethnicity. Neonates with seizures are often critically ill, and some do not survive their initial hospital admission (16% in-hospital mortality in the *Neonatal Seizure Registry*). We will only enroll newborns who survive to hospital discharge.

Inclusion of Women & Minorities.
Neonatal seizures affect boys slightly more often than girls (*Neonatal Seizure Registry* data: 55% male, 45% female), but children of all races and ethnicities are affected. Among the *Neonatal Seizure Registry's* subjects, the distribution of race/ethnicity is similar to the American pediatric population. We anticipate a similar distribution for the proposed follow-up study, which will be representative of American children.

Inclusion of Children. All study subjects will be children.

Potential participant subgroups [RQ-4; HT-1 to 4].
Our study is powered to evaluate the primary outcome (development at 24 months) across a wide-ranging population of neonates with seizures. This will improve generalizability. We will also have an opportunity to perform exploratory secondary analyses for some subgroups:

- *EEG confirmed vs. clinically diagnosed neonatal seizures*: Although all *Neonatal Seizure Registry* sites conform to the ACNS Guidelines for neonatal EEG monitoring[38], there are occasions in which an at-risk infant's clinical events resolve prior to the initiation of EEG. In the proper clinical context, many such newborns are treated empirically with anticonvulsant medications. In two small studies, the risk for subsequent epilepsy was higher among infants with EEG-confirmed neonatal seizures than those with clinically diagnosed seizures[3,39]. Therefore, we will evaluate for differences in 24-month outcomes between those with clinical versus EEG-confirmed seizures.
- *Gestational age at birth (preterm vs. term)*. The long-term effects of treatment with phenobarbital on preterm neonates are not known and the potential variability of individual responses to *discontinuation* of phenobarbital is a major knowledge gap. Therefore, we will conduct secondary analyses of the effect of prematurity on neurodevelopmental, epilepsy, and family well-being outcomes in the context of duration of phenobarbital exposure. For this secondary analysis, we will use phenobarbital treatment as a continuous variable (number of days of treatment), to avoid overlap between short vs. prolonged treatment groups since preterm infants are often cared for in the NICU for weeks or months. Since just 15% of the *Neonatal Seizure Registry* subjects are preterm, conclusions regarding the analyses of this subgroup will be tentative. The detectable effect size for the full term group (85% of the cohort) will only increase by 8% compared to the overall analysis, so the results will be precise and conclusions will be just as strong for the term subgroup as for the full sample.
- *Gender:* To our knowledge, no published study has established whether outcomes after neonatal seizures vary according to gender. It is plausible to hypothesize that boys with neonatal seizures are at higher risk for adverse neurodevelopmental consequences than girls. The *Neonatal Seizure Registry*, which enrolls *every* newborn with seizures, confirms that males are more often affected than girls (55% male neonates in the first 488 enrolled patients). Studies of preterm infants have consistently demonstrated male sex as a risk factor for developmental delay[40] and animal models suggest enhanced neuroprotective effects of therapeutic hypothermia in female as compared to male rodents after equivalent hypoxia-ischemia[41]. We will, therefore, include gender in our statistical models, to determine whether male sex is an independent risk factor for adverse outcomes after neonatal seizures.
- *Treatment with levetiracetam:* There is increasing use of levetiracetam for treatment of acute symptomatic neonatal seizures, and maintenance of this medication at the time of discharge from hospital. Levetiracetam is less sedating than phenobarbital, and may have a more favorable neurotoxicity profile

according to pre-clinical studies[42]. Therefore, levetiracetam could have less impact than phenobarbital on neurodevelopmental outcomes. We will analyze the small subset of infants who are maintained on levetiracetam as a separate subgroup to obtain preliminary data regarding the impact of this medication on neurodevelopmental outcomes, epilepsy, length of stay, and parent and family well-being.

Subject recruitment. A study investigator or research coordinator will identify eligible newborns during the neonatal admission at each of the participating study sites. A study investigator will approach the parents/guardians of eligible patients and, using a consent form approved by the local Institutional Review Board, will describe the anticipated risks and benefits of the study. The consent team will include only experienced team members who are sensitive to the vulnerable nature of this population and who emphasize the voluntary nature of research. Since this study will place infants at no more than minimal risk, and could augment patient care through standard provision of the follow-up EEG, we anticipate excellent consent rates. Based on feedback from our Parent Partners, we have also attempted to minimize burden to families, and loss to follow-up, through use of a telephone-based follow-up assessment, rather than requiring in-person developmental testing.

Barriers to recruitment. Based on our extensive collective experience with long-term follow-up for neonates at risk for epilepsy – for example the PIs' NIH-supported studies (5K23HD068402, K23NS066137) and the Prevention of West Syndrome study (funded by CURE), as well as the UCSF P01NS082330-01 *Repair after Neonatal Brain Injury, which has enrolled and followed more than 750 neonates since its inception in the 1990s* – we anticipate optimal recruitment when families are approached prior to hospital discharge. Since some of the *Neonatal Seizures Registry* sites draw patients from significant geographical distances, families will be provided a stipend to off-set travel expenses associated with the follow-up EEG. The EEG will be paid for by the PCORI grant, unless the treating physician orders it on clinical grounds.

All study participants will be followed longitudinally per local clinical guidelines through the Pediatric Neurology and/or Intensive Care Follow Up Programs. Children meeting study eligibility criteria are routinely followed through early childhood because of their risk for neurodevelopmental disability and epilepsy. A research coordinator will maintain frequent contact with the families to improve retention.

F. Research Team and Environment

Capabilities of the Research Team

Study Sites for the *Neonatal Seizure Registry* and for this application were chosen based on the following:

1) Ability to perform continuous, video-EEG as recommended by the American Clinical Neurophysiology Society[37]
2) Neurophysiologist(s) with experience interpreting neonatal and pediatric EEG
3) Technologists with experience in applying the neonatal EEG montage
4) State of the art neonatal neurology and pediatric epilepsy care

The study sites are tertiary children's hospitals located across the U.S.A. These sites provide care to a diverse range of children from all races, ethnicities, and socioeconomic strata. Therefore, we are confident that the enrolled newborns and families will be representative of the American population and that the treatment recommendations derived from the study results will be easy to implement in real-world settings.

Investigators for this study have been working together for several years, initially as part of the *NEonatal Seizure Treatment Trial* (NESTT) group (which was established using seed funding from the Child Neurology Foundation), and more recently through the *Neonatal Seizure Registry* (which was established using seed funding from the Pediatric Epilepsy Research Foundation). We have a strong track record of collaborative academic accomplishments, including management guidelines and a recent, high-impact original science paper in *Neurology*[24,37,43]. Furthermore, we have shown that we are capable of enrolling relevant newborns, now with more than 480 consecutive neonates enrolled into the *Neonatal Seizure Registry*.

Investigators

Dr. Renée Shellhaas, co-PI, is Clinical Associate Professor of Pediatrics and Communicable Diseases (Division of Neurology) at the University of Michigan. She completed her training in in Child Neurology and in Clinical

Neurophysiology at the Children's Hospital of Philadelphia. She holds a Master's Degree in Clinical Research Design and Statistics from the University of Michigan School of Public Health. Dr. Shellhaas has received funding from the Child Neurology Foundation, NICHD, the American Sleep Medicine Foundation, and several intramural grants for her research on multimodality neonatal brain monitoring. She is a member of the *Neonatal Seizure Registry*'s Executive Committee and serves as site-PI for several relevant multi-center studies (e.g. Pediatric Epilepsy Research Consortium, Prevention of West Syndrome). Dr. Shellhaas was a member of the EEG core for the multi-center Epilepsy Phenome-Genome Project (NIH U01-NS053998) and is therefore well-prepared to co-ordinate and execute the blinded EEG reviews for Aim 1b.

Dr. Hannah Glass, co-PI, is Associate Professor of Neurology, Pediatrics, and Epidemiology and Biostatistics and Director of Neonatal Critical Care Services at the UCSF Benioff Children's Hospital. She completed training in Child Neurology at the University of Calgary. She trained in Neonatal Neurology and earned a master's degree in clinical research at UCSF. Dr. Glass has received funding from the NIH, March of Dimes, the Pediatric Epilepsy Research Foundation, and the Cerebral Palsy Alliance, and is the PI of the *Neonatal Seizure Registry*. She participates in research that uses advanced imaging and brain monitoring to predict outcomes following newborn brain injury.

Drs. Shellhaas and Glass have worked together on several projects, including the *Neonatal Seizure Registry*, which was established in 2012. They have already co-authored two publications: (1) Glass HC, Wusthoff CJ, Shellhaas RA, et al, Risk factors for EEG seizures in neonates treated with hypothermia: a multicenter cohort study. *Neurology*. 2014; 82:1-6, and (2) Glass HC, Wusthoff CJ, Shellhaas RA. Amplitude-integrated electro-encephalography: the child neurologist's perspective. *J Child Neurol*. 2013; 28:1342-1350).

Dr. Linda Franck, co-investigator, is Professor and Endowed Chair of Pediatric Nursing at the UCSF School of Nursing. Dr. Franck has over 25 years of experience as an investigator in the NICU setting, leading clinical research studies that involve recruitment and enrollment of infants, parents and/or NICU staff. She has experience in a variety of quantitative, qualitative and mixed methods designs and analytic approaches. She was at the forefront of the movement to engage patients and families as partners in the research process in the United Kingdom, and influenced policy and practice in this regard. Over the past decade, she has developed and refined approaches for engaging parents in the planning, implementation and dissemination phases of research and has developed strong links with parent and child advocacy groups. Dr. Franck will oversee Aim 3.

Dr. Charles McCulloch, co-investigator, is the Head of the Division of Biostatistics at the Department of Epidemiology and Statistics at UCSF. Dr. McCulloch has wide-ranging experience in both the development of statistical methodology and the novel application of advanced statistical methods. His research focus is on methods for correlated data including longitudinal data models for normally or non-normally outcomes, latent variable and latent class models. Dr. McCulloch will oversee all aspects of biostatistical analysis.

Dr. Elizabeth Rogers, co-investigator, is an Assistant Professor of Pediatrics (Division of Neonatology) and the Director of the Intensive Care Nursery Follow-Up Program at UCSF. Dr. Rogers has extensive experience with outcomes research among cohorts of former preterm and critically ill infants. She has participated in the design, ascertainment and analysis of several large clinical studies, including Trial of Late Surfactant for Prevention of Bronchopulmonary Dysplasia (TOLSURF, NCT01022580) and Neonatal Erythropoietin in Asphyxiated Term Newborns (NEAT, NCT00719407). Dr. Rogers will oversee developmental follow-up for the proposed study.

Dr. Courtney Wusthoff, site PI and Neurophysiologist, is an Assistant Professor of Neurology at Stanford University and the Neurology Director of the Lucile Packard Children's Hospital NeuroNICU. Dr. Wusthoff is a neurophysiologist with special research and clinical interest in the NICU. Dr. Wusthoff will be responsible for reading the 2-4 month EEGs, along with Dr. Shellhaas, and she will continue to oversee enrollment for the *Neonatal Seizure Registry* at her site.

Dr. Janet Soul, site PI, is an Associate Professor in Neurology at Harvard Medical Center and leads an NIH funded clinical trial in neonatal seizure management (NCT00830531). Dr. Soul will continue to oversee enrollment for the *Neonatal Seizure Registry* at her site.

Dr. Nicholas Abend, site PI, is an Associate Professor of Neurology & Pediatrics at the Perelman School of Medicine at the University of Pennsylvania & the Children's Hospital of Philadelphia. Dr. Abend is a neurophysiologist with special clinical and research interest in EEG monitoring in critically ill children. Dr. Abend will continue to oversee enrollment for the *Neonatal Seizure Registry* at his site.

Dr. Taeun Chang, site PI, is an Assistant Professor of Neurology at George Washington University School of Medicine & Health Sciences and Director of Neonatal Neurology at the Children's National Medical Center. Dr. Chang has extensive experience recruiting neonates for clinical trials. Dr. Chang will continue to oversee enrollment for the *Neonatal Seizure Registry* at her site.

Dr. Catherine Chu, site PI, is an Assistant Professor of Neurology at Harvard Medical Center, and Director of the Pediatric Inpatient Long Term EEG Monitoring Program at the Massachusetts General Hospital. Dr. Chu will continue to oversee enrollment for the *Neonatal Seizure Registry* at her site.

G. Engagement Plan

1. Planning the Study. Stakeholders are fully integrated in all aspects of the proposed study [Criterion 5].

"We would love to help you any way we can with this grant... Any opportunity to improve the lives of these kids we are all in."

- Marty Barnes, Parent Stakeholder and volunteer at Hand to Hold

We established several critical partnerships to develop this proposal. Our 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. More than 19,000 NICU parents sought support from *Hand to Hold* this year through their Helping Hand mentor program and their Life After NICU online support forum. *Hand to Hold*'s comprehensive website welcomed more than 400,000 unique visitors this year. They also have a very active social media presence through Facebook, Twitter, and Pinterest. Parents can access videos about topics of importance to NICU families through their YouTube Channel. *Hand to Hold* recently launched a new online education series – NICU 101 – through Facebook which is reaching more than 3,000 parents and professionals each month. 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, personally advised the team about study design, and is committed to continued partnership to support the study's execution and dissemination of results.

Parent Partners helped to design the study and selected the most relevant outcome measures. Since newborn infants are unable to act as direct patient stakeholders, parents must serve as proxy stakeholders. We worked with the CHEAR Patient and Family Research Council to develop the research idea and refine the overall study design. We then recruited 10 parents of children who experienced neonatal seizures to form our Parent Partner panel (Table 7). Seven were recruited from the study sites, to mitigate concern regarding exclusion of parents who are not part of online social media. Three were recruited via their connections with *Hand to Hold* and *CaseyBarnes.org*. They come from all regions of the USA, have diverse racial/ethnic backgrounds, and 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 their child's seizure management 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 impact on the family. Parent Partners were fully supportive of the plans for Aims 1 & 2. They also confirmed the pertinence of the outcome measurement time points (NICU discharge and when the infant is 24 months of age). Parents discussed the pros and cons of different 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.

Table 7: Parent Partner Panel Members

Name	Parent Partner Advisory Panel	Online Parent Survey	Advocacy Organization Representative	Home State
Kelli Kelley		✓	✓ Handtohold.org	Texas
Marty Barnes	✓	✓	✓ Caseybarnes.com	Texas
Elizabeth Hill	✓	✓		Michigan
Dana Annis	✓			Maryland
Karla Contreras	✓			Texas
Lisa Grossbauer	✓			Pennsylvania
Jennifer Guerriero	✓			Massachusetts
Catherine Jimenez	✓			Colorado
Gwen Ma	✓			California
Meg Spodick	✓			Massachusetts
Justin Yan	✓			Washington

2. Conducting the Study. Stakeholders will remain involved during all 3 years of the study. The Parent Partner panel has committed to meet monthly by telephone conference to assist with the following:

1) Development of study-related documents (*e.g.* consent forms, brochures, etc.)
2) Provision of guidance on optimal recruitment and retention practices
3) Optimization of study procedures
4) Review of study results
5) Implementation of the plan to disseminate key findings to professional and parent/family stakeholders

3. Disseminating the study results. Parent stakeholders will be central in the dissemination of results:

1) Announcements and updates to social media platforms, including the Hand to Hold website and Facebook page.
2) Presentation of results, together with PIs, at Departmental Grand Rounds and Society Meetings. For example, annual meetings of the American Epilepsy Society and Pediatric Academic Societies.
3) Developing newsletters detailing the results of the study to be sent to participating families.

Patient Advocacy Groups and Professional Societies will be engaged in dissemination of results:

1) Kelli Kelley, director of *Hand to Hold*, has pledged to use her organization's wide network of more than 250,000 parents and professionals to help promote this research and disseminate key findings. She, and members of the Hand to Hold staff, are also available to participate in collaborative presentations at local and national meetings of physicians and parent stakeholders.
2) Both the *Child Neurology Society* and the *American Academy of Pediatrics* have agreed to review evidence based guidelines based on this study's results (see letters of support). Such guidelines would be made widely available to professionals and parents through published articles and online resources.

4. Principles for Engagement.

Reciprocal relationships. We have recruited 10 parents of infants with neonatal seizures to serve as our Parent Partner Panel. These parents have already shown motivation and insight during the design of this proposal. They have agreed to participate in monthly research team meetings (by teleconference) to be updated on the project's progress, to approve of all major decisions, and to participate in planning the dissemination of findings. The PIs and Parent Partners have already established a pattern of discussion and partnership for decision-making for this proposal. As outlined elsewhere in this submission, the Parent Partner Advisory Panel, in collaboration with Dr. Franck, and in consultation with the PIs, have both an overall study advisory role and a specific role in the development of Aim 3. The Parent Partners have been instrumental for decision-making regarding design of the study protocol (**Table 8**).

Table 8: Parent Partner Advisory Panel Timeline.

		Months					
	Pre-submission	**1-6**	**7-12**	**13-18**	**19-24**	**15-30**	**31-36**
Planning							
- Recruit parents to the Parent Partner Advisory Panel	✓						
- Initial and follow-up focus groups to discuss well-being domains and select validated instruments	✓	✓	✓	✓	✓	✓	✓
- Monthly telephone conferences		✓	✓	✓	✓	✓	✓
Document Review							
- Review Manual of Operations and Case Report Forms		✓					
Dissemination							
- Preparation of newsletter to disseminate results						✓	✓
- Presentation at society conferences						✓	✓
- Updates to websites (e.g. Hand to Hold)						✓	✓

Colearning. Parents and stakeholders have already engaged in frequent, open dialogues with the PIs regarding the study design. The PIs have been teaching the parents and other stakeholders about the scientific evidence and options of research protocol design. The PIs have participated in PCORI webinars and have discussed the project with a PCORI ambassador. The Parent Partners focus groups contained a specific educational segment on patient-centered research and PCORI.

Meanwhile, the stakeholders have been critical in informing the PIs about parents' priorities and the best assessment instruments for use in the parent and family well-being outcome assessments. Together with Marty Barnes and Kelli Kelley, Dr. Hill composed the parent web survey that was posted to the Hand to Hold website and inquired about families' experiences with neonatal seizures and their treatment. Data generated from that survey were critical for informing the design of this proposal.

Additional opportunities for reciprocal relationships and co-learning include:

- Monthly teleconferences for project updates and mutual decision-making.
- Development of publications and presentations for dissemination of study results to parent groups.

Partnership. Parent Partners will be compensated for their time. Our Parent Partners have shown a clear commitment to engaging with us. We will offer financial compensation to each of our Parent Partners to participate in monthly telephone conference calls and focus groups. Parents of children with special needs, especially those with seizures, are busy people. They balance multiple childcare, healthcare, and professional commitments. We have specifically discussed the level of commitment required, and compensation available, for the present proposal with each of our stakeholders and partners, and the proposal and budget reflect the results of those discussions. Each Parent Partner has agreed to the commitments outlined above.

Trust, Transparency, and Honesty. From its conception, this study has included both clinicians and parent stakeholders (who must serve as proxies since newborn infants are unable to serve as direct patient partners). We have worked in close collaboration with our Parent Partners to create a proposal that serves: 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.

As a fully integrated study team, we are committed to continued trust, transparency, and honesty about study design, implementation, and result reporting. Our stakeholders and Parent Partners have shown their full commitment to this work, through multiple in-person and telephone meetings, as well as frequent electronic mail correspondence.

The physician investigators and stakeholders remain committed to sustained parent and stakeholder integration throughout the study's planning, implementation, and analysis phases. We all look forward to communicating this study's crucial findings rapidly, broadly, and in a clinically useful manner. We aim to disseminate our findings to families and their clinical care teams through traditional scientific papers, online posts on websites and social media, and will work with the Child Neurology Society and the American Academy of Pediatrics to produce practice guidelines based on this PCORI-funded research.

DISSEMINATION AND IMPLEMENTATION POTENTIAL

A. Describe the potential for disseminating and implementing the results of this research in other settings.

Our project has great potential for rapid dissemination and implementation in clinical and community practice, as outlined below.

Management Guidelines and Scientific Manuscripts: The investigators of this application are leaders in the field of neonatal neurology and neonatal seizures, and together have published dozens of manuscripts on the subject of neonatal seizures in high quality journals, including the nationally recognized guidelines for monitoring neonatal seizures[24,37], and a recent, high-impact manuscript on monitoring and seizures in neonates[43]. These important manuscripts resulted from the collaborative efforts of many members of the study team.

It is our intention to develop the proposed study's research findings into a high-impact clinical practice guideline related to the optimal duration of treatment after neonatal seizures. We have already been in discussions with the Practice Committee of the Child Neurology Society (CNS) and the American Academy of Pediatrics Section on Neurology (AAP SoN) and both national organizations have provided letters indicating their strong support for this application. Both the CNS and AAP SoN agree that the proposed study will generate critical, clinically relevant data, and they are committed to assisting the study team with dissemination of the results. In addition, we will apply to the American Academy of Neurology and the American Academy of Pediatrics for consideration of this guideline. We selected these organizations as they reach the most relevant clinicians (neurologists, child neurologists, pediatricians, and neonatologists) and have a track record of creating high-quality patient education materials based on their published guidelines.

Society Meetings: The investigators are the former and/or current leaders of Special Interest Groups in Neonatal Neurology (Child Neurology Society) and Neonatal Seizures (American Epilepsy Society), and serve on the Scientific Planning Committees for the Pediatric Academic Societies and Child Neurology Society annual meetings. We are, therefore, well positioned to quickly disseminate results to more than 10,000 neurologists, neurophysiologists and neonatologists within a year of completion of our study. In order to achieve quick dissemination, we will submit abstracts and propose scientific symposia at multiple meetings.

Educational Programs: The Investigators of this application are invited lecturers for multiple national and international educational programs, including teaching at both the American Academy of Neurology and the American Academic of Pediatrics annual "Neonatal Neurology" sessions, as well as the IPOKRaTES Foundation seminars in neonatology and the International Conference on Brain Monitoring & Neuroprotection in the Newborn. Results of this study will be directly relevant to these audiences of all levels of training, and can be quickly incorporated into presentations for these high-impact venues, which target trainees and faculty in neonatology, pediatrics, and neurology. Furthermore, Dr. Hill is well positioned to create educational materials that can be widely disseminated to residents in Pediatrics.

Parent Support and Advocacy Group: Our key stakeholder partner, *Hand to Hold*, is a premier parent peer support and advocacy group for families with children who required neonatal intensive care. The group has an important online presence (handtohold.org) and a network of 250,000 parents and professionals. This organization is poised to widely disseminate our results to the families and professionals included in their membership through their vast social media network, as well as local state, national, and international family groups. Our results will be highly relevant to parents of neonates with seizures, who will be empowered to ask for discontinuation or continuation of anticonvulsant medications based on the results of our study.

B. Describe possible barriers to disseminating and implementing the results of this research in other settings.

Dissemination: As discussed above, we are poised to rapidly disseminate results of our study to the scientific community and parent groups within one calendar year. Development and publication of clinical practice guidelines will be a longer process, but we and our sponsors at the relevant national societies are committed to completing this larger, high-impact manuscript.

Implementation: Potential barriers to implementation of the results in routine clinical practice may include inertia, unwillingness to change clinical practice, and fear of stopping medications. Centers that are unable to perform continuous video-EEG monitoring may be unable to confirm presence and termination of electrographic seizures and may, therefore elect to continue medications. We will explicitly address these concerns in our dissemination products and have planned a subgroup analysis for newborns with clinical-only seizures. We are also planning to collaborate with Dr. Hill (pediatric resident and parent partner) to develop educational materials for trainees in Pediatrics, in order to provide optimal education for the next generation of clinicians who will care for and treat newborns with seizures.

C. Describe how you will make study results available to study participants after you complete your analyses.

Participating families will be notified of the study results via email or post (depending on parent preference) in the form of a newsletter that outlines the research questions and results. The Parent Partner Advisory Panel will be responsible for drafting the newsletter to ensure that it is parent friendly. Participants in the CHEAR Patient Family Research Council specified that "*humanizing the results… in English, not in medicalese*" and including family narratives are priorities for dissemination of results.

REPLICATION AND REPRODUCIBILITY OF RESEARCH AND DATA SHARING

A. Describe the ability to reproduce potentially important findings from this research in other data sets and populations.

This will be a multicenter study with regional representation from across the United States. The majority of newborns included in the study will have EEG confirmation of their seizures, which is much more reliable than diagnosis and quantification based on clinical observation alone[44,45]. This will substantially enhance reproducibility of study findings.

B. Describe how you will make available, within nine months of the end of the final year of funding, a complete, cleaned, de-identified copy of the final data set used in conducting the final analyses or your data-sharing plan, including the method by which you will make this data set available, if requested.

Neonatal and Follow-Up Data. The clinical data and EEGs that we analyze will already be de-identified at the patient level. We will further de-identify the records in regard to hospital of birth, as there may be some concern that hospital level data could be used to identify a specific participating hospital. This data set will be prepared within nine months of the end of the final year of funding. The data will then be available to PCORI representatives, and to any other interested party on an as needed basis. For those who are not PCORI representatives (for example, other investigators or agencies), we will accept requests to be reviewed by the PIs, co-investigators, and Parent Partner Advisory Panel, and will release the data as deemed appropriate. We will ask for a data use agreement such that the data will only be used for the purposes of the request and not made publicly available.

C. Propose a budget to cover costs of your data-sharing plan, if requested.

No budget has been requested for data-sharing. One advantage of the REDCap system is that it is very easy to create de-identified records, which can be circulated using common file extensions for statistical software program (*e.g.,* SAS, Stata), as needed.

PROTECTION OF HUMAN SUBJECTS

Describe the protection of human subjects who will be involved in your research.

This Human Subjects Research meets the definition of "Clinical Research." We plan to study 300 human newborns (<44 weeks gestational age at the time of seizures) who are enrolled at one of the participating centers of the *Neonatal Seizure Registry*.

Potential Risks

We do not anticipate any significant risks to participants, as the study is observational in nature. Participating families may face some risk for loss of privacy or confidentiality, which will be mitigated as detailed below.

Protection Against Risks

Recruitment and Informed Consent: Because we are working with a vulnerable population of infants who cannot give informed consent, and parents who are faced with difficult medical decisions regarding health care for their children, our consent teams will include only experienced personnel who are sensitive to these ethical issues, and who emphasize the voluntary nature of research. Families will be advised that they may stop participation at any time. All research staff will undergo appropriate human subjects research training through the CITI program and/or equivalent local institutional training. Parents of eligible neonates will be identified by research staff at participating Intensive Care Nurseries with the help of healthcare providers. After initial permission to make contact, research staff will describe the purpose and design of the study, the potential risks and benefits of study participation, the procedures in place to protect against risk to participants, and the available levels of participation. We will make sure to be sensitive of the needs of families, noting at multiple occasions that the study is voluntary and that participants can request to stop being part of the study at any time.

Loss of Privacy: All participants will be assigned a study-identifier number. The list of names and corresponding study ID numbers will be stored on a secure computer server in a separate password-protected location from the study data. Contact information will be collected from families of study participants, since this information is necessary to enable 12-month, 18-month, and 24 month follow-up assessments. Access to the study roster will be restricted to appropriate research staff. Data will be maintained in a locked office, within either locked file cabinets or on a computer that is encrypted and password-protected. The REDCap program, a secure, web-based data capture system (https://redcap.ucsfopenresearch.org) will be used for data entry and data export. The data collected by EEG will not be linked to individuals. Datasets used for presentation or publication will contain no personally identifying subject information.

EEG: There are no known risks related to recording routine EEG, aside from a slight risk of transient redness of the scalp. In order to minimize skin breakdown, technicians trained in neonatal/infant EEG will apply the leads for all studies.

Potential Benefits to Participants and Others

The infants will potentially benefit from early detection of seizures or delayed developmental milestones, which may allow early start to epilepsy treatment, physical therapy and/or occupational therapy. The follow-up EEG results will be available to the infants' treating clinicians, and could add to medical decision-making.

Characteristics of the Participant Population

We will be enrolling newborns from centers from across the United States, and so we expect excellent representation of the US population in terms of gender, race, and ethnicity. Indeed, the newborns enrolled in the first years of the *Neonatal Seizure Registry* were representative of the American population.

Table 8. *Neonatal Seizure Registry* Race/Ethnicity.

Race	Neonatal Seizure Registry (N=489)	USA Pediatric Population (2013)*
White	53.8%	73.2%
Black	12.1%	15.1%
American Indian/Alaska Native	0.2%	1.6%
Asian	6.3%	4.9%
Native Hawaiian & Other Pacific Islander	0.3%	0.3%
More than one race	1.6%	4.9%
Other	8.2%	-
Unknown/Not Reported	17.6%	-
Ethnicity		
Hispanic	18.4%	24.1%

**Data from www.childstats.gov*).

CONSORTIUM CONTRACTUAL ARRANGEMENTS

Describe the proposed research projects that will be performed by subcontracted organizations. Explain the strengths that these partners bring to the overall project.

The *Neonatal Seizure Registry* (PI Glass) is a collaborative of institutions that have worked together since 2012 to collect data regarding the management of neonatal seizures. We will build upon the infrastructure and relationships built over the last several years for the *Neonatal Seizure Registry* to execute the proposed comparative effectiveness study. A multicenter study is required to enroll sufficient participants in order to achieve the milestones outlined in this proposal. Each of the sites will enroll new subjects, as well as previously registered infants, as described above.

The participating sites represent the highest-ranked academic institutions and children's hospitals in the USA:

1) University of Michigan - Mott Children's Hospital (Shellhaas, co-PI, neurophysiologist, & site PI)
2) University of California, San Francisco - Benioff Children's Hospital (Glass, co-PI & site PI)
3) Harvard Medical Center- Boston Children's Hospital (Soul, site PI)
4) Perelman School of Medicine at the University of Pennsylvania - Children's Hospital of Philadelphia (Abend, site PI)
5) George Washington School of Medicine - Children's National Medical Center (Chang, site PI)
6) Stanford University - Lucile Packard Children's Hospital (Wusthoff, neurophysiologist & site PI)
7) Harvard Medical Center - Massachusetts General Hospital (Chu, site PI)

This is an outstanding group with strong academic histories and proven ability to collaborate through the *Neonatal Seizure Registry*, as well as for numerous original science publications, guidelines and reviews, including:

1: **Glass HC, Wusthoff CJ, Shellhaas RA**, Tsuchida TN, Bonifacio SL, Cordeiro M, Sullivan J, **Abend NS, Chang T**. Risk factors for EEG seizures in neonates treated with hypothermia: a multicenter cohort study. Neurology. 2014;82(14):1239-44.

2: **Glass HC, Wusthoff CJ, Shellhaas RA**. Amplitude-integrated electro-encephalography: the child neurologist's perspective. J Child Neurol. 2013;28(10):1342-50.

3: Tsuchida TN, **Wusthoff CJ, Shellhaas RA, Abend NS**, Hahn CD, Sullivan JE, Nguyen S, Weinstein S, Scher MS, Riviello JJ, Clancy RR; American Clinical Neurophysiology Society Critical Care Monitoring Committee. American clinical neurophysiology society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society critical care monitoring committee. J Clin Neurophysiol. 2013;30(2):161-73.

4: **Shellhaas RA, Chang T**, Tsuchida T, Scher MS, Riviello JJ, **Abend NS**, Nguyen S, **Wusthoff CJ**, Clancy RR. The American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates. J Clin Neurophysiol. 2011;28(6):611-7.

5: **Wusthoff CJ, Shellhaas RA**, Clancy RR. Limitations of single-channel EEG on the forehead for neonatal seizure detection. J Perinatol. 2009;29(3):237-42.

6: **Abend NS, Wusthoff CJ**, Goldberg EM, Dlugos DJ. Electrographic seizures and status epilepticus in critically ill children and neonates with encephalopathy. Lancet Neurol. 2013;12(12):1170-9.

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In order to incentivize the sites to enroll eligible participants, we have budgeted per patient allocations, as well as a stipend for startup, recruitment and retention efforts, and close out at each site. This approach has worked well for the *Neonatal Seizure Registry*.

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APPENDIX (optional)

Appendix 1: *Neonatal Seizure Registry Case Report Form*

Confidential

Neonatal Seizure Registry

Patient Information

Study ID	_____
Institution	◯ 01 UCSF ◯ 02 University of Michigan ◯ 03 Massachusetts General ◯ 04 Lucile Packard Children's Hospital ◯ 05 Brigham and Women's ◯ 06 Children's National Medical Center ◯ 07 Children's Hospital Boston ◯ 08 Children's Hospital of Philadelphia (Indicate one answer only. Study IDs should be written in the following 5-digit format 01001, 01002, 01003, etc. with the first two digits being the institution number.)
Sex	◯ Female ◯ Male ◯ Indeterminate
Race	◯ American Indian / Alaska Native ◯ Asian ◯ Black / African American ◯ White ◯ Native Hawaiian / Other Pacific Islander ◯ Other ◯ More than one race ◯ Unknown / Not Reported (Indicate one answer only. See MOP for race definitions.)
Ethnicity	◯ Hispanic or Latino ◯ NOT Hispanic or Latino ◯ Unknown / Not reported (Indicate one answer only. See MOP for race definitions.)
Age in hours at admission (e.g. for 1hr30min, indicate 1.5)	_____ (Use provided excel spreadsheet calculator to determine age. Age in hours should be recorded to one decimal point.)
Patient enrolled in a concurrent study?	☐ No ☐ Yes - observational study ☐ Yes - interventional study ☐ Unknown (Check all that apply)
Name of observational or interventional study	_____

Appendix 2: 2-4 Month Convalescent EEG Assessment

1) Date_____
2) Subject # _____
3) Person completing EEG assessment _____
4) Subject's chronological age at EEG (in weeks)_____
5) Postmenstrual age at birth (in weeks)_____
6) Duration of recording (minutes):_____
7) Quality of recording: Acceptable Unable to interpret
8) **Overall interpretation of the EEG**:
    a. Normal
    b. Abnormal
        i. Abnormal with epileptiform features
        ii. Abnormal with NO epileptiform features
        iii. Hypsarhythmia (_classic; or _____modified)
9) **Specific elements**:
    a. Waking background
        i. Well-organized
        ii. Disorganized
        iii. Abnormal slowing (_____Focal slowing; _____Diffuse slowing; _both)
        iv. Persistent hemispheric asymmetry (which side is abnormal: __Left____Right)
        v. No wakefulness recorded
    b. Sleep background
        i. Drowsy- yes, no
        ii. Stage 2- yes, no
        iii. SWS- yes, no
        iv. Sleep spindles present and normal
        v. Sleep spindles absent
        vi. Sleep architecture asymmetric or otherwise abnormal
        vii. No sleep recorded
    c. Epileptiform abnormalities
        i. Focal sharp waves or spikes
            1. Yes
            2. No
        ii. Multifocal sharp waves or spikes
            1. Yes
            2. No
        iii. Generalized spike-wave discharges
            1. Yes
            2. No
        iv. Electrodecrements
            1. Present
            2. Absent
        v. Recorded seizure
            1. Yes
            2. No

    d. Other abnormalities (specify; e.g. excessive beta)

Appendix 3: 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 4: 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 5: Parent and Family 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 6: Standards for Data Registries [DR-1 to DR-3]

Patient Follow-up will be at pre-specified ages as outlined in the proposal. The initial follow-up (2-4 month EEG) will be arranged at the time of enrollment for the N=150 prospectively enrolled infants. The Aim1 12-month, 18-month, and 24-month follow-up assessments for all participants will be conducted by telephone and will include:

- WIDEA FS (functional neurodevelopmental outcome, which is the primary endpoint, **Appendix 3**)
- Epilepsy assessment – (**Appendix 4**)

As requested by our Parent Partner Advisory Panel, participating families may complete 12-month follow-up family well-being assessment for Aim 3 either by mail (paper copies of the questionnaires) or via online questionnaire administration (**Appendix 5**).

The 24-month contact is planned to be the last contact with patients and their families.

Adequacy of Follow-Up Duration: 24-month follow-up is both scientifically justified and practical. By 12 months, those with significant developmental delays can be identified using standard neurodevelopmental assessment instruments, such as the WIDEA FS. Additionally, those with the most severe forms of post-neonatal epilepsy, such as infantile spasms, typically present before the child's first birthday. Although more subtle developmental differences may emerge later, in school age children, longer follow-up is not feasible within a 3-year grant cycle. We plan to request permission from enrolled families to contact them at a later date for long-term outcome assessment, once additional funding is secured.

Retention and Expected Loss to Follow-Up: We anticipate excellent retention, since all neonates enrolled in this study will have close clinical follow-up with the study centers through a high-risk developmental follow-up program, pediatric neurology, and/or pediatric epilepsy. We have designed the protocol to avoid unnecessary travel to the study centers. The follow-up EEG will be recorded between ages 2 and 4 months, a timeframe during which typical neurology clinical assessments are scheduled. The assessments will be conducted via telephone interview (Aim 1), and online or by mail (Aim 3), rather than in-person evaluations. Despite this, we have accounted for a 15% loss to follow-up in our analysis plan.

Possible biases due to differential loss to follow-up: It is possible that infants who are discharged from the initial hospital admission *without* anticonvulsant medication will be more likely to be lost to follow-up, since they will not need to present to a neurology clinic for prescription medication refills. In our clinical experience, however, these families want to return to clinic at least at the 2-4 month time point, so that a specialist can evaluate their child's growth and development. If a child is doing well, families who live farther from the study site may be less likely to follow-up at later time points. We have designed the assessment to avoid this problem by utilizing telephone interviews, online and mailed surveys. Even for families who do not complete the assessments, the medical chart can be reviewed. In cases where a family cannot be reached by telephone, a diagnosis of epilepsy will be readily apparent from electronic medical record review.

Data Safety and Security: Local Institutional Review Boards approvals for the *Neonatal Seizure Registry Sites* will be amended to reflect changes to the study design. Data will be collected using REDCap, an online, HIPAA compliant database that is designed for use in health care. Data will be de-identified, with each site maintaining local record of the patient medical record number in a secure manner (either on an encrypted and password protected computer that is maintained in a locked room, or paper file that is maintained in a locked cabinet in a locked room). Data that were collected for the *Neonatal Seizure Registry* prior to initiation of this proposal will be used only following informed consent from families.

Informed Consent: A study investigator will contact the parents/legal guardians of eligible patients and, using a consent form approved by the local Committee on Human Research (Institutional Review Board), describe the known risks and benefits of the study. The consent teams will include only experienced study personnel who are sensitive to the vulnerable nature of this population and who will emphasize the voluntary nature of research.

Data Quality Assurance
Data will be collected and entered into a REDCap database according to policies established for the *Neonatal Seizure Registry*.

Training: For the purposes of this proposal, the two study coordinators from the primary institutions will provide additional training for coordinators at the other study sites. For the purposes of the *Neonatal Seizure Registry,* we have audited 100% of sites and have found very good agreement for the variables that will be included in the proposed analysis. We expect a similar high fidelity for additional data collection.
Data Accuracy and Editing: The database limits range values for numerical data and will utilize radio buttons or drop down lists rather than free text for qualitative data.
Updating: REDCap automatically creates a historical record of past saved data for each field so that errors can be traced.
Data and Form Checks: Database quality is maintained through analyses that target anomalies, delinquent data, and data entry errors. Along with built-in data validation, the Study Coordinator performs a quarterly check for discrepancies in data that includes: incorrect data types, out-of-range or erroneous data, inconsistent and illogical over-time dates, fields on a "completed form" actually not completed; or no reason for missing data is provided. Sites are notified of data discrepancies and are asked to verify and correct discrepancies within 2 weeks of notification.
Data Review and Verification Procedures: Database quality will be maintained through analyses that target anomalies, delinquent data, and data entry errors. Along with built-in data validation, the Study Coordinators will perform a quarterly check for discrepancies in data that includes: incorrect data types, out-of-range or erroneous data, inconsistent and illogical over-time dates, fields on a "completed form" actually not completed; or no reason for missing data is provided. Sites will be notified of data discrepancies and are asked to verify and correct discrepancies within 2 weeks of notification.

Modifications to the Protocol will be based on consensus of the co-Pis after discussion with Parent Partner Advisory Panel. Any changes will trigger an update to the Manual of Operations, which will be sent electronically to every site PI and study coordinator. Changes will be highlighted during conference calls and the main study coordinators will communicate directly with each site coordinator to insure timely and accurate implementation of any change.

Consistent Data Collection: We will use the existing data dictionary for the *Neonatal Seizure Registry*, which is based on recent literature review and widely used definitions. Standard instructions and definitions are included in the Manual of Operations.

Systematic Patient Enrollment and Follow-up: Every infant diagnosed with neonatal seizures at the participating centers will be a potential candidate for enrollment. Only families whose infants survive to hospital discharge will be approached for consent (~16% in-hospital acute mortality among those already enrolled in the *Neonatal Seizure Registry*). This will avoid selection bias and allow for the most widely applicable data set. Each site will maintain a log of families who decline to consent for this study. The log will include gender, race/ethnicity, and the reason for the neonatal seizures (these data are already gathered through the *Neonatal Seizure Registry)*. This will allow for prospective identification of any biases in enrollment, so that changes in the consent process may be implemented as needed to enhance generalizability of the study sample.

Procedures to Monitor and Minimize Loss to Follow-up: Quarterly enrollment and follow-up reports will be generated for each site, so that the follow-up rates are clear and any center for which the target appears to be in jeopardy can be readily identified before the follow-up target is missed. The target is >85% follow-up for the 24-month assessments. We will prospectively determine the actions to be employed in the event that this target is in jeopardy. At the outset of the study, we will develop a patient retention plan that documents when a patient will be considered lost to follow-up and what actions will be taken to minimize such loss.

- At the time of enrollment, the following data will be collected: Telephone, mailing address, and email address for the neonate's parent/legal guardian, as well as alternate contact information for that parent/guardian (e.g. a grandparent or close friend's contact information, with that person's permission).
- The 2-4 month follow-up EEG will be planned and scheduled at the time of study enrollment, with every effort made to coordinate that appointment with another clinically-indicated appointment (*e.g.,* the pediatric neurology follow-up clinic visit). This will minimize travel for infant and family and should enhance retention.
- The family will be given a reminder telephone call several days before the 2-4 month visit.
- Contact information will be verified and updated when the family comes to the 2-4 month EEG.
- If a family misses the 2-4 month EEG, then they will be contacted via telephone call within 3 days of the missed appointment. If there is no response, then an email will be sent after 5-7 days and/or a telephone call will be placed to the alternate phone number. The EEG will be rescheduled if at all possible.
- When the infant reaches 11 months, a letter will be mailed and/or emailed to the family, to remind them of the 12-month telephone assessment. Families will be asked to contact the study coordinator to arrange a mutually convenient time for the 12-month telephone interview. If the family does not reply, the study coordinator will contact them via telephone and/or email to confirm an appointment for the follow-up assessment.
- In the event that an enrolled infant dies, the site's electronic medical record will be updated per local protocol. Many of the sites utilize an electronic medical record that automatically notifies a study team of a participant's death. The site study coordinators will verify that the patient is listed as living prior to extending an invitation for follow-up. If the patient is listed as deceased, the family will not be contacted.
- If a family withdraws from the study, the coordinators will attempt to document the reason for withdrawal so that issues can be identified and addressed.

Data Collection to Address Confounding: We will prospectively collect data for potential confounders to allow for the planned propensity scoring analysis, including:

- Term *versus* preterm at birth
- Confirmation of electrographic seizures *versus* diagnosis on clinical grounds alone
- Severity of seizures
- Etiology of seizures
- Number of seizure medications during the inpatient hospitalization
- Highest recorded phenobarbital level
- Abnormal neurological examination (consciousness, tone, or reflexes) at the time of discharge
- NICU length of stay
- Institution

Robust Analysis of Confounding Factors [DR-3]: Our plans to address analysis of confounding factors are addressed in the application's data analysis plan sections (see pages 9-12).