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Perspectives from the Society for Pediatric Research- Neonatal Encephalopathy Clinical Trials: Developing the Future

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Abstract

The next phase of clinical trials in neonatal encephalopathy (NE) focuses on hypothermia adjuvant therapies targeting alternative recovery mechanisms during the process of hypoxic brain injury.

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Identifying infants eligible for neuroprotective therapies begins with the clinical detection of brain injury and classification of severity. Combining a variety of biomarkers (serum, clinical exam, EEG, movement patterns) with innovative clinical trial design and analyses will help target infants with the most appropriate and timely treatments. The timing of magnetic resonance imaging (MRI) and MR spectroscopy after NE both assists in identifying the acute perinatal nature of the injury (days 3–7) and evaluates the full extent and evolution of the injury (days 10–21). Early, intermediate outcome of neuroprotective interventions may be best defined by the 21-day neuroimaging, with recognition that the full neurodevelopmental trajectory is not yet defined. An initial evaluation of each new therapy at this time point may allow higher-throughput selection of promising therapies for more extensive investigation. Functional recovery can be assessed using a trajectory of neurodevelopmental evaluations targeted to a pre-specified and mechanistically-derived hypothesis of drug action. As precision medicine revolutionizes healthcare, it should also include the redesign of NE clinical trials to allow safe, efficient and targeted therapeutics.

INTRODUCTION

Neonatal encephalopathy (NE), defined as disturbed neurologic function in the earliest postnatal days, manifests with a subnormal level of consciousness or seizures, difficulty maintaining respiration and depressed tone and reflexes.(1) Neonatal encephalopathy is complex and dynamic, and clinical examinations may evolve from lethargy to hyperexcitability to stupor over the first few hours and days of life.(2) The design of NE therapeutic strategies began with understanding the sequence of mechanisms involved in brain injury, where oxidative stress, excitotoxicity and inflammation contribute to accelerated cell death over the first hours, days and weeks of life.(3) Therapeutic hypothermia (TH), in infants with moderate to severe NE, reduces death or major neurodevelopmental disability and increases rates of survival with normal neurologic function.(4–6) Although rates of death and disability in infants receiving hypothermia are lower than in early trials(4,7), they still range between 16% and 29% in recent studies(8–10). Improved outcomes have been attributed to translation of TH into routine care, wider use of passive cooling after resuscitation and treatment of infants with milder NE.(8–10) Because adverse outcomes are less frequent, designing future trials of therapeutics has become more challenging: eligibility criteria for those at highest risk of poor outcomes may have changed, and trials may require larger sample sizes when using traditional neurodevelopmental measures.(8,10) Changes in the timing of the insult and multiplicity of underlying mechanisms (hypoxic, inflammatory, infectious, metabolic) leading to the clinical and biochemical presentation of NE may also contribute to recent outcomes variability.(11,12) However, while research in novel treatments continues and the landscape of NE is changing, the design of clinical trials to test safety and efficacy of novel agents has not changed in the past twenty years. The same designs, assessment tools and analyses are repeated in trial after trial, in contrast to research in fields such infectious diseases or genomics where high throughput systems and new models are revolutionizing clinical testing.

In response to this challenge, an expert panel met at the “*Hypoxic-Ischemic Encephalopathy Symposium: Developing the Future*” in Norfolk, Virginia to discuss current and future

treatment of NE. The goal was to recognize hurdles and opportunities in clinical trial design, assessment modalities, neurodevelopmental testing, biomarker use and biostatistical analyses of NE clinical trials. The experts had as their mandate to envision the future of NE clinical trials, by critically examining the past and avoiding preconceptions. A combination of the Delphi method and nominal group technique(13) was utilized to establish consensus. The organizing committee put together a broad range of current topics and questions around NE and invited a panel of experts to answer these questions. The experts convened and presented their summaries to an audience ranging from academics to industry partners. Following this, audience and organizers questioned the experts during round table gatherings. Comments and clarifying points were recorded and incorporated into a summary which was circulated back to the expert panel to reach a consensus. Finally, the draft of the summary was sent to the Society for Pediatric Research (SPR) which provided an outside perspective from the greater research community and requested clarifications and additions. The final consensus is presented in this manuscript.

SUMMARY OF CURRENT AND POTENTIAL FUTURE THERAPIES FOR NE

The next phase of NE clinical trials focuses on adjuvant therapies to hypothermia to further improve neurodevelopmental outcomes. Of interest are therapies to promote neuronal regeneration, functional and structural recovery from injury, neurovascular remodeling, optimal healing and ongoing development.(14) While TH primarily works in the latent and secondary phases of NE, new therapies also target the tertiary phase.(14) Examples of ongoing trials and potential future therapies for NE are presented in Table 1.(15,16,25,17–24)

TOOLS FOR CLASSIFICATION AND PROGNOSIS

Neurological Examination

Clinical detection of brain injury and classification of severity leverages clinical neurological examination scoring systems that allow classification of the degree of encephalopathy. However, many (Sarnat, Thompson) were developed for use in the first week of life, for the purpose of prediction rather than classification.(26) The National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN) scoring system and Score of the Iberoamerican Society of Neonatology (SIBEN) Neurologic Score were developed to define severity of NE to assist in selection of appropriate patients for TH and have been widely used in large clinical trials.(5,6,9,26,27) Regardless of the neurological classification system used, past and future trials must critically examine the rigorous nature of training and establishment of examiner reliability to ensure reproducibility of trial results. (5,6,9,27,28) The neurological examination within the first 6 hours of life is complicated by provider subjectivity, maternal or neonatal anesthesia/analgesia, dynamic evolution of the neurologic injury and compensatory responses, and timing of initiation of TH and neuroprotective therapies. The neurological examination performed in the first 6 hours has moderate predictive value for long-term outcomes.(8,29,30) However, repeated exams throughout hospitalization and discharge can improve predictive value.(31)

Serum Biomarkers

Serial measurements of serum neuronal and inflammatory biomarkers may classify the severity of NE, determine the timing, pathophysiology and extent of brain injury, identify infants for appropriate adjuvant neuroprotective therapies and assist in predicting neurodevelopmental outcomes. Biomarkers have the potential to advance the current landscape of NE clinical trials by monitoring real-time response to treatment and predict functional outcome rather than waiting 5–7 years to evaluate the success of a new therapy. (32)

For neuronal injury, multiple protein-derived markers have potential for biomarkers from neurons (neuron specific enolase [NSE] and ubiquitin carboxy-terminal hydrolase-L1 [UCH-L1]), glial cells (glial fibrillary acidic protein [GFAP] and S100B protein), Tau protein; inflammatory cytokines and chemokines (interleukins [IL], interferon gamma [IFN- γ], tumor necrosis factor alpha [TNF- α], brain-derived neurotrophic factor [BDNF], monocyte chemoattractant protein-1 [MCP-1] and vascular endothelial growth factor [VEGF]) are also promising.(32–34) For example, Chalak et al(35), demonstrated a concentration-dependent relationship between serum GFAP and UCH-L1 at birth and severity of encephalopathy, with GFAP predictive of later abnormal outcomes; Massaro et al(15) proposed BDNF as a marker of neuronal repair with higher levels at day 5 associated with reduced brain injury on magnetic resonance imaging (MRI) and improved motor performance at 1 year.

Neonatal Electroencephalogram

When infants experience neural insults, the electroencephalogram (EEG) commonly reverts back to primitive and premature patterns.(36) EEG can display background abnormalities of amplitude, continuity, frequency, symmetry, interhemispheric synchrony, sleep states, and maturation.(36)

Inter-rater agreement in neonatal EEG background scoring is highest for voltage, seizure presence, continuity, burst voltage, suppressed background presence and overall impression but poor or inconsistent for other patterns, highlighting the importance of using major neonatal EEG background categories for interpretation.(37) EEG background activity at 24, 36 and 48 hours after birth is highly predictive of severity of brain injury on MRI and later neurodevelopmental outcomes in infants with NE undergoing TH.(38–40) Finally, amplitude-integrated EEG (aEEG) background at 6 hours in infants undergoing TH has some limited positive predictive value.(41) However, the progression of aEEG patterns in the setting of hypothermia (particularly, time to normalization of the background and the time of onset of sleep-wake cycling) have important prognostic value over time; an aEEG that remains abnormal at 48 hours is predictive of an adverse outcome.(41–43) Prognostic power of early aEEG improves substantially when combined with a standardized clinical neurological examination.(44,45)

Near-Infrared Spectroscopy

Dysfunctional vasoreactivity and autoregulation in NE may contribute to secondary brain injury and poor neurologic outcomes.(46–48) Impaired cerebral autoregulation, measured by

near-infrared spectroscopy (NIRS) parameters correlates with neurologic injury on MRI(47,49–53) and 2-year neurodevelopmental outcomes in NE.(54) NIRS can determine an individual neonates' ideal mean arterial pressure to optimize autoregulatory vasoreactivity.(46) Maintenance of mean arterial pressure within this individualized optimal range, correlates with neurologic injury on MRI and later neurodevelopmental outcomes. (46,52–54) NIRS, blood pressure and EEG metrics have been combined into a novel, wavelet neurovascular bundle analytical system to allow real-time, non-invasive quantification of cerebral autoregulation and neurovascular coupling at the bedside. (51,55,56) While still being validated in larger cohorts, this bundle may facilitate a precision medicine approach to patients with NE, facilitating individualized risk-stratification and addition of adjunct neuroprotective therapies.(47,55,56)

Neuroimaging

MRI with proton MR spectroscopy (MRS) in neonates with NE is an important prognostication tool as it provides the best anatomical delineation of brain structure and injury with multiple complementary sequences available.(57) However, challenges with MRI in neonates include transportation and distance of tertiary care centers, potential need for sedation, and requirement of expert interpretation. Typical MR imaging protocols in NE include structural sequences (T1, T2), diffusion weighted sequences (diffusion tensor imaging [DTI], diffusion weighted imaging [DWI], apparent diffusion coefficient [ADC]), susceptibility weighted imaging (SWI) and spectroscopy (MRS).(58)

Due to the pathophysiology of perinatal asphyxia with initial ischemia and subsequent reperfusion, diffusion imaging injury patterns evolve over time (Figure 1).(59,60) Existing challenges include the ability to obtain high quality, high resolution imaging without motion, and the effects of variability of timing and nature of injury on diffusion patterns, as well as the subjective nature of interpretation. Recently, progress has substantially improved standardization of diffusion imaging interpretation through publicly available, normative, age-specific ADC atlases.(61)

The search for optimal MR biomarkers has recently focused on MR spectroscopy. A meta-analysis of prognostic accuracy of cerebral MR biomarkers in infants with NE demonstrated that in the first 30 days, MRS measures, particularly the deep gray matter lactate/N-acetyl-aspartate (NAA) ratio, most accurately predicted an adverse neurodevelopmental outcome. (62,63) However, the biggest roadblock in widespread use of MRS as a biomarker in NE has been the difficulty of achieving harmonization across multiple centers and models of MR scanners.(8,63) In the MARBLE study, a large prospective, multicenter cohort study of MRS biomarkers, harmonization of robust thalamic proton MRS biomarkers across several centers was achieved using 3.0 Tesla MR systems from three different manufacturers. MR spectroscopy thalamic NAA concentration alone, accurately predicted an adverse neurodevelopmental outcome at 2 years (AUC 0.99, sensitivity 100%, specificity 97%).(8) Thalamic NAA concentration outperformed other current predictive methods such as the NICHD neurological exam (within 6 hours of birth and at discharge), aEEG background (within 6 hours of birth) and other MR sequences. The MRS protocol developed from this study is being validated in a trial of TH in low and middle income countries.(64) Ongoing

research will assess whether adjunctive neuroprotective interventions affect MRS metrics and whether changes in these biomarkers reflect later neurodevelopmental outcome.(17,64) MRS biomarkers could improve the efficiency of neonatal neuroprotective trials by functioning as surrogate outcome measures in phase 2 studies(65) or by allowing optimizing of protocols prior to phase 3 trials.(8,10)

NEONATAL ENCEPHALOPATHY CLINICAL TRIAL OVERSIGHT

Multicenter parallel design randomized controlled trials (RCT) have been the mainstay of NE intervention testing. Most have leveraged large academic networks and professional centers specializing in data coordination(66), while others have added additional study management knowledge gained from industry-sponsored trials.(17) Lessons learned from the multicenter High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) trial can help rethink trial management processes and infrastructure to design the next generation of NE neuroprotection RCTs, with particular focus on process building, efficiency, and customer service.

NE trials frequently enroll subjects within hours of birth, while addressing the challenges of shocked families facing a critically ill neonate and often separation from transfer to a tertiary hospital. In trials involving administration of study drug, clinical pharmacies may be called upon to prepare medication at off-hours when investigational pharmacies are closed; laboratory and informed consent procedures are often required at precise times, outside of standard work hours. These challenges require unique solutions and well-organized study management.

Study Design and Startup

When designing any RCT, it is critical that all study decisions be made with study end-goals and primary endpoints in mind. Primary endpoints should be clearly articulated, and must address the study goals, whether they be regulatory approval, change in clinical practice, data collection for future studies, or reimbursement. Prior to creating data collection instruments, it is more efficient to create initial shell tables for future publications, with consort diagrams as integrated components.(67) Ensuring all essential data are collected in an appropriate and consistent manner is critical to study success and collection points can be viewed as process flow measures.

Then, as study processes are designed, pre-specified study endpoints should be referred to frequently in developing flows, lest a change to a study procedure inadvertently compromise crucial study data.

Because NE trials often involve enrollments at multiple sites, site-by-site processes may differ. Through collaborative central coordination, awareness of site practice differences, and use of flexible process templates created by a central study team, consistency across sites can be achieved. Efficient NE trial processes may necessitate having a rotating call schedule for evening and weekend enrollments. In a trial involving the investigational drug service (IDS) division of pharmacy, individual meetings with each IDS director are important to establish logistics of potential off-hours enrollment. Study teams must also develop primary

and contingency plans for biological samples processing (personnel, equipment, and long-term storage). If neuroimaging endpoints are used, harmonization across multiple neuroimaging platforms, and processes for central image archiving and review should be considered.(17) NE trials often include neurodevelopmental follow-up extending into childhood. Participating sites should therefore have the proven capacity not just to enroll subjects, but to have high long-term follow-up rates. The study should also consider how standardization of neurodevelopmental scales will occur, as clinical exams are often not performed with the consistency and level of rigor that a clinical trial outcome measure demands. For all of these processes, clear and consistent methods should be communicated to participating sites in a collaborative manner. This approach is common in industry where Lean Six Sigma and other efficiency tools are standard.(68)

Study Management and Oversight

After study startup, trial leadership should make themselves personally accessible to answer time-sensitive study questions, ensuring consistency amongst enrollments and continued engagement. Frequent communication of enrollment and deliverable achievement is a motivational technique that also updates collaborators on trial progress. Collaborative regular team meetings may include smaller leadership groups, and separately, the larger study team. Communication of pre-specified metrics helps clarify expectations and ensure a common goal. Suggested metrics include overall and site-specific study enrollment, follow-up rates, and compliance with data entry and data quality expectations. For many NE studies, enrollment and consent processes may be complex and a study monitoring plan is necessary. On-site monitoring visits may be required in addition to remote conferencing to ensure regulatory compliance, and provide an opportunity to review source data for critical study data fields.

BIostatistical CHALLENGES AND OPPORTUNITIES IN TRIAL DESIGN AND ANALYSIS

Challenges to statistical design and analyses plans in NE clinical trials include reproducibility, efficient data use, limited eligible subject pool (especially in single-center designs), and long-term follow-up. Using pre-specified, innovative biostatistical analyses can help overcome many of these challenges.

Bayesian Analyses

Bayesian analysis integrates prior information with newly collected data to obtain a posterior estimate of the effect of difference.(69,70) It is a natural way to incorporate prior evidence into the analysis of current data in the setting of a limited sample size. The late cooling trial (JAMA 2017) used a pre-specified Bayesian analysis given the anticipated limited sample size.(27) This analysis can produce clinically meaningful measures, such as the probability of treatment benefit.

Criticism of this method lies in the fact that using prior information is a form of assumption. To overcome this, Laptook et al(27) represented the prior information with several different

options—a neutral, skeptical and enthusiastic prior, generating different final summaries of the evidence.(70)

Adaptive Clinical Trials

Adaptive clinical trials allow planned modifications to one or more aspects of the design, based on data collected from the study's subjects while the trial is still ongoing. This type of design may allow patients to access the most significant benefit of a treatment by allocating more subjects to the most clinically efficacious arm or dose, after an interim analysis. Adaptive clinical trials allow investigators to use information not available at the start of the trial to improve efficiency and provide a greater chance of detecting the true effect of an intervention, often with a smaller sample size or in a shorter timeframe. This can reduce the number of patients exposed to unnecessary risks or ineffective investigational treatments; it can even increase the willingness of parents to enroll their children in these types of trials as they increase the probability that subjects will be assigned to the most effective treatments. (71,72)

Biostatistical Opportunities in Clinical Trial Design

Investigators can utilize internet resources to improve standard surveys, experiments, and health reporting. Incorporating modern statistical methodology (and Bayesian methods) can increase efficient use of all available information. Complex designs benefit from early statistical involvement with carefully considered and pre-specified analysis plans.

INTERMEDIATE AND LONG-TERM NEUROPHYSIOLOGY AND DEVELOPMENT

Monitoring of Neurodevelopmental Trajectories

Neurodevelopment is a complex continuum, occurring in the context of maturation, genetics and experiences.(73) Additionally, trajectories can change with experience and environmental factors, infants can form new neuronal connections and develop new functionality. This neuroplasticity, which peaks in the first 3 years of life is however also an area of vulnerability. Evidence-based interventions, focused on cognition, feeding, language, motor, pain, parenting, spasticity management, sleep, or vision, many of which start in infancy, take advantage of this plasticity after perinatal brain injury. Previous and current NE clinical trials focus on neurodevelopmental trajectories that include only term-equivalent age (TEA) and 18–26 month time points. However, this “trajectory” is poorly predictive of school age and later outcomes as it does not account for the complexity of factors occurring between these two time points, some confounded by treatment allocation.(74–76) While the 2-year Bayley does not accurately predict outcomes from childhood to adolescence, using the Bayley at multiple time points, to obtain a true developmental slope may be more predictive. An ideal early neurodevelopmental trajectory as illustrated in Figure 2, would include a variety of time points with targeted assessments from TEA to 2 years. However, not every outcome may be of interest for every NE treatment.

Tests of Neurophysiological Responses

Tests of neurophysiological responses including standardized scorable neurological exams and functional neuroelectrical imaging commonly allow longitudinal evaluation; however these tests may be less sensitive to interventions in the short-term.

Standardized scorable neurological exams—While the modified Sarnat has been used widely to quickly categorize stages of NE, it was never intended to be a tool to determine patient eligibility for randomized controlled trials.(26) It is therefore intrinsically limited and may need revisions for use in newer clinical trials. Other exams may provide a more precise characterization of neurological condition, but with increasing complexity and more validation of inter- and intra-rater reliability to ensure rigor and reproducibility. Such an assessment, the Hammersmith Neonatal Neurological Examination (HNNE) is reliable as early as the first few hours of life(77) throughout the newborn period to TEA, allowing for longitudinal evaluation with a single, quantitative test.(78) Age-specific optimality scores allow comparisons with neurophysiologic and imaging findings, with good correspondence between HNNE scores and neuroimaging.(78,79) The Hammersmith Infant Neurological Examination (HINE), for infants aged 2–24 months demonstrates good correspondence between MRI findings and HINE scores in infants with NE.(80) Sequential use of the HNNE in the newborn period and the HINE through 2 years of age, offers a continuum for assessment of neurologic function and allows identification of early signs of cerebral palsy (CP) and other neurological disorders.

Functional neuroelectrical imaging—At its simplest, functional neuroelectrical imaging (time-locked EEG/event-related potential [ERP]) can test the cortical processing of a single stimulus using somatosensory (SEP) or visual evoked potentials (VEP). Combining somatosensory or visual evoked potentials with MRI and EEG improves prediction of later global neurodevelopment. SEP and VEP are especially important prognostic tools in infants with a normal MRI after NE and TH.(81) Advanced analysis techniques leveraging topographic analyses and inverse-source localization can allow measurement of more involved functions such as speech sound discrimination, touch processing or multisensory integration to accurately predict more complex, functional processing later in life.(82–84)

Behavioral Tests of Systemic Function

Behavioral tests of systemic function can be divided into those that evaluate a single major domain or those that test multiple domains. Each test has strengths and drawbacks; some allow for longitudinal evaluation (Bayley Scales of Infant and Toddler Development, 3rd and 4th editions [Bayley-III and Bayley-IV], Infant/Toddler Sensory Profile [ITSP], Child Behavior Checklist [CBCL]); some are very sensitive to interventions (Peabody Developmental Motor Scales[PDMS-2]); many have difficulties adapting for children with neurosensory or motor impairments.(85) Predictive validity for school-age outcomes differs with each individual test, but overall increases with age at testing. Systematic reviews exist for many of the individual domain tests and are detailed in Table 2.(85–94)

While single domain tests can isolate the area of concern and may be quicker to perform, the feasibility of training personnel for testing, analyzing and scoring each can be problematic.

Advantages of multi-domain assessments include efficiency, a global assessment of the child's strengths and weaknesses at a single time point, with value for longitudinal assessments. Conversely, multi-domain assessments can be time-consuming, costly, require extensive reliability monitoring, and have mixed predictive value into adulthood when performed at 2 years.(95,96)

Biomarkers of neurologic function

Neurodevelopmental biomarkers include movement patterns (Prechtl's General Movements Assessment [GMA]), HNNE/HINE optimality and cutoff scores and scoring/classification systems (Gross Motor Function Classification System [GMFCS]). These biomarkers are used at a single time point evaluation, may not respond to interventions and were developed for their diagnostic, classification or prognostic value. The GMA evaluates spontaneous movements originating in the brainstem that begin in fetal life and function to build neural connectivity between motor and sensory systems.(97) Movement patterns such as cramped-synchronized movements at TEA and absent fidgety movements at 3–5 months are predictive of CP and other developmental problems.(98) The HINE optimality score is based on the frequency distribution of the scores in the normal population.(99) Specific HINE cut-off scores, with a high sensitivity and specificity for prediction of CP during the first year of age are reported in both preterm and term-born high-risk infants (99) For children with CP, classification systems exist for multiple functional domains (fine and gross motor, communication) which often predict late childhood or adult function, when performed after 2 years of age.(100,101)

PERSPECTIVES FROM THE SPR

The next phase of NE clinical trials focuses on hypothermia adjuvant therapies.(15–19,22,24,25) Many adjuvant therapies target alternative recovery mechanisms or multiple phases during the progression of hypoxic brain injury.(14) Future clinical trial designs could incorporate new paradigms to address common challenges, considering various phases of injury and recovery, and no longer a pseudo-normalization of 2-year test-scores (see Table 3 for a summary of recommendations).(8,10,56–60,63,64,71,73,74,15,75,77–79,81–84,98,102,17,103–111,27,30,32,35,47,55)

- 1. Identification and classification of trial participants:** Solutions to optimize the predictive value of the neurologic exam include performing consistently-timed, serial exams, standardization through extensive practice in other newborn populations, video recording of the exam, and use of standardized, scorable and predictive exams such as the HNNE.(77–79) A panel of multiple inflammatory and neuronal biomarkers may also advance the current landscape of NE clinical trials and individualize care by characterizing degree of initial injury, risk stratification, and acute assessment of treatment efficacy. For example, metabolomic profiling could characterize mechanisms of injury that differentiate mild from more severe NE and need for specific adjuvants.(112) Finally, use of early aEEG augmented by new machine-learning algorithms holds promise in classifying the presence of neural insults even when overt signs may not be clear or in settings where other approaches are challenging.(102)

2. **Timing of evaluation after NE is critical.** Two recommended MRI time points assist in identifying the acute perinatal nature of the injury (days 3–7) as well as the full extent and evolution of the injury (days 10–21).(58,113) The later in this window follow-up imaging occurs, the more likely it is to reflect the full evolution of injury and a possible intermediate endpoint. However, return to the hospital soon after discharge can be challenging for families, often necessitating an earlier follow-up MRI (day 10) while injury is still evolving. Finally, MRS biomarkers obtained between 4 and 14 days of life can provide added value for prediction of adverse neurodevelopmental outcomes in cooled neonates with NE with recognition that the full neurodevelopmental trajectory is not completely defined at this time point.(8) An initial evaluation of each new therapy at this time point, with neuroimaging and other measures (Figure 3) may allow higher-throughput selection of promising therapies for more extensive investigation. Ultimately, this approach would circumvent the impact of concurrent clinical trials of post-discharge interventions and rehabilitative therapies that may mask global effects traditionally measured at 2 years.
3. **Rethinking trial management processes and infrastructure** with attention to aspects of process building, efficiency and customer service, along with leveraging hospital quality improvement policies, can help focus study design and management. The following strategies can be useful: making study metrics regularly available to site teams (through automation or standardized processes); augmenting on-site visits with remote, database review allowing sites to correct anomalous data in near-real time(114); and videoconference check-ins after the first 3 patients enrolled to support process flow review. Additionally, using pre-specified, innovative biostatistical analyses, such as Bayesian analyses or adaptive clinical trials, can help overcome challenges to statistical designs and analysis plans, decreasing wasted time and resources in vulnerable and rare populations.(27,70,71)
4. **A developmental trajectory:** Rather than reducing the complex human brain and nervous system to a single poorly predictive primary outcome at 2 years, targeting a trajectory of multiple developmental assessments, exams and biomarkers used for evaluation at critical inflection points allows detection of intervention-specific outcomes (Figure 2). As innovative therapies evolve from “shotgun” approaches to precision medicine, so should developmental testing. Feasibility and predictive value increase as the specificity of the outcomes desired increase, whether they be improved parent-infant interactions or motor function. However, behavioral, emotional and executive function outcomes at school-age remains the ultimate safety metric of all neonatal trials.

CONCLUSION

While new neuroprotective therapies appear promising, the design of clinical trials to test the safety and efficacy of these agents has hardly changed in the past twenty years. Combining a variety of biomarkers with innovative and carefully planned clinical trial design and analysis

will help target infants with the most appropriate and timely treatments (Table 3 and Figure 3). The combination of serial, standardized neurological examinations, serum biomarkers, EEG background patterns and neuroimaging may give the best indication of early and intermediate recovery from injury.(38,39) Functional recovery can be assessed using a trajectory of neurodevelopmental evaluations targeted to a pre-specified and mechanistically-derived hypothesis of drug action. Ultimately, recovery after NE occurs on a continuum, first at a cellular and microstructural level, and eventually at functional levels with each step dependent and building on the previous (Figure 3). As precision medicine revolutionizes healthcare, it should also include the redesign of NE clinical trials to allow safe, efficient and targeted therapeutics.

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Impact

What is the key message of your article?

- As precision medicine revolutionizes healthcare, it should also include the redesign of NE clinical trials to allow faster development of safe, effective and targeted therapeutics.

What does it add to the existing literature?

- This article provides a multidisciplinary perspective on the future of clinical trials in NE; novel trial design, study management and oversight, biostatistical methods and a combination of serum, imaging and neurodevelopmental biomarkers can advance the field and improve outcomes for infants affected by NE.

What is the impact?

- Innovative clinical trial designs, new intermediate trial end points and a trajectory of neurodevelopmental evaluations targeted to a pre-specified and mechanistically-derived hypothesis of drug action can help address common challenges in NE clinical trials, allow for faster selection and validation of promising therapies for more extensive investigation.

Time post-injury	Conventional	Diffusion	Spectroscopy
First 24 hours	Negative	Mild changes	↑lactate
24-72 hours	Negative	↓ADC	↑↑lactate
4-7 days	Minimal change	↓↓ADC ? ↓ FA	↑ lactate ↑↓ NAA
7-14 days	T1 and T2 changes evolve	Normal ADC in regions of injury ↓↓ ADC in Wallerian degeneration	↑ or normal lactate ↓NAA
>14 days	Atrophy of lesion	↑ADC ↓FA	↓NAA

Figure 1. Evolution of Injury on MRI.

The evolution of injury patterns seen on MRI (conventional, diffusion and spectroscopy sequences) from 24 hours post-injury to more than 2 weeks post-injury. Diffusion abnormalities normalize over time with pseudo-normalization occurring after the first week of life.(59,60) The interval between initial insult and pseudo-normalization presents an opportunity for recovery using additional neuroprotective strategies.

MRI, magnetic resonance imaging; *ADC*, apparent diffusion coefficient; *FA*, fractional anisotropy; *NAA*, N-acetyl aspartate.

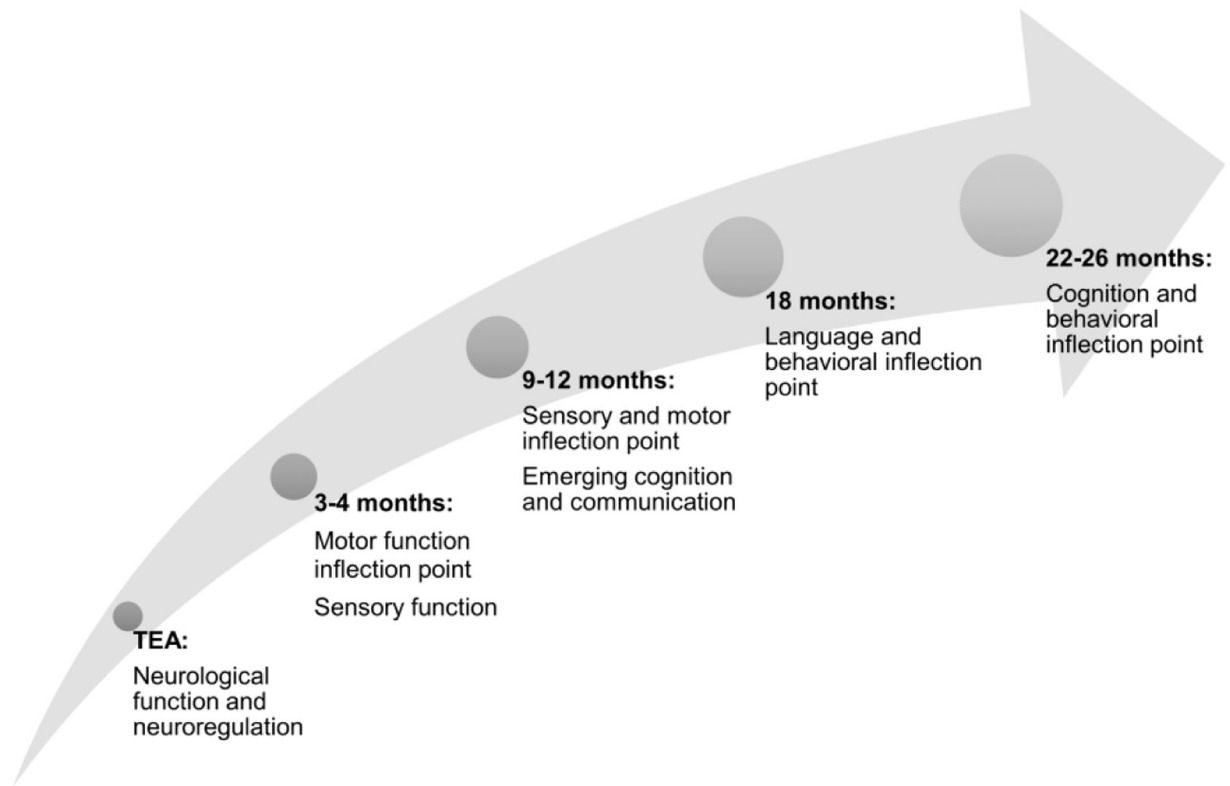


Figure 2. A True Neurodevelopmental Trajectory.

An ideal early neurodevelopmental trajectory includes a variety of time points, each of which represent a specific developmental domain inflection point with targeted assessments from TEA to 2 years.

TEA, term-equivalent age.

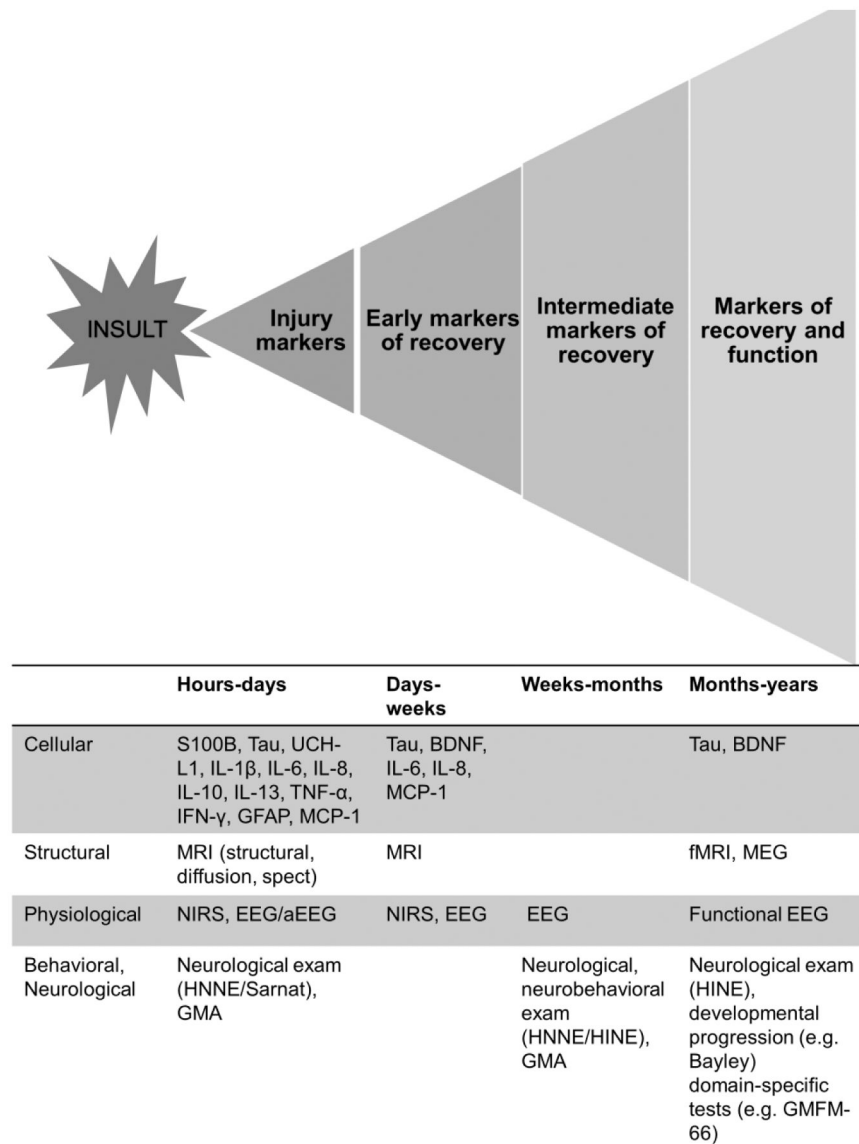


Figure 3. Measurements in the Continuum of Injury and Recovery in NE.

Markers of injury and recovery after neonatal NE as measured at the cellular, structural, physiologic, behavioral and neurological level. Recovery after NE occurs on a continuum, first with recovery at the cellular and microstructural level and leading to functional recovery with each step dependent and building on the previous. As time from injury increases, the imprecision of prediction provided by the assessment also increases as reflected in the pyramidal shape in the figure.

aEEG, amplitude-integrated electroencephalogram; Bayley, Bayley Scales of Infant Development; BDNF, brain-derived neurotrophic factor; EEG, electroencephalogram; fMRI, functional magnetic resonance imaging; GFAP, glial fibrillary acidic protein; GMA, Preclt's General Movements Assessment; GMFM-66, Gross Motor Function Measure; HINE, Hammersmith Infant Neurological Examination; HNNE, Hammersmith Neonatal Neurological Examination IFN- γ , interferon gamma; IL, interleukin-1 β , IL-6, IL-8, IL-10,

IL-13; MCP-1, monocyte chemotactic protein-1; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NE, neonatal encephalopathy; NIRS, near-infrared spectroscopy; TNF- α , tumor necrosis factor alpha; UCHL1, ubiquitin carboxy-terminal hydrolase-L1

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TABLE 1.

Current and Potential Future Therapies for NE

Current NE Clinical Trials		
Agent	Highlighted results	Ongoing studies
Erythropoietin	NEATO (phase II) trial with decreased brain injury on MRI and improved short-term motor outcomes.(15,16)	HEAL (phase III): multicenter, double-blind, placebo-controlled study of high-dose erythropoietin.(17)
Cord blood/stem cells	Phase-I open-label study of term neonates with NE demonstrated safety and feasibility.(18)	Phase II randomized, double-blind, placebo-controlled, multi-site trial of autologous cord blood cells for NE. (19)
Melatonin	Neuroprotective in preclinical studies(20,21)	Phase I, open-label, dose-escalation trial of melatonin in neonates with NE undergoing TH.(22)
Anti-epileptics	Prophylactic barbiturate therapy for NE not recommended.(23) Topiramate adjuvant to TH is safe, did not reduce combined frequency of mortality and severe neurologic disability.(24)	Randomized, double-blind, placebo- controlled trial of topiramate as adjuvant to TH.(25)

NEATO, Neonatal Erythropoietin and Therapeutic Hypothermia Outcomes; *NE*, neonatal encephalopathy; *MRI*, magnetic resonance imaging; *HEAL*, High-Dose Erythropoietin for Asphyxia and Encephalopathy; *TH*, therapeutic hypothermia.

TABLE 2.

Examples of Single Domain Assessments

Domain	Tests	Systematic Reviews
Motor	AIMS, Bayley-III, BOT-2, MABC-2, MAND, Mullen, NSMDA, PDMS-2	Griffiths 2018(86) Kjolbye 2018(87)
Sensory Processing	TSFI, SRS, ITSP	Eeles 2013(88)
Communication	Bayley-III, CAT/CLAMS, CSBS-DP, Mullen, REEL-3, PLS-5	Nelson 2006(89)
Adaptive Behavior/Social Emotional	ABAS-II, ADEC, CARS-2, CBCL, ITSEA, Vineland SEEC	Hanratty 2015(90) Halle 2016(91) McCrae 2018(92)
Cognitive	Bayley-III, DAS-II, FTII, GMDS, SB-5, WJ-III, WPPSI, Mullen, MMFC	Brydges 2018(93) Morgan 2019(85) Wong 2016(94)

ABAS-II, Adaptive Behavior Assessment System; **ADEC**, Autism Detection in Early Childhood; **AIMS**, Alberta Infant Motor Scale, **Bayley-III**, Bayley Scale of Infant and Toddler Development 3rd edition; **BOT-2**, Bruininks-Oseretsky Test of Motor Proficiency; **CARS-2**, Childhood Autism Rating Scale second edition; **CBCL**, Child Behavior Checklist; **CAT/CLAMS**, Clinical Adaptive Test/Clinical Linguistic Auditory Milestone Scale; **CSBS-DP**, Communication and Symbolic Behavior Scales-Developmental Profile; **DAS-II**, Differential Ability Scales; **FTII**, Fagan Test of Infant Intelligence; **GMDS**, Griffiths Mental Development Scales; **ITSEA**, Infant Toddler Social Emotional Assessment; **MABC-2**, Movement Assessment Battery for Children; **MAND**, McCarron Assessment of Neuromuscular Development; **MMFC**, Mayes Motor-Free Compilation; **Mullen**, Mullen Scales of Early Learning; **NSMDA**, Neurological Sensory Motor Developmental Assessment; **PDMS-2**, Peabody Developmental Motor Scales; **SB-5**, Stanford-Binet Intelligence Scales; **TSFI**, Test of Sensory Function in Infants; **SRS**, Sensory Rating Scale for Infants and Young Children; **ITSP**, Infant/Toddler Sensory Profile; **Vineland SEEC**, Vineland Social-Emotional Early Childhood Scales; **WJ-III**, Woodcock-Johnson III Tests of Cognitive Abilities; **WPPSI-III**, Wechsler Preschool and Primary Scale of Intelligence

TABLE 3:

Future of Neuroprotection Trials for NE: Recommendations and Future Directions

Identification of appropriate neonates for TH and for adjunctive neuroprotective therapies	<ul style="list-style-type: none"> Consistently-timed, serial neurologic exams in the first 24 hours (i.e. 1 hour, 3 hours, etc.) (30,77–79) Standardization of the neurological exam through rigorous training and validation of each examiner Video-recording of the neurological exam to refine practice and improve validity and reliability Continued research to develop a panel of inflammatory and neuronal blood based-biomarkers to allow more accurate assessment of the degree of initial injury and stratification for clinical trials(15,32,35) Early aEEG augmented by machine-learning algorithms to assist in clinical classification and seizure detection(102) Novel NIRS analyses to facilitate individualized risk stratification and addition of adjunct neuroprotective therapies(47,55,56)
Predicting response to TH	<ul style="list-style-type: none"> Investigation of presence/modulation of cold shock proteins or cold shock hormones to optimize TH-mediated neuroprotection in NE. These represent potential novel therapeutic drug targets. (103,104) Use of immune responses as predictors of patient response to TH to identify patients who may benefit most from adjuvant therapies(105) Use of novel MRS biomarkers to allow early evaluation of response to TH, not only of injury severity(8)
Methodology for improved trial consistency	<ul style="list-style-type: none"> Regular and automated distribution of study metrics to site teams(17) On-site and remote database review to allow for correction of anomalous data in real-time Process flow review after the first 3 patients enrolled at each site, and again at half of projected enrollment Pre-specified, innovative biostatistical analysis designs (i.e. Bayesian analyses, adaptive clinical trials)(27,71)
Timing of neuroimaging	<p>Two MRI scans:</p> <ol style="list-style-type: none"> 1 Early (days 3–7): delineate injury on diffusion imaging, estimate timing of injury, MRS biomarkers(8,59,60,63) 2 Late (days 10–21): delineate injury on conventional sequences, prediction of neurodevelopmental outcome(57,58,60)
Surrogate endpoints	<ul style="list-style-type: none"> MRS biomarkers (NAA concentration, NAA-lactate ratio) to allow evaluation of early response to new neuroprotectants and speed up stepwise testing(8,10) Day 21 MRI, resting state connectivity, cerebral blood flow patterns, other novel neuroimaging techniques(58,106–110) Early motor patterns (GMA)(98) Electrophysiological markers during task-based paradigms, resting state and functional connectivity(81–84)
Long-term neurodevelopmental follow-up	<ul style="list-style-type: none"> Re-thinking neurodevelopment as a trajectory with developmental assessments, exams and biomarkers used for evaluation at critical inflection points and examination of the slope of changes(73–75) Targeted developmental testing based on neuroprotective therapies received and their specific actions
TH and trial design in LMIC	<ul style="list-style-type: none"> Safety and efficacy of TH in LMIC (represent 99% of encephalopathy burden) remains unclear (HELIX trial ongoing in India, Sri Lanka and Bangladesh)(64)

- Assessments and therapeutic design need to be adapted and field tested for specific environments to be effective, especially accounting for poverty and other sociodemographic factors.(111)

aEEG, amplitude-integrated electroencephalogram; *GMA*, Prechtl's General Movements Assessment; *HELIX*, hypothermia for encephalopathy in low and middle-income countries; *LMIC*, low- and middle-income countries; *MRI*, magnetic-resonance imaging; *MRS*, proton magnetic-resonance spectroscopy; *NAA*, N-acetyl-aspartate; *NE*, neonatal encephalopathy; *NIRS*, near-infrared spectroscopy; *TH*, therapeutic hypothermia

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