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The Neonatal Research Network: History since 2003, future directions and challenges

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Abstract

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) was established in 1986 in response to the need for rigorous studies to guide care and management of sick and premature newborns. The network is comprised of clinical centers that perform clinical protocols to investigate the safety and efficacy of treatment and management strategies for newborn infants as well as a data coordinating center. Infrastructure is set up for observational and interventional studies as well as neurodevelopmental follow-up of patients. The network has conducted trials and observational studies on major neonatal problems including pulmonary disease, neuroprotection, sepsis and infection, necrotizing enterocolitis, vaccine administration to preterm infants, retinopathy of prematurity, cardiovascular issues including blood pressure, human milk, growth and nutrition, hematologic issues, resuscitation, pulmonary hypertension, and neurodevelopmental outcome. This mechanism of clinical research for newborns has led to changes in care practices leading to improved outcomes for high-risk infants.

Network background and infrastructure

The NRN was established in 1986 in response to the need for well-designed multicenter studies in neonatology. Prior to the establishment of the network, very few neonatal intensive care unit (NICU) therapies and management approaches were subjected to rigorous investigation prior to institution into general practice. The network is configured based on a Request for Applications (RFA), which has been issued at 5-year interval beginning in 1986. The RFA stipulates eligibility information as well as expectations for the clinical centers. The goals of the NRN are (a) to perform randomized controlled trials of unproven or promising therapies, (b) to conduct observational studies of infants at highest risk and evaluating their neurodevelopmental, cognitive and behavioural outcomes, (c) to disseminate results of NRN studies to the scientific and lay community, and (d) to involve young faculty in NRN activities.

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Network advantages

There are a significant number of advantages with establishing a neonatal network. There are large numbers of patients available for common as well as rare diseases. The RFA for the clinical sites stipulates that the centers have access to patients with high risk pregnancies and level III–IV newborn intensive care units (NICUs) with adequate numbers for potential research studies. Outpatient capability to follow high risk infants are necessary as well as pediatric medical and surgical subspecialty involvement in individual protocols, research pharmacy, data systems, and institutional support. The applications submitted in response to the RFA undergo peer-reviewed by an NICHD convened study section and a second level of review by the NICHD Advisory Council with subsequent funding.

The network has the collective knowledge of the principal investigators, co-investigators, follow-up investigators, and data coordinating expertise. There is a separate RFA for the data coordinating center (DCC) applications. The DCC plays a central role with respect to study development, implementation, data management, statistical analysis, and reporting of results in peer-reviewed literature. The DCC also provides logistics for training, communications, meetings, development of data collection forms and manual of procedures (MOP) and other necessary tasks involved with running clinical studies. The NRN has set policies and procedures that are revised periodically to accommodate changing needs. They include operating procedures, protocol development and review processes, subcommittee membership and publications policies including authorship. The NRN data forms and MOP are shared with any researchers requesting these documents following approval of the request by the Steering Committee of site principal investigators, DCC PI, and NICHD NRN Program Scientist.

The NICHD NRN has been very successful with respect to recruiting and retaining patients thanks to the dedication of the clinical sites and their staff. The Figure shows a graphical representation of NRN studies over time. The follow-up rates exceed 90% for clinical studies. The clinical sites have various measures in place to achieve high compliance rates including early identification of infants for follow-up, tracking and maintaining contact with families, institutional research board (IRB) approved incentives for families, scheduling and procedures for rescheduling missed visits, seeing children at other network locations, and home visit for follow-up in specific cases.

The NICHD NRN has challenges in conducting multicenter research. Center differences are the most important challenge: populations may be different, practice styles vary, and equipment may be different at different hospitals. Many units have written policies or guidelines for specific management such as nutrition, respiratory care, cardiorespiratory monitor alarm limits, and so forth. Developing a clinical study oftentimes requires compromise as opposed to consensus. Simple definitions can be a challenge if there is variation across sites. Determination of primary and secondary outcomes can be an area of lively debate. Further, determination of equipoise at any site may be a challenge, particularly if there are passionate views on a management strategies or entrenched systems of belief in patient care. Agreement from the staff in the intensive care nursery including physicians, nurses, therapists, and consultants to participate in the studies can be challenging to

overcome. Review of the existing evidence for practice can generally be productive as well as eye-opening for the various sites. Center differences may account for variance equal to or greater than the anticipated treatment effect in trials; thus, center is accounted for in statistical analyses, usually as a random effect.

Education and in-service training are performed prior to the launch of a new study/trial and on an on-going basis. Time to study start can be highly variable depending on staff, IRB lead time for submission, review and approval, and appropriate training or certification at individual sites and centers. Studies or trials that require recruitment in a short time window or at the time of delivery can pose significant challenges with research staff coverage on nights, weekends, and holidays. Many successful clinical sites participate in multiple research projects at any one time, so the issue of conflicting trials must be addressed for each study. NRN centers also have the challenge of on-going research projects for trainees, both residents and fellows.

The large population of infants available through the network is generally a positive feature. However, market forces can sometimes result in changes in institutional contracts, insurance participation, and hospital events, which can affect the populations available for the clinical trials. There is also variation in IRB timelines as well as specific institutional, state, and local rules that can affect study start times.

Many centers in the NRN have more than one recruiting hospital. This may occur when there is a university delivery hospital as well as a stand-alone (or connected) children's hospital. Many centers staff additional hospitals in their local areas and are able to recruit and retain patients from these institutions. Additionally, several sites have formed consortium arrangements with other academic or private hospitals (satellite sites) to increase the available population for recruitment as well as increase the intellectual contributions from these institutions. The satellite sites are expected to perform in the same manner as the parent institution with respect to recruitment and follow-up of patients. It is therefore essential for the main NRN site to develop mechanisms for working with satellite sites to get appropriate IRB approvals, collaboration from clinicians to conduct protocols, reporting of adverse effects or protocol violations per the NRN as well as satellite site regulations and perform data entry. Satellite sites need to have appropriate resources to conduct research within the framework of the NRN budget process. The advantages of participation include being represented on the NICHD NRN public website as well as all investigators being acknowledged in all publications.

Network contributions to newborn health

The network has made significant contributions to newborn health as highlighted by this edition of *Seminars in Perinatology*. By assembling a group of motivated investigators along with their successful teams, protocols can be performed in a rigorous manner, and lead to changes in practice. NRN studies that have changed clinical practice include hypothermia as neuroprotection for neonatal encephalopathy,^{1,2} phototherapy for extremely low gestational age neonates,³ and the SUPPORT trial.⁴⁻⁶ The registry data from the generic data base as well as follow-up has been the source of multiple publications, many of whom have had

junior faculty members as first authors with NRN principal investigators as mentors. The registry data has made contributions to knowledge gaps including outcome following congenital heart disease,⁷ antenatal corticosteroid use,⁸ fetal growth restriction,^{9,10} Trisomy 13 and 18,¹¹ and neuroimaging among extremely low gestational age infants.^{12,13}

NRN partnership opportunities

With infrastructure established to carry out neonatal research, the NRN has been attractive to other institutes at NIH as well as other agencies. There is cost savings as the infrastructure is established and maintained by NICHD. Funding allocated to the Best Pharmaceuticals for Children Act (BPCA) has been used for studies directed at neonatal blood pressure and neuromonitoring.^{14–16} Several institutes at NIH including National Institute for Drug Abuse (NIDA), National Institute of Heart, Lung and Blood Disorders (NHLBI), and the National Eye Institute (NEI) have funded portions of studies. The Centers for Disease Control (CDC) has funded various sepsis protocols.^{17,18} Generally the co-funders contribute to capitation, investigators support and data coordinating center costs. The overall process results in a cost savings as the infrastructure is already set up for observational and interventional studies. NRN has also partnered with other network trial groups including the Maternal–Fetal Medicine Network.

Without parents and their commitment to research, NRN studies would not go forward. We are indebted to the infants and their parents who agreed to take part in this study. Further, our dedicated medical and nursing colleagues as well as other NICU and follow-up staff make the studies possible to pave the way for improvements in care and outcomes.

References

1. Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med*. 2005; 353(15):1574–1584. [PubMed: 16221780]
2. Shankaran S, Pappas A, McDonald SA, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. *N Engl J Med*. 2012; 366(22):2085–2092. [PubMed: 22646631]
3. Morris BH, Oh W, Tyson JE, et al. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. *N Engl J Med*. 2008; 359(18):1885–1896. [PubMed: 18971491]
4. Carlo Waldemar A, Finer Neil N, Walsh Michele C, et al. Higgins, for the NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010; 362:1959–1969. [PubMed: 20472937]
5. Finer Neil N, Carlo Waldemar A, Walsh Michele C, et al. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010; 362:1970–1979. [PubMed: 20472939]
6. Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med*. 2012; 367(26):2495–2504. [PubMed: 23268664]
7. Pappas A, Shankaran S, Hansen NI, et al. Outcome of extremely preterm infants (<1,000 g) with congenital heart defects from the National Institute of Child Health and Human Development Neonatal Research Network. *Pediatr Cardiol*. 2012 [Epub ahead of print].
8. Carlo WA, McDonald SA, Fanaroff AA, et al. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. *J Am Med Assoc*. 2011; 306(21):2348–2358.
9. Shankaran S, Das A, Bauer CR, et al. Fetal origin of childhood disease: intrauterine growth restriction in term infants and risk for hypertension at 6 years of age. *Arch Pediatr Adolesc Med*. 2006; 160(9):977–981. [PubMed: 16953023]

10. Shankaran S, Das A, Bauer CR, et al. Prenatal cocaine exposure and small-for-gestational-age status: effects on growth at 6years of age. *Neurotoxicol Teratol.* 2011; 33(5):575–581. [PubMed: 21849244]
11. Boghossian NS, Hansen NI, Bell EF, et al. Mortality and morbidity of VLBW infants with trisomy 13 or trisomy 18. *Pediatrics.* 2014 [Epub ahead of print].
12. Hintz SR, Slovis T, Bulas D, et al. Interobserver reliability and accuracy of cranial ultrasound scanning interpretation in premature infants. *J Pediatr.* 2007; 150(6):592–6. 596.e1–5. [PubMed: 17517240]
13. Hintz SR, Barnes PD, Bulas D, et al. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. *Pediatrics.* 2015; 135(1):e32–e42. [PubMed: 25554820]
14. Batton BJ, Li L, Newman NS, et al. Feasibility study of early blood pressure management in extremely preterm infants. *J Pediatr.* 2012 [Epub ahead of print].
15. Batton B, Li L, Newman NS, et al. Use of antihypertensive therapies in extremely preterm infants. *Pediatrics.* 2013 [Epub ahead of print].
16. Batton, B.; Li, L.; Newman, NS., et al. Early blood pressure, antihypotensive therapy and outcomes at 18–22 months' corrected age in extremely preterm infants. *Arch Dis Child Fetal Neonatal Ed.* 2015. <http://dx.doi.org/10.1136/archdischild-2015-308899> pii: fetalneonatal-2015-308899 [Epub ahead of print]
17. Stoll BJ, Hansen NI, Sánchez PJ, et al. Early onset neonatal sepsis: the burden of Group B Streptococcal and *E. coli* disease continues. *Pediatrics.* 2011; 127(5):817–826. [PubMed: 21518717]
18. Weissman SJ, Hansen NI, Zaterka-Baxter K, Higgins RD, Stoll BJ. Emergence of antibiotic resistance-associated clones among escherichia coli recovered from newborns with early-onset sepsis and meningitis in the United States, 2008–2009. *J Pediatr Infect Dis Soc.* 2015 pii: piv013 [Epub ahead of print].

Fig.
Neonatal research network study timeline.