Seminars in Perinatology ▮ (2016) ▮▮▮–▮▮▮

Available online at www.sciencedirect.com

Seminars in Perinatology

www.seminperinat.com

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

*Rosemary D. Higgins, MD*[a,*], *and Seetha Shankaran, MD*[b]

[a]*Pregnancy and Perinatology Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institues of Health, 6710B Rockledge Drive, Room 2233, MSC 7002, Bethesda, MD 20892*

[b]*Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI*

ARTICLE INFO

*Keywords:*
Neonatal
Research
Infant
Trial
Study

ABSTRACT

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neontal 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 comprise of clinical centers that perform clinical protocols to investigate the safety and efficay of treatment and management strategies for newborn infants as well as a data cordinating 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.

Published by Elsevier Inc.

## 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 intervals 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 behabioural outcomes, (c) to disseminate results of NRN studies to the scientific and lay commiunity, and (d) to involve young faculty in NRN activities.

## Network advantages

There are a significant number of advantages with establishing a neonatal network. There are large numbers of pateints available for common as well as rare diseases. The RFA for

*Corresponding author.
E-mail address: higginsr@mail.nih.gov (R.D. Higgins).

http://dx.doi.org/10.1053/j.semperi.2016.05.002
0146-0005/Published by Elsevier Inc.

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 subspeciality 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 coordinting center (DCC) applications. The DCC plays a central role with respect to study development, implementation, data mangement, 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 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

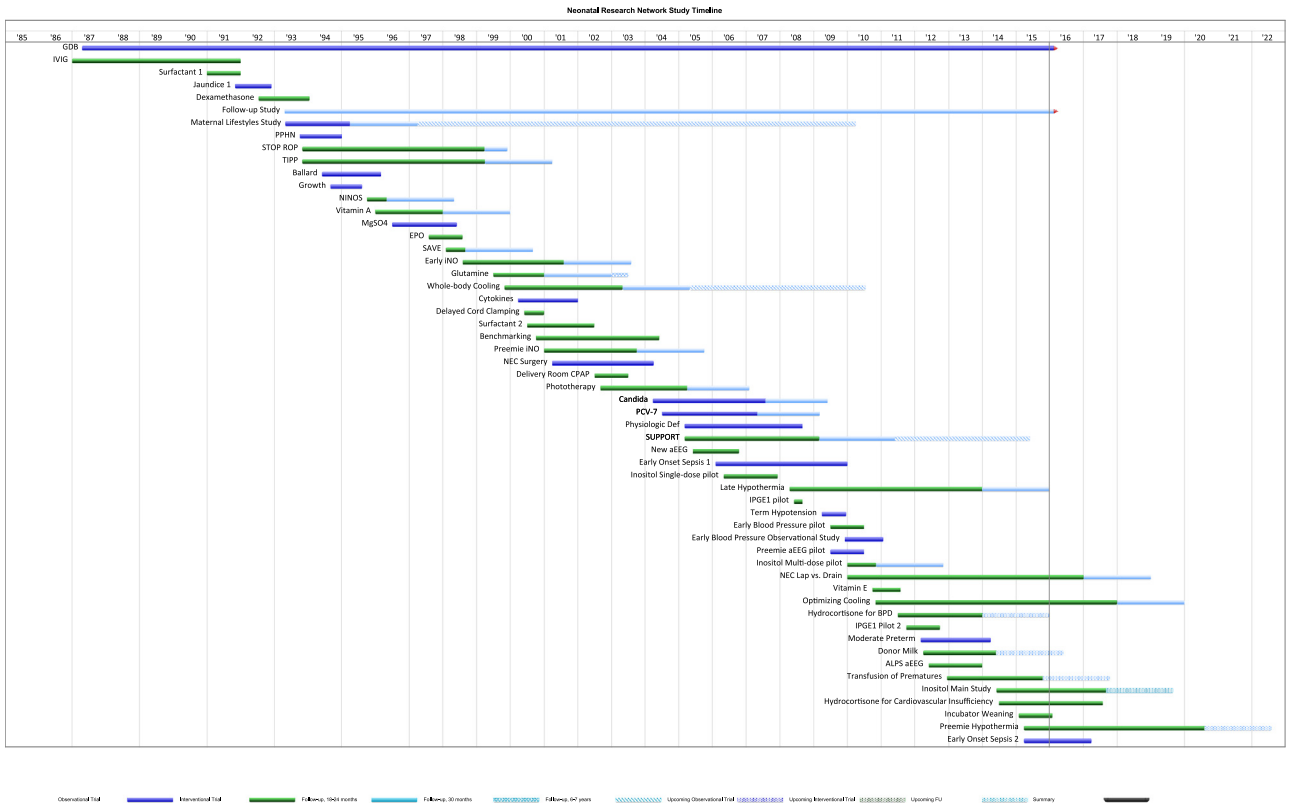


**Fig – Neonatal research network study timeline.**