First Annual NeuroNEXT Network-linked Open Conference (NLOC)

Acute Symptomatic Neonatal Seizures: biomarkers and impact of acute anticonvulsant therapy on risk of future epileptogenesis

AGENDA

Thursday, May 23, 2024 (VIRTUAL)
10:00 am – 5:00 pm EST

Join Via Zoom:
https://partners.zoom.us/j/87822360857?pwd=V3lvR2RpSFpHYlVDUGJIY3pRSWlIUT09

Meeting ID: 878 2236 0857
Passcode: 546405

NeuroNEXT Network-linked Open Conference (NLOC) Overview:

NLOC Mandate:

The NeuroNEXT (NN) Clinical Coordinating Center (CCC) and Data Coordinating Center (DCC) will organize with the collaboration of NeuroNEXT network sites, Network-linked Open Conferences to facilitate stakeholder discussions to identify areas of high unmet need and priority. At least one conference annually in person if possible and virtual, if necessary, will be organized focused on different disease or subspecialty areas for each iteration. The goal will be to proactively identify areas in which projects could be proposed to NINDS for implementation at the network. Participation will include at the minimum the members of the NEC and the members of the specific subspecialty interest group, representatives for the interest area from each site, unless already covered through NEC or interest group membership, key opinion leaders from outside the network, and other stakeholders as relevant to the subject area.

Inaugural Conference: For the inaugural Network-linked Open Conference, the CCC and DCC selected Child Neurology as the domain and asked the Pediatric NeuroNEXT Consortium to identify a key priority suitable for a NeuroNEXT study.

Conference Goal: To discuss design for a pediatric NeuroNEXT Phase I/II Clinical Trial inclusive of key biomarkers and outcomes.

Specific Proposal for Discussion:

Unmet Need: The NN Pediatric Consortium, consisting of Pediatric Neurologists from current NN sites identified the need for effective management and identification of biomarkers predictive of epileptogenesis in acute symptomatic neonatal seizures as a key unmet need. Current treatments, including phenobarbital, have not changed outcomes in several decades. Long-term implications of acute clinical and subclinical seizures in neonates remain incompletely understood and prognostication is hindered by a lack of laboratory, electroencephalographic and neuroimaging biomarkers that predict risk for future epilepsy. The majority of research on outcomes post-acute seizures in neonates have focused on neurodevelopmental outcomes and have often been limited to specific populations, such as infants with hypoxic ischemic encephalopathy (HIE). Therapeutic studies have included protocols for cooling which have demonstrated efficacy in mitigating risk for neurodevelopmental disability in term infants with HIE. A recent comparator study of Levetiracetam demonstrated inferiority in seizure control compared to phenobarbital. Given concerns for the long-term impact of phenobarbital on brain tissue, and short-term risks for sedation, impairment in feeding, and prolongation of hospitalization, there remains an imperative to identify superior antiseizure therapies.

Conference Objective: To convene a key stakeholder one day virtual conference focused on designing a clinical trial comparing phenobarbital to a less neurotoxic antiseizure medicine (ASM) in neonates with acute symptomatic seizures inclusive of key biomarkers (laboratory, EEG and MRI). The trial will have a primary short-term outcome (cessation or reduction in total seizure burden measured in minutes/day) and a primary long-term (4 year) outcome (development of epilepsy).

Agenda focus: The conference will focus on the 3 main areas (i) Biomarkers; (ii) Clinical Trial comparing 2 anti-seizure agents, and (iii) Outcomes. There will be breakout sessions focused on each of these areas.

Clinical Trial: (Chair: Janet Soul): The clinical trial group will design a Phase II study comparing phenobarbital (standard of care) vs a newer agent (potentially IV Topiramate). In advance of the May 23 meeting, the clinical trial group will draft a preliminary design for debate at the meeting. The group will include thought leaders from completed and active trials (NEMOS, proposed PCORI study, and others). Lessons learned from recent comparator trials will be discussed and distilled for sharing at the May meeting.

Biomarkers: (Co-Chairs: Adam Numis [serum/plasma biomarkers] and Courtney Wusthoff ** [EEG biomarkers]): The biomarker group will propose key laboratory, MRI, EEG, and genetic testing metrics to include in the proposed NeuroNext trial. Serum/plasma biomarkers will be proposed based on recent studies showing both acute and predictive validity in acute neonatal seizures. EEG studies, with careful consideration of published efforts describing optimal EEG scoring, duration of cEEG monitoring, and plans for sites with limited/no access to cEEG will be discussed. MRI analyses, using clinically-acquired vs research scans will be proposed, with a centralized MRI analytical team to be proposed for the future study.

Outcomes: (Co-Chairs: Janet Soul, Hannah Glass and Renee Shellhaas): The outcomes group will define early and long-term outcomes for the proposed trial, including development of epilepsy, developmental outcome, and parent well-being. Outcome measures (standardized) will be discussed and proposed, with consideration of optimal timing of follow-up examinations. Considerations for virtual monitoring and parent-reported outcomes will be discussed in order to enhance feasibility.

Conference AGENDA:

(All times EST and may vary)

10:00 am – 10:10 am:	**Welcome and Introductions** Brenda Banwell, Josh Bonkowsky and Amy Brooks-Kayal (Meeting Co-Chairs)
10:10 am – 10:20 am:	**Overview of NeuroNEXT and NN Pediatric Consortium** Merit Cudkowicz, Christopher Coffey, Sophie Cho
10:20 am – 10:30 am:	**Review of the meeting objectives and overview of the proposed study plan** Brenda Banwell
10:30 am – 10:45 am:	**Clinical Trial for Acute Neonatal Seizures** Janet Soul
10:45 am – 11:00 am:	**Biomarkers for Acute Neonatal Seizures** Adam Numis and Courtney Wusthoff
11:00 am – 11:15 am:	**Outcomes for Acute Neonatal Seizures** Janet Soul
11:15 am -12:00 pm:	**Group discussion** All attendees
12:00 pm -12:30 pm:	**BREAK**
12:30 pm – 1:30 pm:	**Stakeholder perspectives**
12:30 – 1:00 pm	Betsy Pilon - Hope for HIE
1:00 – 1:30 pm	Open discussion

1:30 pm – 3:30 pm: **Break-out groups: Clinical Trials, Biomarkers, Outcomes**

For each breakout session, the breakout group leader and supporting NeuroNext lead member will guide the discussion with the following goals:

1. What are the opportunities for studies of new treatments or biomarkers or outcomes in acute neonatal seizures?
2. What activities are underway or already completed relative to each of the 3 topics?
3. What are the greatest unmet needs?

4. What are specific considerations (i.e.; for trial design, feasibility) or for biomarkers (sample requirements, shipping, measurement accuracy etc) or outcomes (which ones, at what age, by whom) that need to be considered.

NOTE: The first break out session will run from 1:30 – 2:30 pm. A second session will run from 2:45- 3:30 pm. At the time of each session, each attendee will be given the option to self-select which break-out group to attend (Clinical Trials, Biomarkers, Outcomes. Attendees may choose the same or a different break-out group for each session. Break-out group leaders will remain in their roles for both sessions.

1:30-2:30	Break-out Session 1
2:30-2:45	Break (attendees will self-select group for Session 2)
2:45-3:30	Break-out groups II

3:30 pm – 4:15 pm: **Break-out group leader presentations**

3:30 pm – 3:45 pm	Janet Soul (Clinical Trials)
3:45 pm – 4:00 pm	Adam Numis and Courtney Wusthoff (Biomarkers)
4:00 pm – 4:15 pm	Hannah Glass, Renée Shellhaas and Brenda Banwell(Outcomes)

4:15 pm- 4:45 pm: **Overall Discussion**

Brenda Banwell, Josh Bonkowsky and Amy Brooks-Kayal

(Meeting Co-Chairs)

4:45 pm – 5:00 pm: **Summary and Next Steps**

5:00 pm **Adjourn**