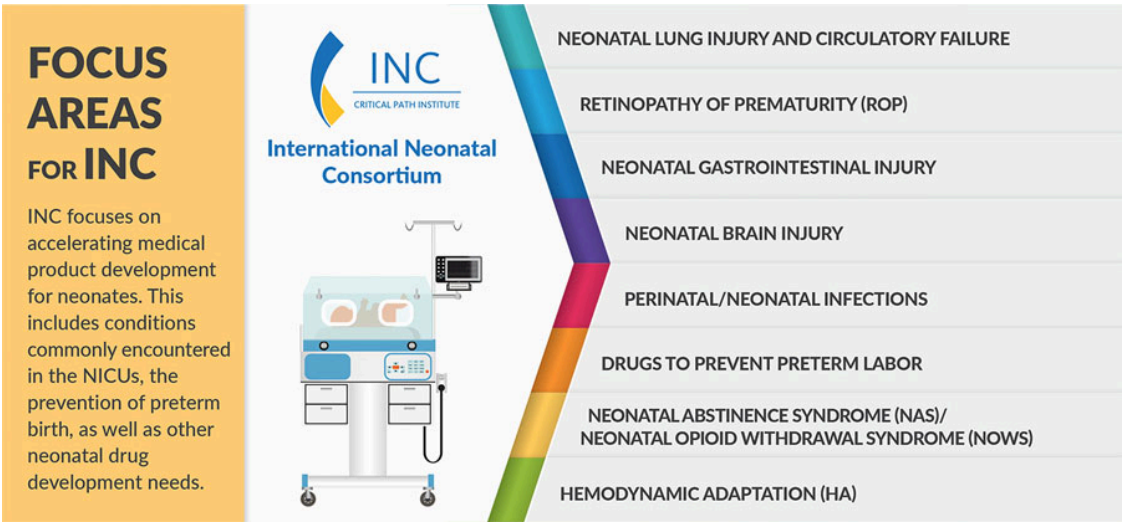
CRITICAL PATH INSTITUTE 20 YEARS OF IMPACT

Advancing Drug Development. Improving Lives. Together.

June 2025

INTERNATIONAL NEONATAL CONSORTIUM NEWSLETTER

Welcome to the biannual INC Newsletter. Each edition is designed to highlight the ongoing progress and achievements of our workgroups, reflecting the collective efforts and collaboration across the consortium. We appreciate your continued engagement and look forward to sharing these important updates with you.



INC is a public-private partnership comprised of diverse stakeholders, including industry members, academic researchers, nurses, families, and regulators. Its mission is to accelerate drug development in neonates. Operating as a pre-competitive collaboration, the partnership focuses on addressing the measurement and assessment of clinical outcomes in neonates by leveraging teams that share data and expertise to advance regulatory science. Additionally, it aims to improve the predictability of neonatal drug development, fostering innovation and progress in this critical area of healthcare.

INC Membership

INC membership consists of a diverse array of organizations spanning the globe. For a complete list of all INC members, please visit c-path.org/inc.

Member Highlights

Members of our Pain Workgroup published a call to action “Moments that Matter” (Slater et al., BMC medicine 2025; Hirekodi et al Lancet child 2025) highlighting the importance of treating pain in early life.

An RCT was published (Hauck et al., 2024) using noxious stimulus-evoked EEG signal as a primary outcome measure to investigate the value of parental touch.

A registered report was conducted (Aspbury et al 2024) demonstrating the reproducibility of the noxious stimulus-evoked EEG measure.

Members of the Seizure Workgroup have been very active investigating neonatal seizure definition, diagnosis, characterization and management, including but not limited to trials. These include recent, ongoing and planned trials, as well as numerous publications from the Neonatal Seizure Registry (NSR) and other non-NSR publications, and ILAE publications regarding neonatal seizure definition and management.

Examples of trials published since the first INC Seizure Workgroup publication, include:

- “A Pilot Randomized, Control Double-Blind Trial of Bumetanide to Treat Neonatal Seizures” (Soul et al.)
- “Levetiracetam Verus Phenobarbital for Neonatal Seizures: A Randomized Controlled Trial” (Sharpe et al.)

- "Safety of Early Discontinuation of Antiseizure Medication After Acute Symptomatic Neonatal Seizures" (Glass, Soul, et al.)
- "Sequential Levetiracetam and Phenytoin in Electroencephalographic Neonatal Seizures Unresponsive to Phenobarbital: A Multicenter Prospective Observation Study" (Pressler et al.)
- "Temporal Evolution of Electrographic Seizures in Newborn Infants with Hypoxic-Ischaemic Encephalopathy Requiring Therapeutic Hypothermia: A Secondary Analysis of the ANSeR Studies" (Pressler et al.)

Cell and Gene Therapy Workgroup Highlights

Main Workgroup

Goal/Mission:
To improve Rx development efficiency in regen Rx programs that focus on diseases of infancy

Past Success, Present Drive: Project Highlights & What's Underway:

This year the Cell and Gene Therapy workgroup has 'democratized' prioritization in two areas of focus: the use of RWE for regulatory decision making and implementation of LTFU studies. Currently, the workgroup's two subgroups are focused on key deliverables for the second half of 2025: the RWE subgroup is developing a registry quality assessment, while the Long-Term Follow-Up subgroup is preparing a recommendations paper.

Long Term Follow-up Subgroup

Goal/Mission:
To optimize the regulatory and scientific ecosystem for the development and long-term follow-up of cell and gene therapies in neonates and children by advancing harmonized approaches to safety data collection, real-world evidence, biomarkers, and patient-centered outcomes.

Past Success, Present Drive: Project Highlights & What's Underway:

In 2024, the subgroup launched a multi-stakeholder white paper effort focused on harmonizing global regulatory expectations for long-term follow-up in pediatric gene therapy trials, incorporating perspectives from FDA, EMA, MHRA, industry, academia, and patient groups.

Currently a white paper is being developed that explores the challenges and opportunities associated with long-term follow-up (LTFU) in pediatric gene therapy trials, with the goal of promoting greater alignment across global regulatory agencies. The paper is expected to be finalized in early 2026.

Utilization of RWE/RWD Subgroup

Goal/Mission:
The Cell and Gene Therapy (CGT) Real-World Evidence (RWE) Subgroup, part of the INC, is focused on advancing the development of CGT for neonates and infants. The project aims to map existing patient registries that support CGT development globally for infants and provide recommendations for key data elements needed in these registries. This effort will contribute to improved regulatory alignment, patient recruitment, and potential for external controls for CGT clinical trials.

Please see our one-page summary as a communication tool, here.

Past Success, Present Drive: Project Highlights & What's Underway:

The Real-World Evidence (RWE) Working Group (WG) was pleased to welcome C-Path intern Tina Akbarzadeh, Pharm.D., a Ph.D., student in the Department of Pharmacology and Toxicology at the University of Arizona this year. As part of her internship, Tina conducted a comprehensive review of the Every Cure database for the subgroup. Supporting and mentoring future leaders like Tina is a key priority for the subgroup, as we work to accelerate the development of therapies for infants.

"During my internship with the INC RWE workgroup, I had the valuable opportunity to explore the critical unmet medical needs of infants, particularly in the emerging fields of cell and gene therapy. I witnessed how a multistakeholder collaboration, uniting experts from academia, industry, regulatory agencies, and patient advocacy, plays a vital role in shaping policies and accelerating innovation. My internship encompassed a landscape analysis of rare disease patient organizations for pediatric conditions and cell and gene therapy potential. For this project, we defined "infant" as children under 24 months of age. I reviewed 286 patient organization websites. Approximately 73% of the websites contain disease information that include "infant" or "are likely to be present in infants" and approximately 77% either have existing cell and gene therapy options or are associated with genetic mutations that may be treatable through such therapies. Before this rotation, I had not realized how many families of affected neonates are actively seeking solutions and support. This internship opportunity has profoundly shaped my perspective on the urgent need for targeted therapeutic development in this space and deepened my understanding of the unique challenges in developing and delivering these advanced therapies for pediatric populations, especially neonates."- Tina Akbarzadeh

Currently, this subgroup is working to identify and prioritize rare disease registries globally that include infants and are relevant to CGT development to be completed in 2025.

Development of a comprehensive survey to gather information about global patient registries supporting CGT development for neonates and infants is also underway, projected to be completed in 2025.

Lab Values Workgroup Highlights

Goal/Mission:
To develop standardized, age- and weight-specific laboratory reference ranges in neonates using real-world data from over 30 NICUs to support clinical trial design, safety signal interpretation, and regulatory decision-making.

Past Success, Present Drive: Project Highlights & What's Underway:

In 2024, the Lab Values Workgroup successfully submitted a concept proposal for neonatal lab reference ranges to a peer-reviewed journal and completed a cross-consortium stakeholder review involving industry, academic neonatologists, and regulators. In addition, an app that provides Graphical User Interface to access lab values is under development. Currently, this workgroup is building a digital application to enable real-time access to validated neonatal lab reference values, stratified by gestational age, postnatal age, and birthweight. Beta testing is expected in mid-2025.

Pain Workgroup Highlights

Goal/Mission:
The goal of this workgroup is to establish a measure that accurately and reproducibly evaluates acute pain in neonates that is capable of being used to support neonatal analgesic drug development.

Past Success, Present Drive: Project Highlights & What's Underway:

In 2024, the Pain Workgroup has completed a protocol detailing an individual participant data (IPD) meta-analysis to evaluate a noxious stimulus-evoked EEG signal as a reliable, valid, and interpretable biomarker of acute pain in neonates, to inform outcome selection in future analgesic trials.

- "Is Noxious Stimulus-Evoked Electroencephalopathy Response a Reliable, Valid and Interpretable Outcome Measure to Assess Analgesic Efficacy in Neonates? A Systematic Review and Individual Participant Data (IPD) Meta-Analysis Protocol" (Baxter, Van Deer Vaart, Allegaert, Davis, Turner, Darsey, Bhatt, Van Der Anker, Massaro, Walls, Song, Singh, Slater et al.)

Currently a scoping review is being conducted which identifies 48 global studies using EEG during painful neonatal procedures, highlighting available datasets and variability in methods. It establishes a foundation for the IPD meta-analysis and aims to unite researchers working on brain-based neonatal pain measures.

Seizure Workgroup Highlights

Goal/Mission:
To develop recommendations for the design of neonatal seizure treatments that will improve neurologic outcome.

Past Success, Present Drive: Project Highlights & What's Underway:

In 2025 the Seizure Workgroup added to and updated the initial publication of 2019 (PMID #30584262) based on data and experiences from recently completed neonatal seizure treatment trials - this publication has just been completed and will be submitted soon.

- "Recommendations for the Design of Therapeutic Trials for Neonatal Seizures" (Soul, Pressler, Allen, Rabe, Portman, Romero, Denne, Auvin, Marlow, Davis et al.)

As above, our current project is nearly completed. Ideally, work would continue to develop a Master Protocol for Platform trial of neonatal seizure treatment, potentially combined with treatment of neonatal hypoxic-ischemic encephalopathy, the most common cause of neonatal seizures.

Three-Year Research Plan Goals

INC's research plan focuses on developing an integrated, standardized patient-level database by aggregating data from global EHRs, neonatal registries, and clinical trials. It also aims to develop a modeling analysis plan to incorporate external control arms into neonatal clinical trials, prioritizing diseases that would benefit most and addressing data comparability and missingness. Additionally, the consortium is working on a regulatory endorsement strategy, engaging with agencies and stakeholders to ensure the tools developed meet necessary standards and support sustainable use of real-world data in clinical research.

Upcoming Conferences

C-Path Global Impact Conference, September 2025 in Washington D.C. Register now!

- INC Day, Monday, September 8, Marriott Metro in Washington, DC, from 9 AM to 3:45 PM.
- A broader forward-looking strategy session reflecting both our neonatal foundation and our expanding engagement with pediatric drug development. We've crafted an agenda that balances substantive deep dives into core INC initiatives with forward-facing strategic discussions, allowing for interactive dialogue across stakeholders.

    - **Highlights from the agenda:**
        - **Lab Values Initiative:** Reference range analysis from 380,000 NICU patients and live demo of the new app
        - **NAESS 2.0:** Digital tool development and global implementation planning
        - **Neonatal Brain Injury Collaborative:** MRI injury score qualification and international data integration
        - **Cross-Cutting Strategy Session:** Exploring new frontiers in pediatric therapeutics—such as early obesity risk tracking—linking neonatal insights to long-term health outcomes

- Don't miss the panel **"The Missing Voices in Neonatal Drug Development: Harnessing Patient Advocacy for Impact"** on September 9, 2025, 1:30-2:20 PM.
    - Discover the impact of patient advocacy on neonatal drug development.
    - This panel unites diverse perspectives—from those who have lived the lifelong consequences of prematurity, to parents navigating the system for their children, and regulatory experts who understand patient engagement's role in shaping policy. Explore how patient advocacy can help accelerate neonatal drug development through compelling discussions and shared experiences.

The Pain Workgroup team is presenting their work at the International Symposium on Paediatric Pain (ISPP) 2025 in Glasgow.

Child Neurology Society meeting in Charlotte, NC, October 2025.

ASCGT 29th Annual Meeting May 12-16, 2026.

17th International Newborn Brain Conference - INBBC 2026 in Naples, Italy, February 2026.

Pediatric Academic Societies Meeting in Boston, MA, April 2026.

New Developments

Neonatal Adverse Event Severity Scale (NAESS) 2.0 Workgroup
This workgroup's goal is to revise and expand the current NAESS tool to include a broader range of neonatal adverse events, improve usability, and align with regulatory and clinical trial needs through a digital interface. In 2025, INC consolidated user feedback from industry and academic partners on NAESS 1.0 and began formal redevelopment of the tool's structure, terminology, and digital interface. We are currently redesigning NAESS to include new AE categories (e.g., neonatal neurology), create standardized severity grading rubrics, and launch a digital version by mid-2026.

Neonatal Brain Injury Collaborative
The Neonatal Brain Injury Collaborative (NBIC) aims to accelerate the development of therapies for conditions such as hypoxic-ischemic encephalopathy (HIE) and neonatal white matter injury. Launched in 2025, NBIC brings together academic investigators, regulatory advisors from FDA and EMA, industry sponsors, and patient advocates to address critical challenges in trial design, biomarker development, and regulatory alignment. Initial efforts are focused on developing a regulatory-grade strategy for incorporating imaging, physiologic, and blood-based biomarkers into clinical trials, alongside the creation of trial simulation tools to support more efficient and informative study designs. A draft regulatory submission is anticipated within the next 2–3 years.

If you would like to get involved with INC, please reach out to us at incinfo@c-path.org.

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FDA Acknowledgment