CRITICAL PATH INSTITUTE 20 YEARS OF IMPACT

Advancing Drug Development. Improving Lives. Together.

December 18, 2025

International Neonatal Consortium Newsletter

As INC celebrates its 10-year anniversary, this edition highlights a decade of collaboration, innovation, and meaningful impact. In the last ten years, our community has united around a common mission, improving the lives of neonatal babies and their families, building stronger partnerships and inspiring meaningful, lasting change.

In this commemorative issue, we spotlight the people, initiatives, and milestones that have helped define INC over the past decade. Thank you to everyone who has contributed to this journey, your dedication is the foundation of our success.

Mission Statement

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 Partnerships

INC membership consists of a diverse array of organizations spanning the globe. For a complete list of all INC members, go here.

Wakako Ekland

We'd like to take a moment to thank Wakako Ekland, our NANN Liaison for INC, whose dedication and leadership have made a tremendous impact. We'd also like to thank Jill Beck, who will be stepping in as the NANN Liaison, for her willingness to take on this role while Wakako transitions out.

Cell and Gene Therapy Workgroup Highlights

Long-Term Follow-Up (LTFU) 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.

Overview & Key Achievements

The rapid expansion of cell and gene therapies has created unprecedented promise for pediatric and neonatal populations, while simultaneously introducing significant

uncertainty around long-term safety, durability, and appropriate follow-up expectations. These challenges are amplified in early-life populations, where ongoing growth and development complicate conventional long-term monitoring paradigms.

The INC **Long-Term Follow-Up (LTFU) Subgroup** was established to address this complexity through a global, pre-competitive collaboration of regulators, industry sponsors, academic experts, and patient advocates. A central focus of the subgroup is to bring clarity and alignment to long-term follow-up expectations by examining how known and theoretical safety risks in pediatric cell and gene therapy programs map to appropriate follow-up strategies.

A key deliverable of the subgroup is a planned **consensus manuscript** focused on **regulatory harmonization**, including a structured crosswalk between safety considerations specific to pediatric and neonatal cell and gene therapies and corresponding long-term follow-up expectations. This work is intended to synthesize regulatory perspectives, existing guidance, and real-world implementation challenges into a coherent framework. The manuscript is expected to develop into a **comprehensive, centralized resource** designed to serve as a one-stop reference for sponsors. This resource will support informed decision-making around long-term follow-up planning, including duration, data elements, use of real-world evidence, and alignment with regulatory expectations across jurisdictions.

Impact

The LTFU Subgroup is creating a critical enabling infrastructure for responsible and sustainable pediatric cell and gene therapy development. By harmonizing regulatory expectations, clarifying safety-to-follow-up linkages, and providing a practical, sponsor-facing resource, INC is reducing uncertainty, improving trial planning, and strengthening confidence in long-term safety strategies. This work supports both regulators and developers in balancing patient protection with feasibility, helping ensure that transformative therapies can reach children and neonates with appropriate long-term oversight.

Utilization of RWE/RWD Subgroup

Goal/Mission

The Cell and Gene Therapy (CGT) Real-World Evidence (RWE) Subgroup, part of the International Neonatal Consortium (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.

Project Highlights

A **survey** is currently underway to capture information on registries and natural history studies involving children under 24 months of age with conditions potentially amenable to CGTs. To identify appropriate registries, the workgroup has drawn from multiple sources, including the **NORD IAMRARE** site, **the Every Cure List**, the **HMA–EMA Real-World Data Catalogues**, and a review of registries and natural history studies listed on **ClinicalTrials.gov.**

Your support is vital—we invite you to help us connect with key registry stakeholders, raise awareness of the survey, and encourage participation. If you or your colleagues are involved in relevant registries—or can help disseminate the

survey within the neonatal, rare disease, or gene therapy communities—your engagement can make a meaningful difference.

Here is the link to the survey.

Lab Values Workgroup & Neonatal Lab Values GUI

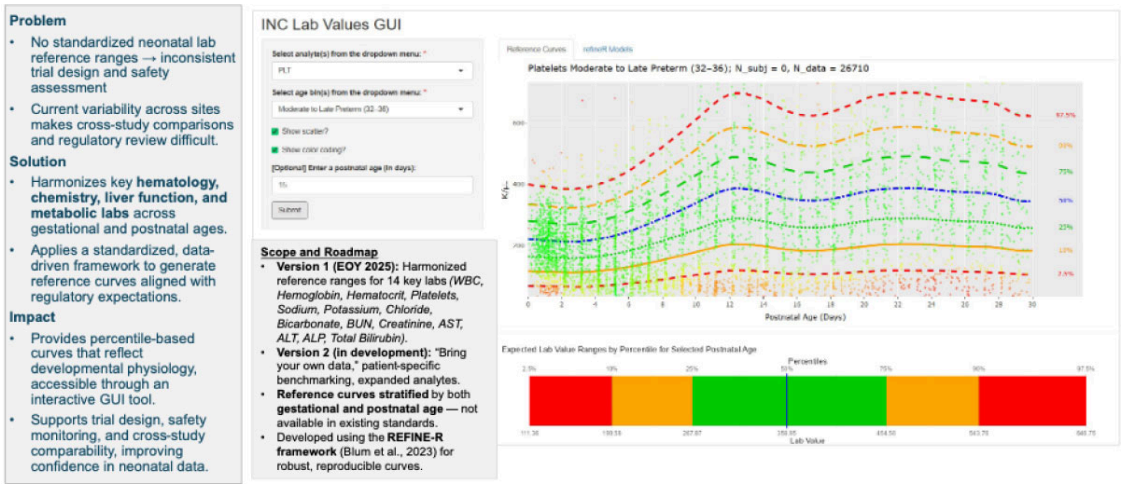
Goal/Mission

To develop standardized, age- and weight-specific laboratory reference ranges in neonates using real-world data from over 30 NICUs, enabling more accurate clinical trial design, safety signal interpretation, and regulatory decision-making in neonatal drug development.

Overview & Key Achievements

Over the past decade, the INC Lab Values Workgroup has addressed one of neonatology's most persistent evidence gaps — the lack of reliable, population-specific laboratory reference ranges for premature and term infants. By curating and harmonizing large-scale real-world data from more than 30 neonatal intensive care units, the workgroup developed statistically robust reference ranges for a core set of analytes critical to neonatal physiology, including ALT, AST, GGT, BUN, Creatinine, Platelets, Hemoglobin, Hematocrit, WBC count, Glucose, Calcium, Sodium, Potassium, and Lactate.

These reference ranges are delivered through the INC Neonatal Lab Values Graphical User Interface (Neo-LV), an interactive visualization platform that allows researchers, clinicians, industry partners, and regulators to explore laboratory value distributions by gestational age, postnatal age, and weight categories in a transparent and intuitive manner. The tool supports comparisons across multiple analytes and facilitates evidence-based interpretation of neonatal lab results in clinical trials and safety monitoring. Neo-LV is publicly accessible here: https://cpath.shinyapps.io/lvgui/.



Impact

The Lab Values initiative represents a foundational advance in neonatal regulatory science. By replacing fragmented, institution-specific norms with standardized, population-level reference ranges and a readily accessible GUI tool, INC has enabled more consistent interpretation of laboratory abnormalities, reduced uncertainty in safety assessments, and strengthened the evidentiary basis for neonatal clinical trials. This work establishes a scalable, regulatory-grade framework that can be expanded to additional analytes and integrated with other INC drug development tools, helping to accelerate safe and effective therapies for newborns.

Bronchopulmonary Dysplasia (BPD) Working Group

Goal/Mission

To modernize and accelerate drug development for bronchopulmonary dysplasia (BPD) by advancing fit-for-purpose endpoints, trial designs, and data frameworks that reflect contemporary neonatal care and regulatory expectations.

Overview & Key Achievements

Bronchopulmonary dysplasia remains one of the most common and devastating complications of extreme prematurity, yet **no new pharmacologic therapies have been approved for BPD in more than three decades**. Progress has been hindered by evolving clinical practices, heterogeneous disease definitions, limited consensus on meaningful endpoints, and the operational challenges of conducting trials in fragile neonatal populations.

The INC **BPD Working Group** was established to confront these challenges through a global, pre-competitive collaboration of clinicians, industry sponsors, regulators, and data scientists. The group is focused on re-examining how BPD is defined, measured, and studied, with particular emphasis on aligning trial endpoints with both short-term respiratory outcomes and longer-term clinical relevance.

A core pillar of the workgroup is the use of **high-resolution real-world neonatal data** to better characterize BPD disease trajectories, identify patient subgroups, and inform innovative trial designs, including external control arms and trial simulation approaches. By integrating real-world evidence with regulatory science principles, the group aims to reduce trial complexity while preserving scientific rigor.

Impact

The BPD Working Group represents a critical effort to break decades of stagnation in neonatal respiratory drug development. By modernizing endpoints, leveraging real-world data, and aligning stakeholders around a shared development strategy, INC is lowering barriers to investment and improve the feasibility of BPD clinical trials. This work has the potential to reinvigorate therapeutic pipelines and ultimately deliver meaningful treatments to premature infants at the highest risk for chronic lung disease.

Neonatal Adverse Event Severity Scale (NAESS & NAESS 2.0)

Goal/Mission

To establish a standardized, clinically meaningful framework for grading adverse event (AE) severity in neonatal and early infancy clinical trials, enabling consistent safety reporting, cross-trial comparability, and regulatory confidence in safety assessments.

Overview & Key Achievements

The original **Neonatal Adverse Event Severity Scale (NAESS)** was developed to address a critical gap in neonatal drug development: the absence of a standardized, age-appropriate system for grading adverse event severity in newborns. Through a rigorous, multi-stakeholder consensus process involving clinicians, industry, and regulators, NAESS defined severity criteria for 35 core neonatal adverse events, reflecting the unique physiology and clinical context of neonates.

Since its release, NAESS has become the **de facto standard for adverse event severity grading** not only in neonatal trials but increasingly in **infancy-age clinical studies**, enabling consistent interpretation of safety signals across studies, sponsors, and

therapeutic areas. Its widespread adoption has improved the quality, consistency, and credibility of safety data generated in early-life clinical trials.

Building on this success, INC has now launched **NAESS 2.0**, an expanded and modernized initiative designed to extend AE definitions beyond the original 35 terms and to better reflect the breadth and complexity of adverse events observed in contemporary neonatal and infant trials. A core component of NAESS 2.0 is the development of a **digital, trial-ready tool** that enables direct integration of standardized AE severity grading into clinical trial operations, data capture workflows, and downstream analyses.

Impact

NAESS represents a landmark advancement in neonatal safety science. By providing a common language for AE severity grading tailored to neonates and infants, NAESS has reduced ambiguity in safety interpretation, improved cross-trial comparability, and strengthened regulatory confidence in early-life drug development programs. NAESS 2.0 builds on this foundation by expanding clinical coverage and embedding standardization directly into trial operations, positioning INC to further modernize safety assessment and accelerate the development of safe and effective therapies for the youngest patients.

Neonatal Brain Injury Collaborative (NBIC)

Goal/Mission

To accelerate drug development for neonatal brain injury by advancing standardized endpoints, biomarkers, and data frameworks that enable more efficient, interpretable, and regulatory-ready clinical trials.

Overview & Key Achievements

The **Neonatal Brain Injury Collaborative (NBIC)** was launched to address long-standing scientific and regulatory challenges in drug development for neonatal brain injury, including hypoxic-ischemic encephalopathy (HIE) and related conditions. Despite decades of research, therapeutic progress in this area has been limited by heterogeneity in disease definitions, variability in outcome measures, and uncertainty around the optimal use of imaging and neurodevelopmental endpoints.

NBIC brings together a global, pre-competitive partnership of regulators, industry, academic experts, and patient advocacy organizations to align on common scientific and regulatory priorities. A central focus of the collaborative is the appropriate use of **MRI injury scores** as prognostic and enrichment tools, and their relationship to longer-term neurodevelopmental outcomes, including standardized assessments in early childhood.

Through structured workgroups and consensus-driven discussions, NBIC is building a shared evidence base to inform endpoint selection, trial design, and regulatory decision-making in neonatal brain injury studies. The initiative also serves as a platform for integrating historical clinical trial data with real-world evidence to better characterize disease trajectories and treatment effects.

Impact

NBIC represents a strategic step forward in an area of profound unmet medical needs. By aligning stakeholders around standardized biomarkers, endpoints, and trial design principles, the collaborative is reducing uncertainty and lowering barriers to investment in neonatal brain injury drug development. This work has the potential to shorten development timelines, improve trial efficiency, and ultimately increase the likelihood that effective therapies reach newborns and families affected by devastating brain injuries.

Upcoming Conferences

ASCGT 29th Annual Meeting in Boston, Mass. In May 2026. 2026 Annual Meeting | ASGCT.

Newborn Brain Society meeting in Naples, Italy in Feb 2026. 17th International Newborn Brain Conference - INBBC 2026.

Pediatric Academic Societies Meeting in Boston, Mass. in April, 2026. 2026 MEETING – PAS Meeting.

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

Help support our mission. MAKE A GIFT TODAY

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FDA Acknowledgment