CRITICAL PATH INSTITUTE

INTERNATIONAL NEONATAL CONSORTIUM'S IMPACT ON DRUG DEVELOPMENT

FOSTERING INNOVATION

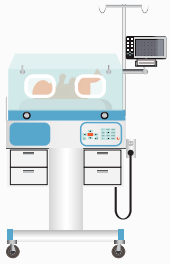
Public-private partnership of stakeholders from industry, academia, clinicians, nurses, families and regulators. INC enables pre-competitive collaboration and evidence-based science for all stakeholders to:

- Address the measurement and assessment of clinical outcomes in neonates, through teams that share data and expertise to advance regulatory science
- Improve the predictability of neonatal drug development
- Accelerate drug development process in neonates

FOCUS AREAS FOR INC

INC focuses on accelerating medical product development for neonates. This includes conditions commonly encountered in the NICUs, the prevention of preterm birth, as well as other neonatal drug development needs.

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium



- NEONATAL LUNG INJURY AND CIRCULATORY FAILURE
- RETINOPATHY OF PREMATURITY (ROP)
- NEONATAL GASTROINTESTINAL INJURY
- NEONATAL BRAIN INJURY
- PERINATAL/NEONATAL INFECTIONS
- DRUGS TO PREVENT PRETERM LABOR
- NEONATAL ABSTINENCE SYNDROME (NAS)/ NEONATAL OPIOID WITHDRAWAL SYNDROME (NOWS)
- HEMODYNAMIC ADAPTATION (HA)

OPPORTUNITIES TO ACCELERATE DRUG DEVELOPMENT IN NEONATES

Through collaboration, INC leverages all five C-Path core competencies (data, modeling, biomarkers, clinical outcome assessments, and regulatory science), to transform patient-level data into actionable solutions that can meet the following opportunities in accelerating drug development for neonates.

- Neonates are therapeutic orphans. The last drug that significantly impacted survival in preterm neonates was approved > 30 years ago.
- Clinical trial activity in neonatal population is limited (<1% of currently registered trials are in neonates), and most drugs (>60-90%) are used off-label[1], which greatly impacts an objective evaluation of safety and efficacy of these drugs.
- There are significant temporal changes in neonatal physiology, which have not been described in sufficient detail to allow predictable drug development.
- Neonatal laboratory value normative ranges are not defined, which limits their utility as safety markers.
- The adverse event reporting system currently used is not tailored to neonates.
- There are differences in how neonatal research processes are perceived by key stakeholders integral to the care of neonates in the NICU.
- There is insufficient multidisciplinary engagement with families and nurses to promote research in NICUs.
- These issues increase the cost of doing trials and aggravate safety concerns, which greatly impacts the feasibility of conducting clinical trials in this small population of neonates.

MOVING NEONATOLOGY RESEARCH TOWARDS DRUG DEVELOPMENT SOLUTIONS

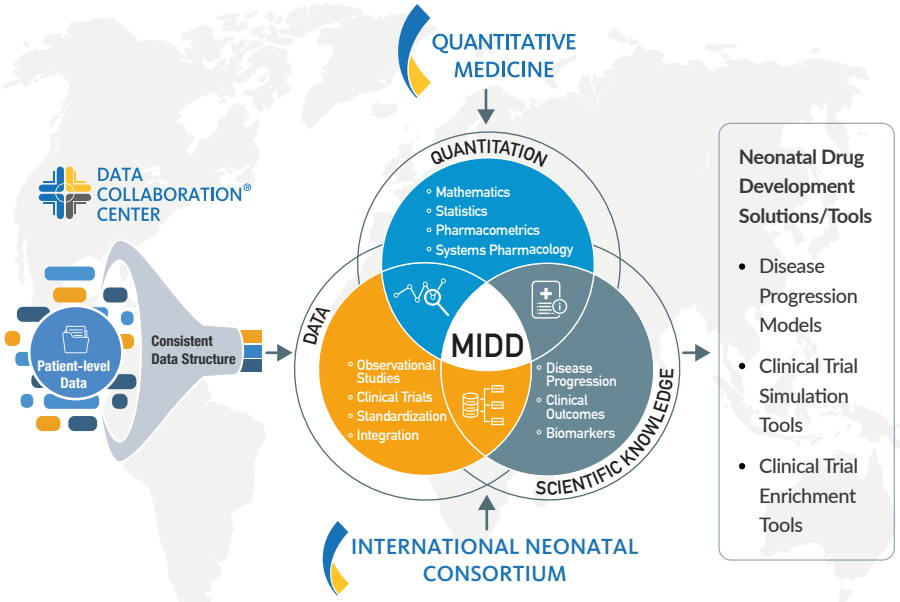
Real-World Data Analytics Platform (RW-DAP)

With the support of FDA's Office of Medical Policy, INC has initiated an ambitious real-world data integration effort, which will greatly accelerate drug development in neonates.

Building on C-Path's expertise in data integration, analysis, model-informed drug development (MIDD), and regulatory submissions, this effort has already integrated >200,000 patient-level data points (Electronic Health Records, registries, clinical trials) and is currently focused on:

- Constructing a quantitative disease progression model for bronchopulmonary dysplasia
- Establishing generalizable neonatal laboratory value reference ranges by age, gender, ethnicity, and other patient-level characteristics.

Data integration activities from additional sources are ongoing. RW-DAP is scalable, MIDD process is disease agnostic, and upcoming efforts will focus on creating drug development tools for other neonatal diseases of highest unmet need. The current data are already capable of supporting other neonatal disease areas.



Neonatal Adverse Event Severity Scale (NAESS): An effort to standardize safety assessment and reporting in neonatal clinical trials

- Recognition and classification of adverse events in neonates is challenging due to complex physiology, multi-organ system involvement, and symptoms not similar to classification systems in adults and older children
- INC developed a standardized 5-grade, 35-point NAESS that will make safety reporting more reliable and comparable across neonatal clinical trials[2]
- NAESS has been published on NCI/NIH website[3], translated to Japanese, and adopted by regulatory agencies for safety reporting in neonatal clinical trials

Standardizing measurements of Blood Pressure (BP) in neonates

- Current gold standard methods of accurately measuring BP in neonates involve invasive methodologies
- INC provided recommendations based on a systematic review and analysis of published literature on methods of measuring BP in neonates[4]
- These recommendations will form the basis of a standardized BP measurement protocol in neonates, reduce variability as well as improve routine clinical care

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.

OTHER INC SUCCESSES

- ***Clinical Pharmacology:*** Published a white paper to provide recommendations on the need to focus on the unique aspects of neonatal physiology and clinical pharmacology during the neonatal clinical trial design phase. The white paper significantly contributed to the subsequent development of FDA Guidance for Industry on "General Clinical Pharmacology Considerations for Neonatal Studies for Drugs and Biological Products[1]."
- ***Neonatal seizures:*** Provided recommendations for clinical trial design components of anti-seizure medications in neonates with input from clinical care providers, researchers, nurses, industry, regulatory agencies and parents.
- ***Neonatal pain:*** Conducted a Critical Path Innovation Meeting (CPIM) attended by over 50 members of FDA, leading to the launch of the neonatal pain workgroup, with the objectives of validating EEG based metrics to reliably and objectively measure acute pain in neonates.
- ***Retinopathy of prematurity:*** Published a retinopathy of prematurity activity scale and clinical outcome measures for use in neonatal clinical trials[5].
- ***Necrotizing enterocolitis:*** Addressed key issues that relate to the diagnosis, prevention, and treatment of necrotizing enterocolitis, and suggesting a path forward to evaluate the safety and efficacy of development and licensing of medicinal products for the prevention and/or treatment of necrotizing enterocolitis[6].
- ***Neurodevelopmental follow-up:*** Conceptualized specific recommendations for long-term neurodevelopmental outcome assessments in neonatal therapeutic trials[7].

Thank you for everything you do.
We look forward to your support in making a meaningful and positive impact in the lives of neonates worldwide!

References

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5. Development of a Retinopathy of Prematurity Activity Scale and Clinical Outcome Measures for Use in Clinical Trials. JAMA Ophthalmol. 2019 Mar 1;137(3):305-311
6. Necrotizing Enterocolitis: Using Regulatory Science and Drug Development to Improve Outcomes J Pediatr. 2019 Sep;212:208-215.e1.
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