

INC NEWS



Reflections On Our First Year: A Message From the INC Co-Directors

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Jonathan Davis (Professor of Pediatrics, Tufts University)



The first year of this multi-stakeholder consortium has been remarkably successful. Families and advocacy organizations, neonatal nurses, regulatory authorities, industry as well as academic researchers, and funders have coalesced around the mission of accelerating the development of safe and effective therapies for neonates. This consortium of over 100 members in 26 countries held a major meeting at both the FDA and EMA during this last year, and after careful consideration selected and launched 4 initial INC workgroups. Workgroups focus on conditions commonly encountered in neonatal care or cross-cutting efforts to develop research tools for neonatal trials.

Now INC is poised to take on additional initiatives that address the need for measurement and assessment of clinical outcomes in neonates through teams that share data, knowledge, and expertise to advance medical innovation and regulatory science. The annual workshop at the FDA and the EMA provide an important forum for assessing gaps and prioritizing research tools. For each initiative, INC will develop approaches that integrate neonatal nurses and families, regulatory authorities, industry and other sponsors as well as academic researchers into the design and implementation of clinical studies. Key to INC's continuing success will be meaningful involvement of

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"Accelerating the development of safe and effective therapies for neonates."

"The consortium is a great example of a public private partnership that is developing both a forum for global knowledge exchange and beginning the formation of a collaborative network to make sure that high quality studies are performed."

-Robert Califf, FDA Commissioner

multicultural stakeholders, especially families, all focused on the needs of neonates.

Upfront: Highlights from the 2nd Annual INC Workshop at FDA

On March 7 & 8, the INC met at the FDA to review the overall progress of the consortium and the specific deliverables of the 4 Workgroups (clinical pharmacology, data, bronchopulmonary dysplasia, and seizures).

INC Co-chair Jon Davis invigorated the consortium with his welcoming “We have a dream” speech. The attendees were then addressed by FDA Commissioner Robert Califf who reflected on his own experience as a parent of a neonate who required the expert care of a NICU. He advised the members to involve parents in every aspect of our research given the instructive nature of a parent-powered network. He also

noted his “excitement” for the vision of the INC and the importance of collaboration and data-sharing in an era of globalization.

In her keynote address on day 2, Janet Woodcock (Director of CDER, FDA) further iterated how the lack of standardization has handicapped successful research in neonates, and the role for a consortium based approach to drive regulatory practice and attract investment in neonatal drug development.

The workshop also engaged in identifying additional initiatives in regulatory science including dedicated sessions to discuss retinopathy of prematurity (ROP), bacterial infections



FDA Commissioner Robert Califf

including necrotizing enterocolitis, and hemodynamic adaptation. Of these initiatives, attendees prioritized identifying (1) standards for data capture and defining outcomes related to ROP, (2) developing standard protocols and assessments of efficacy in the CNS related to infection, and (3) standards for blood pressure measurement and defining neonatal shock.

We have a dream

“Every newborn admitted to the NICU will enroll in a study protocol to optimize outcomes; The definition for our most important outcomes will be the same worldwide; We will collect standardized data on all infants, and the databases will be shared, harmonized and readily searchable; We will be able to easily examine survival and outcome based on region of the world and adopt best practices; We will have established normal lab values based on birthweight, gestational age and postnatal age.”

-Jon Davis



Deb Discenza (PremieWorld LLC)



Wiley Chambers (FDA), Reiko Shimizu (PMDA), Ralph Bax (EMA)



Janet Soul (Harvard University)



Ron Ariagno (Stanford University)



The Data Workgroup co-chaired by Kate Costeloe (Queen Mary Univ. of London) and Thomas Diacovo (Columbia Univ. Medical Center)

Achieving Milestones Through Cross-Stakeholder Collaboration: Updates From the INC Working Groups

In the first year, the INC membership has concentrated their work in 4 key areas: clinical pharmacology, data, bronchopulmonary dysplasia (BPD), and seizures. Workgroups have been created to standardize methods and drive consensus-derived standards of care, develop master protocols incorporating innovative trial design, draft decision criteria for conducting clinical trials of new therapies for neonates, and to develop tools that may be endorsed or qualified by regulatory agencies for their application in clinical trials.

Clinical Pharmacology

The clinical pharmacology workgroup co-chaired by Karel Allegaert (Univ. Leuven), Jeffrey Barrett (Sanofi), and Bob Ward (Univ. Utah) has deftly accomplished the task of aligning a broad array of stakeholders in drafting a White Paper. The

document is intended to assist investigators and sponsors of studies that evaluate medicines in neonates both for regulatory application and clinical management. The workgroup also intends for the paper to be useful for regulators who evaluate these studies.

The white paper expands upon previous draft guidance from the FDA, EMA, Health Canada and ICH E-13, and addresses general clinical pharmacology considerations for conducting studies in term and preterm neonates. The paper focuses on the clinical pharmacology information that support findings of effectiveness and safety and helps to identify appropriate dosages in the neonatal populations. It also describes the use of quantitative approaches to employ disease and exposure-response knowledge from prior studies to

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design and evaluate future studies in neonates. A goal is to support the standardization and harmonization of regulatory documents for studies in neonates worldwide to facilitate global development of new and existing products. The white paper has been submitted for peer review.

The workgroup will now be turning its attention to providing expertise to the BPD, seizure, and data WGs. Additionally, they have agreed to support the new initiatives to address neonatal abstinence syndrome, including the development of study designs and outcome measures, and will also focus on developing risk assessments for excipients and formulations.

Data

Jeffrey Jacobs, Professor of Surgery and Pediatrics, Johns Hopkins University provided a series of talks on multi-institutional databases. In the general session of the INC, he discussed database utilization as a clinical trial platform providing a study population based on specified eligibility criteria filtered from the database and risk adjusted balanced cohorts for the trial. In subsequent presentations to the Data Workgroup, he addressed the value of multi-institutional databases to report outcomes, improve quality and conduct research, and discussed the steps to build a database and gain

alignment across interested but disparate groups. The workgroup identified key messages to inform their work from this series of presentations, including:

- The need for leaders of existing databases to become champions for this effort
- A stable committed workgroup willing to build upon existing data
- A vision and commitment for the long haul but group must also provide short term deliverables that create interest, alignment and demonstrate progress
- Technology to support the work
- Standard nomenclature in a hierarchical structure that provides terminology, definition and commentary.
- A spirit of collaboration and fun along the way

Co-chairs Tom Diacovo (Columbia Univ. Medical Center) and Kate Costello (Queen Mary Univ. of London) facilitated a series of mini presentations by key stakeholders (regulatory, clinical, academic, industry) which included sessions on biomarkers, laboratory values, standardizing datasets, defining of trial outcomes, and on using electronic health records to support clinical trials. Prior to

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INC Business**2016 Milestones**

- ✓ Publication of clinical pharmacology White Paper
- ✓ Publication of Fall 2015 Meeting White Paper
- ✓ Global definition for BPD
- ✓ Neonatal seizure Master Protocol
- ✓ Pediatric Academic Societies (PAS) INC State-of-the-Art Plenary
- ✓ National Association of Neonatal Nurses (NANN) INC Concurrent Session

**2016 Meeting Dates**

PAS Dinner (Baltimore)
1 May 2016

EMA 2nd Annual
Neonatal Scientific
Workshop (London)

12-13 Sept 2016

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concluding the meeting, the workgroup aligned on prioritizing key deliverables:

High priority - Annotated bibliography of lab values; Gap analysis to guide future work for defining stopping rules, adverse event (AE), serious adverse event (SAE) and population based reference ranges; Recommendations for neonatal CDISC laboratory standards

Medium priority - Develop a case study for a multi-institutional database as a clinical trial platform; White papers (Reporting requirements for neonatal biomarkers and standardizing reporting; Pooling data across neonatal databases).

The work group also discussed future projects which may include a white paper to describe the characteristics of

successful approaches to building terminology relating to safety and efficacy reporting as well as potential mapping of existing neonatal databases to SNOMED or other systems.

Bronchopulmonary Dysplasia

The INC bronchopulmonary dysplasia (BPD) workgroup led by co-chairs Robin Steinhorn (Children's National Medical Center) and Wolfgang Gopel (Univ. of Lubeck) has set as its first goal a consensus definition of BPD in order to enable consistency in clinical diagnosis, especially for drug development. To guide their efforts, six questions were articulated and discussed at the face-to-face meeting:

- 1) How should we define the early respiratory failure associated with prematurity, particularly after the first few days of life?
- 2) What is the optimal timing and definition for the BPD endpoint?
- 3) Are there sufficient predictive models for BPD? Do early comorbidities assist in identifying infants at risk for BPD? Are other surrogate markers available or emerging that will aid in early identification of BPD?
- 4) Are there subtypes of BPD?
- 5) How do we factor in the ongoing morbidity associated with BPD through the first years of life?

- 6) What other outcomes are measureable and of importance to clinicians and families?

While many challenges were articulated, several appealing considerations were also captured to guide the group in defining BPD. Two well-validated endpoints are critical: an early assessment to identify babies at high risk for BPD in the first few days of life, and a late endpoint to assess outcomes. From a drug development standpoint, understanding which babies are most likely to get BPD helps enroll the right patients into clinical trials, those that will most benefit from treatment. The current BPD definition of oxygen requirement at 36 weeks appears to be more predictive of future respiratory challenges than other early assessments, but this definition could be augmented with considerations such as a requirement to justify oxygen supplementation, or looking at cumulative endpoints over time, rather than as a point estimate.

To assess whether a drug intervention actually provided patient benefit, a longer-term assessment of respiratory outcomes is also imperative. Different types of assessments (e.g. respiratory function measures, parent diaries or questionnaires) at time points from 6 months to 2 years were considered. Measures that captured disease impact on babies and their families, such



Robin Steinhorn (Children's National MC) and Wolfgang Gopel (Univ. of Lubeck)

as frequency of coughing, doctor's visits, and medication use, are generally considered clinically meaningful. Instruments to capture these measures must be well-validated.

The BPD workgroup's next steps will be to summarize discussions into a paper articulating the different considerations towards a consensus definition of BPD.

Neonatal Seizures

The neonatal seizure workgroup led by co-chairs Janet Soul (Harvard Univ.) and Ronit Pressler (Great Ormond Street Hospital), has been working in several sub-groups to accomplish the task of writing a master protocol for future clinical trials, specifically for new therapies to treat neonatal seizures.



The Neonatal Seizure Workgroup co-chaired by Janet Soul (Harvard Univ.) and Ronit Pressler (Great Ormond Street Hospital)

Neurologists and neurophysiologists are not available at every facility where there is a newborn service. This reality makes completion of and the availability of a master protocol highly valuable in guiding future clinical trials for neonatal seizure therapies.



Suzie McCune
(FDA)

During the workgroup session, each of the seizure master protocol sub-groups presented their accomplishments to date while members from various disciplines were invited to comment. The discussions began with the reminder that Phenobarbital has been the mainstay of treatment for neonatal seizures for almost 100 years. Other therapies have been studied and licensed for older pediatric populations; however, neonates have not experienced the same benefits.

Researchers, regulators, industry partners and clinicians from different parts of the globe have collaborated to reach consensus on key elements of the master protocol, including

inclusion/exclusion criteria, various methodological trial designs by phase of study (phase 1, 2, 3), endpoint selection, and primary and secondary outcomes measures. The workgroup has also focused on topics such as ethical considerations regarding parental consent, and criterion for determining treatment success. The workgroup membership will now be turning its attention to writing the final master protocol document.

INC Notable references

- ✓ Allegaert K and Sherwin C. *Neonates and medicines: a roadmap to further improve neonatal pharmaceutical care.* Eur J Paediatr. 2016.
- ✓ Allegaert K and Sherwin C. *Therapeutic Orphans.* The Medicine Maker. 2016.
- ✓ Califf R. *A Message from the Commissioner.* (e-mail to FDA staff) 18 March 2016.
- ✓ Short M. *Neonatal Nurses: Key stakeholders to the International Neonatal Consortium.* NeoReviews. 2016.

A Share of Voice: Leveraging INC Multi-stakeholder Collaboration to Address Neonatal Needs

The INC is a consortium made up of many unique voices all who share a common mission – to accelerate the development of safe and effective therapies for neonates. In its first year, the consortium has engaged families, neonatal nurses, academic scientists, clinicians, regulators, pharmaceutical industry, advocacy organizations and funders. On the first night of the 2nd Annual Neonatal Scientific Workshop, a working dinner highlighted the many perspectives of members who are collaborating to achieve the INC Mission.



Cristal Grogan (Premie Parent Alliance)

Cristal Grogan shared her experience after delivering her son at 29 weeks. As a military wife, Cristal and her husband were living in southern Spain when complications of pregnancy led to her son's early birth. She detailed her experience of a complicated NICU stay while in a foreign country, amidst a language barrier and without an essential support system. Cristal noted that this led to her

involvement in the premie community to make sure no other parent was left in the same desperate situation. She stressed that no one should ever under-estimate the role that communication plays for parents who otherwise have no control over their baby's current situation.



L to R: Carole Kenner, Council of International Neonatal Nurses (COINN) Alliance; Connie Chen, Health and Environmental Sciences Institute (HESI); Wakako Eklund, National Association of Neonatal Nurses (NANN)

The evening also featured perspectives from critical collaborators in clinical care and premie outcomes, including Carole Kenner, CEO of the Council of International Neonatal Nurses (COINN), and Wakako Eklund who spoke on behalf of the National Association of Neonatal Nurses (NANN). Wakako shared early data from a NANN survey that assessed nurse perspectives on participating in and contributing to neonatal clinical research and the critical role that access to information plays in facilitating bedside conversations with families. Connie Chen (Health and Environmental Sciences Institute (HESI)) highlighted ongoing work on nonclinical neonatal-pediatric animal models to support neonatal therapeutics in order to identify major gaps in pre-term and term neonatal drug developmental and models of human disease. The evening also featured industry perspectives provided by Jeff Barrett (Sanofi) and a policy update provided by Christina Bucci-Rechtweg (Novartis Pharmaceuticals). INC Co-Director Jon Davis closed the evening emphasizing the value of cross-stakeholder collaboration.

A Discussion With Parents: Nick Hall shares his vision for the INC

Q. How did your experience in the NICU shape you and your family's future?

A. We were building our home and assumed we would be moved in by the time our babies were born. With our twins coming into the world 15 weeks early, our goal became maintaining hope the hope that we would be able to bring our babies home, to any home.

Our experience with our twins in the NICU has impacted us as a family in many ways. We lost our son after 45 days and our daughter stayed in the NICU for 4 months. When your babies are born extremely early, and they go through the ups and downs of the NICU journey, you are struck by the fragility of your baby's life. We know from our own experience, and from talking to hundreds of other parents, that we as parents have a tendency to continue to see our babies as fragile. It impacted us immediately in the NICU and presented as a fear of touching and holding our babies. Not because we did not want to bond but because we were afraid we would hurt them. My number one request to all

NICUs is to do whatever you can to help your parents bond with their babies and help them be a part of their babies' care, so they begin to understand what a difference they can make helping their baby progress from fragile to resilient to strong.

We parents of extreme preemies tend to be a little more cautious and overly protective of our babies. In some ways it can be quite beneficial. For example, in the first year of our daughter's life she had very little contact with anyone outside of our immediate family and only when we knew that they were free of illness. While that was mentally taxing for me, and especially my wife, it did help keep our daughter healthy, which we believe has been beneficial to her longer term health. But our tendency to be overprotective has also transferred somewhat to our daughter, as we have noticed her to be somewhat cautious. Of course, as I write this, my wife just shared that our daughter begged to ride the *Rock It* roller coaster at Universal Studios so maybe she has a bit of fearlessness despite our protective ways!



Nick Hall and his wife Jennifer founded Graham's Foundation in the memory of their son, Graham.

While in the NICU, I also saw how much other families were struggling with the overwhelm of day to day existence not knowing what was happening to their baby, uncertain of their needs, unsure what they could do to help and what the future held. I saw relationships crumble. I saw parents stop showing up. My wife and I felt like we were in survival mode for at least the first two years of our daughter's life. I knew I had to do something. That's why we founded Graham's Foundation.

The next issue of the INC News will feature Part 2 of this discussion.

*International Neonatal Consortium (INC):
Accelerating the development of safe and effective therapies for neonates.*

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