On March 28th the INC met to share regulatory perspectives, review progress of the work groups and partnership efforts, and discuss challenges of trials to prevent preterm birth. Jon Davis (Tufts University, INC Co-Director) welcomed the attendees and proclaimed “INC University in session”. The university analogy is relevant to the experience of the consortium members and stakeholders. Lessons on regulatory science will lead to therapies studied in adherence to regulatory standards with the ultimate goal of treating babies with the right drug at the right dose at the right time.

Suzie McCune (Director of OPT, FDA) pointed to a new era for developing neonatal therapeutics. She cited CDER/FDA Director Janet Woodcock’s address to U.S. Congress, in which INC’s collaborative work was noted as critical for addressing the unmet needs of neonates. She reviewed INC’s progress and focused on partnership as key to addressing the needs that remain in basic science, modelling and simulation, trial designs and IT systems.

Understanding requirements for endpoints in regulated trials is necessary for INC efforts. Global regulators shared their perspectives, lessons learned and recent initiatives. Partnership was identified as a key benefit of INC providing global regulators the opportunity for enhanced interactions. Ralph Bax (EMA) reviewed PIP learnings. Depending on the condition and product, staggering studies from adults to children and then neonates, was not always informative to neonatal development. He discussed the knowledge gaps in primary and secondary neonatal endpoints and the need for consistency across trials. Gerri Baer (FDA) discussed biomarker and endpoint development, highlighting the Qualified Biomarker and Clinical Outcome Assessment processes. She shared alternative approaches to support inclusion in specific development programs (e.g., letters of support for biomarkers; obtaining data and parent input on clinically meaningful endpoints). Agnes Klein (Health Canada) stressed the importance of accurate data collection and reporting. Junko Sato (PMDA) discussed recent initiatives.
including the Regulatory Science Center and use of electronic health data for advanced review, consultation and identifying safety signals.

The current INC priorities focus on common NICU conditions. In the plenary, a session on ‘Challenges in Conducting Registration Trials to Prevent Pre-Term Birth’, was introduced including perspectives from academia, regulatory agencies, industry and parent alliances. The session highlighted common challenges in these trials and neonatal trials (e.g. unmet need, lack of biomarkers, multiple phenotypes, appropriate outcome measurement, ethical concerns). INC will assess what next steps could be collaboratively taken in this area.

The workgroups provided an update on their progress to date (Table 1) in a session led by Ron Portman (Novartis, INC Co-chair).

Ed Connor and Will Treem gave an update on two public-private partnerships to facilitate pediatric research (I-ACT for Children, North America; IMI 2 Pediatric Clinical Trial Network, EU). The networks share the concept of global interoperability to provide efficiency, capacity and sustainability. INC efforts will be supported by the ability of these networks to conduct neonatal research world-wide.

Continuing on the theme of partnerships, Suzie McCune provided an update on the work of ILSI HESI DART’s animal and nonclinical models. DART’s request for INC is to provide the clinical context for the models’ utility.

Mark Turner (University of Liverpool, INC Co-Director) closed the meeting summarizing INC’s progress as a transition from an apple tree to an espalier - from picking low-hanging fruit to building a framework where all fruit is within reach.

Table 1

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<th>Workgroup</th>
<th>Key Accomplishments and Next Steps</th>
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| Retinopathy of Prematurity            | - Alignment on: Structure of white paper, novel integrated ROP activity scale, timing for endpoints [neonatal, 6 mos, 2 yrs, 5 to 5.5 yrs] & novel method [OCT]  
  - White paper will discuss: Limitations, trial optimization, standard protocols with endpoints, outcomes & timing                                                                   |
| Hemodynamic Adaptation                | - Completed literature review to define appropriate methods of measurement & normal values  
  - Ongoing analysis of data from existing networks; Plan is to define prospective data collection  
  - Goal to determine low and high BP thresholds for inclusion/exclusion criteria for neonatal trials                                                                                              |
| Data                                  | - Lab results linked to clinical data from California, Utah, Toronto and Japan will be harmonized for analyses to establish neonatal lab reference intervals by week of gestation  
  - Core neonatal data set for clinical trials has been established  
  - Work with NCIt to identify needed terminology for the collection of neonatal data; Draw on CRFs to initiate development of CDISC standards  
  - Finalize white paper on neonatal databases that outlines the current state, the gaps, and steps towards an ideal state                                                                 |
| Seizures                              | - Master protocol to be published  
  - Protocol elements defined: Inclusion criteria of seizure within 48 hours; Phenobarbital as comparator (placebo deemed not ethical)  
  - Primary outcome is 80% reduction in seizure burden vs. baseline assessed by EEG; Secondary outcomes are immediate neonatal outcome, and outcome assessment at 2 and 5 yrs |
| Bronchopulmonary Dysplasia            | - Proposing renaming BPD to Chronic Pulmonary Insufficiency of Prematurity (CPIP) to better reflect disease state knowledge  
  - White paper submitted on concept of CPIP  
  - Recommendation of grading of BPD at 36 weeks to improve its predictability  
  - Identified outcome assessments at 40 weeks (term equivalent); Long term assessments at 1 yr & 2 to 5 yrs                                                                                                 |
| Clinical Pharmacology                 | - Neonatal Clinical Pharmacology white paper published in Pediatric Research (SANOFI sponsoring open access and hard copy)  
  - Established a generic Severity Grading Scale for Neonatal Adverse Events (AEs) and applied those to neonatal seizures  
  - Begin work to provide CTCAE a listing of neonatal AEs with use of the Severity Grading Scale                                                                                           |
| Communications                        | - Circulation of 2nd edition of INC Newsletter (Nov 2016)  
  - Completed INC-PPA parent feeder survey on parent perspective of US neonatal research culture of communication  
  - Initiated literature review of research communication strategies  
  - Develop and launch multi-regional multi-stakeholder survey on neonatal research culture of communication                                                                 |
A Share of Voice: Leveraging INC Multi-stakeholder Collaboration to Address Neonatal Needs

The INC is a global collaboration uniting research institutions, drug developers, regulatory agencies, patient advocacy groups and other organizations to forge a predictable regulatory path for evaluating the safety and effectiveness of therapies for neonates. This issue of the INC News features representative voices sharing stakeholder perspectives from across the INC regions.

Japan

Hidefumi Nakamura, MD, PhD

*Director for Clinical Research & Development, Department of Development Strategy, Center for Clinical Research and Development, National Center for Child Health and Development*

I was a resident when surfactant was first introduced in Japan in the 1980s. Just minutes after the administration, premature babies who struggled to breathe started to breathe easily, and we could often extubate the babies within a day. That was such a stunning experience to see the huge impact of an advancement of medical care. But, as Dr. Davis often points out, we do not have many new medicines for neonates since then. There are still off-label drugs that are commonly used, and we have hurdles to clear to facilitate the development of new neonatal therapy.

Although Japan is known to have good neonatal care, Japanese NICUs are not necessarily well experienced in the development of new medical therapy. Japan does not have a regulation similar to the ones in the US or the EU to mandate pediatric drug development. Discussion to facilitate pediatric drug development is ongoing, but the necessity for better neonatal care is less recognized. I am hoping that the introduction of INC activities will increase awareness and activity in Japan.

Continued...
Luckily enough, Dr. Satoshi Kusuda agreed to join the INC and he also introduced several leading neonatologists to INC. Junko Sato from the PMDA also joined the Coordinating Committee, and we discussed possible collaboration in the future with INC leaders at the recent Workshop.

Dr. Kusuda is one of the founding members of the Neonatal Research Network (NRN) Japan. Activity of the NRN Japan goes back to 1998 when the randomized controlled trial of indomethacin on intraventricular hemorrhage (IVH) was planned and later conducted. Since then, the NRN Japan have conducted several clinical trials. In 2003, NRN Japan also established a morbidity and mortality database (http://plaza.umin.ac.jp/nrndata/indexe.htm) that covers approximately 45% of the very low birth weight infants born in Japan. The database can be utilized for comparison with other regions and also for global standardization in neonatal care.

Prognosis of high risk neonates in Japan is considered to be better compared to many other developed countries. But there are still complications including BPD, IVH, Periventricular Leukomalacia, NEC, and ROP that need better treatment and prevention. We need to learn from each other and work together to have new medical therapy introduced globally as early as possible. I believe INC can also be a platform for Japanese parent groups and nurses to collaborate internationally. In Japan, we still do not have strong patient advocacy groups focusing on neonates, and I hope the introduction of INC will be a good stimulus.

INC is really a great effort to streamline the development of technologies in neonates with a global perspective in mind. Multi-stakeholder collaboration is the key to make this effort successful. I am grateful to be a part of this consortium and hope to witness our dream “better medical treatment for all the babies” come true.

**United States**

Ronald Ariagno, MD, FAAP

*Emeritus Professor of Pediatrics, Stanford University & Intergovernmental Personnel Act appointment at FDA, OPT, neonatology consultant*

In May of 2017, the March of Dimes (MOD), published a valuable new tool on their website that will facilitate engaging families on the topic of neonatal research:

http://www.marchofdimes.org/complications/clinical-trials-for-your-baby.aspx

**Purpose:**

The MOD article should inform (and empower) expectant mothers and fathers, parents, families, grandparents, neonatal nurses, and the community about the fact that most drugs used in the care of critically ill neonates are “off label” (for example, not approved for safety, efficacy, dose or formulation (viz., how the drug is prepared)). This article also explains what clinical trials are.

**Issue:**

Neonatologists select therapies based on applying the information on drugs approved for children and adult populations; on what is accepted as current “standard of care” (SOC); the availability of drug in the hospital formulary; site, regional or national opinion; and the level of comfort in using the drug in a neonate based on the published literature and advice from “experts” or consultants.

Parents and families will be served by knowing why regulatory research is required to establish safety and efficacy. Neonatal researchers need to learn what is the required regulatory research plan, which includes outcome measures important/significant for parents and for regulatory approval.

**Action:**

The MOD article should enable parents, neonatal nurses, community and parent groups to advocate for neonatal drug studies, comparative SOC clinical investigations and for the discovery of benchmarks for diagnosis, mechanisms of disease and the endpoint/outcome measurements essential for successful regulatory research studies and approval.

We invite parents and families to advocate through communication between the many parent groups and through appropriate Social Media to inspire neonatologists and neonatal nurses and to establish funding for regulatory research, which is essential to improve safety and efficacy of neonatal therapeutics.
Why Our Work in the INC Matters: A Mother’s Perspective
Jennifer Degl

Preemie Mother, Author of “From Hope to Joy: A Memoir of a Mother’s Determination and Her Daughter’s Determination to Beat the Odds” & Board of Directors of The Morgan Leary Vaughan Fund

Five years ago after delivering my daughter at 23 weeks gestation, I had no plans to become an author or an advocate for premature babies, but the universe kept telling me otherwise. As a secondary science teacher and mother of four children, including my premature baby, I had little time for much but I could not suppress the feeling that I had to use our story for something greater. I felt I needed to share both our pains and successes with the world so that other families could benefit from learning about what we went through. This is what led me to become a writer, speaker, and advocate and also how I became involved with INC.

My daughter was born 17 weeks early and weighed just 575 grams. She was only 11 ¾ inches long. I named her Joy because that is what I felt after meeting her for the first time. I was not able to see my daughter for several days after her birth, due to my complications following her delivery. I suffered from placenta percreta and almost lost my life several times during my pregnancy. I was not able to hold my daughter until she was over a month old because of her fragile condition. The 121 days that Joy spent in the NICU were difficult on our whole family and we all found different ways to deal with our emotions. I decided to write, speak and become involved in organizations that effect real change and allow the preemie parent voice to be heard. INC is doing an impressive job at just that.

This past March, I had the privilege to represent The Morgan Leary Vaughan Fund and the Preemie Parent Alliance (PPA) as co-chair of the Communications Workgroup Breakout Session at the 3rd Annual FDA-INC Neonatal Scientific Workshop*.

As a representative for parent organizations and as a mother who spent four months in the NICU due to my daughter’s premature birth and several weeks in the PICU because of her Bronchial Pulmonary Dysplasia, I can speak to the fact that most preemie parents want to participate in something that might not only benefit their baby but also help future premature babies. No NICU parent wishes this experience on another parent.

As a parent of a micro preemie, I am all too familiar with the feelings of overwhelming emotion, fear, stress and guilt that accompany a premature birth. These feelings, along with the likelihood of a mother’s delivery trauma and the resulting physical and emotional wounds can cause a parent to be unwilling to participate in a conversation about enrolling their baby in a clinical study. Most parents understand that pharmaceutical advancements cannot be made without research, but remain resistant. Parents who are approached in a certain way and time, by the correctly trained medical personnel, are more likely to consent to trial research.

This, along with a literature review on the topic of neonatal clinical trials, was discussed at the Breakout Session. One goal of our workgroup is to come up with strategies to enhance communication surrounding research between all stakeholders in the neonatal intensive care unit including physicians, nurses, nurse practitioners, research scientists and parents.

As a representative for parent organizations and as a mother who spent four months in the NICU due to my daughter’s premature birth and several weeks in the PICU because of her Bronchial Pulmonary Dysplasia, I can speak to the fact that most preemie parents want to participate in something that might not only benefit their baby but also help future premature babies. No NICU parent wishes this experience on another parent.

C-Path saw a void in this space and launched INC to accelerate the development of safe, effective therapies for newborns. This puts INC members in a key position - one that allows us all to be “pioneers” if you will, of the future of neonatal research. As medical knowledge and technology advances, babies are surviving at much earlier gestations and these babies need the best chance at not only survival, but at the best quality of life that medicine allows. I have no doubt that INC can accomplish this.

With proper timing and communication strategies in place, I believe that the INC can work to increase the neonatal drug options and availability of those drugs, so that we can improve the lives of our future neonatal population. I am excited to be a part of such important work.

*To learn more about my personal experience at the 3rd Annual FDA-INC Neonatal Scientific Workshop, please visit http://micropreemie.net/blog/3rd-annual-fda-inc.
INC Workgroup Timelines and Deliverables: Turning Stakeholder Collaboration Into Action

There are numerous on-going projects across the established INC workgroups. Since November 2016, two new workgroups have been introduced, including: Communications and Necrotizing Enterocolitis (NEC).

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

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