

# INC NEWS

## Upfront: Highlights from the 2<sup>nd</sup> Annual Neonatal Scientific Workshop at EMA



Paolo Tomasi (EMA), Guido Rasi (EMA), Ron Portman (Novartis, INC co-Chair), Mark Turner (U Liverpool, INC co-Chair), Lynn Hudson (C-Path Institute, INC co-Chair)

On September 11 & 12, the INC met at The European Medicines Agency (EMA) to review the consortium's collaborative efforts to date, and to identify and prioritize new projects to accelerate the development of therapies for neonates.

The Executive Director of the EMA, Dr. Guido Rasi, welcomed the consortium members and encouraged global dialogue to ensure that the meeting was fruitful.

The meeting kicked off with a session dedicated to exploring approaches that the neonatal community can take to embrace a research culture. Neena Modi (Imperial College London) provided an insightful Keynote

Address which provided historical perspectives to guide the INC thinking on where we should move the field of neonatology. She highlighted that clinical uncertainty is at the root of patient safety considerations, noting that when our evidence base is uncertain, a patient will be best served by receiving a treatment unaffected by clinical bias and care delivered along a "clearly designed and closely monitored pathway [clinical trial]". She offered a continuum of considerations to improve care for the critically ill newborn, including: research integrated into clinical care and made efficient, implementation and evaluation by a well-trained workforce, partnerships,

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### Upfront



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

*"...To avoid a gap in treatments, to avoid duplication of efforts, this consortium is a very important approach to achieving improvements for neonates."*

*- Guido Rasi, Executive Director, The European Medicines Agency (EMA)*

advocacy, evidence informed care and policy to improve newborn health.

## Upfront cont'd ...

Dr. Kelly Wade (Children’s Hospital of Philadelphia) provided a look into her institution’s 40 years of experience embedding research into clinical care. She noted the role that awareness, constant presence, breadth of focus (physician and patient, as well as nurse and family-focused), constancy of purpose and family-centered care play in driving a positive research culture.

The workshop also engaged in (1) discussing how clinical pharmacology can contribute to the appropriate use of narcotics for sedation, analgesia, and/or neonatal abstinence syndrome (NAS), (2) examined how studies on precision medicine for neonates should be designed to maximize benefits, (3) analyzed the existing evidence and discussed the challenges and limitations of assessing long-term neurodevelopmental outcomes, and (4)

identified potential projects that the INC could take on to improve the treatment of necrotizing enterocolitis (NEC).

At the conclusion of the workshop, consortium members voted to prioritize their new research projects as follows:

1. Long-term neurodevelopmental outcomes
2. NEC
3. Precision medicine for neonates
4. Embracing a research culture
5. Treatment of NAS

Consortium members identified age and definition of neurodevelopmental outcome, followed by use of data as basis for biomarkers for long-term outcomes as the key long-term neurodevelopmental research priorities. Similarly, for NEC, biomarkers for early diagnosis and unifying on a clear NEC diagnosis were identified as research priorities. Members also identified use of precision medicine to enhance research enrichment strategies, enhancement of communication and public relations around the importance of neonatal research, and identified a need



Kelly Wade (Children’s Hospital of Philadelphia)



Nathalie Seigneuret (The Innovative Medicines Initiative)



Wakako Eklund (NANN), Jordi Llinares-Garcia (EMA)



Merran Thomson (Hillingdon Hospital NH Trust)

to define NAS and develop a standard treatment protocol for NAS as critical research priorities within each of the proposed projects.



Thomas Morgan (NIBR), Stephen Spielberg (DIA)



Lex Doyle (Univ Melbourne)



Neil Marlow (Univ College London)



Michael Caplan (Univ Chicago), Karl Sylvester (Stanford)



The Bronchopulmonary Dysplasia (BPD) Workgroup



The Data Workgroup

## 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 from stakeholder groups, sharing in their own words their vision for the INC.

### National Institutes of Child Health and Human Development

Anne Zajicek, *Chief, Obstetric and Pediatric Pharmacology Therapeutics Branch*

Drug development for neonates has been difficult for multiple reasons. Neonates, especially premature neonates, have medical conditions not found in older infants, children or adults. These neonatal conditions related to prematurity do not appear to be mechanistically similar to other

pediatric or adult conditions, and they may not respond to medications in predictable ways like children or adults. Blood pressure is a commonly used measure in adults, because it has been validated as a surrogate marker of stroke risk. In neonates the concern is poor tissue perfusion as indicated clinically by low urine output, for example, and the assumption that low BP is related in some way to hypoperfusion. To illustrate the point, the Neonatal Research Network undertook a proof-of-principle study of dopamine and hydrocortisone to treat neonatal hypotension. Interesting and unexpectedly, the blood pressure (BP) did not improve with interventions that are typically effective in children and adults: fluid boluses, dopamine, and hydrocortisone. So in thinking about neonates, we do not know what neonatal blood pressure is a biomarker of, nor why

**Continued...**

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neonates did not respond to the interventions. An additional issue that arose from the NRN study was the absence of consensus on normal blood pressure values in neonates of various gestational ages.<sup>1</sup>

There is wide practice variation in treating neonatal conditions. A recent paper from the Canadian Neonatal Network<sup>2</sup> on practice variation in use of narcotics and sedative, which ranged from 3-41% and 2-48% respectively, indicates lack of agreement on medication use, lack of practice guidelines, and lack of standardization of care. With this wide variation, there is no clear means of determining which regimen will produce the best clinical outcomes.

The use of INC under the Critical Path Initiative infrastructure, to gather the thought leaders in neonatology, prioritize therapeutic needs in neonatology, and develop consensus on disease definition, normal values and outcome measures is a rational strategic approach to easing some of the difficulties in neonatal drug development management.

<sup>1</sup> Batton B et al; NICHD Neonatal Research Network. Evolving blood pressure dynamics for extremely preterm infants. *J Perinatol*. 2014;34(4):301-5.

<sup>2</sup> Borenstein L et al. Narcotics and Sedative Use in Preterm Neonates. *J Pediatr*. .doi:10.1016/j.jpeds.2016.08.031. [Epub ahead of print]

## INC Business



- ✓ On-line publication of neonatal Clinical Pharmacology White Paper
- ✓ Neonatal seizures work group drafting master neonatal seizures protocol
- ✓ BPD Work Group working toward BPD definition and drafting BPD manuscript
- ✓ Data Work Group drafting manuscript on international neonatal databases



### Hold the Date:

### FDA 3<sup>rd</sup> Annual Neonatal Scientific Workshop

(Bethesda, MD)

27 - 29 Mar 2017

### Neonatal Nurses

Wakako Eklund, *National Association of Neonatal Nurses* & Carole Kenner, *Council of International Neonatal Nurses*

The INC's primary goal is to accelerate the development of safe and effective therapies for neonates. Many neonatal therapies, especially drug therapies, have not been studied in this population. To achieve this goal, health professionals, industry leaders, basic scientists, and most importantly parents must be involved in creating a culture of understandable research. Nurses are the interface between the neonate/family and other team members. Nurses often explain clinical trials to parents and yet are not always a part of the development of the research protocols. INC recognizes the value of committed nursing professionals as an essential linkage of the multi-stakeholder team.

Nursing representatives congratulate the INC leadership and other participating members on incorporating the theme of "culture change" in the most recent European Medicines Agency (EMA) workshop in London with a dedicated session to discuss "Embracing Research Culture".

Nursing led the discussions about impacting significant culture changes in the Neonatal Intensive Care environment during the last decades. Some

of these include how we strongly advocated to bring family members closer to health professionals, collaborating with family and special advocacy groups to enhance mutual dialogue for the cause of the babies, changing our practices at the bedside by incorporating emerging evidence related to the developmental care concept to improve neonatal outcomes.

Informed nursing members are powerful allies to any stakeholders who are committed to accelerating therapeutic development by breaking down barriers between the families and industry/academic researchers, and enhancing mutual understanding or maximizing existing resources. In any new therapy development, whether it is to refine our understanding of biomarkers related to early diagnosis of necrotizing enterocolitis, or developing mutually agreed protocols, no advance would occur if babies and their families are not brought on board fully to embrace the culture of research as a "MUST" and not an "OPTION".

To this end, nursing representatives at INC are keenly aware that more work is ahead to educate our own colleagues so that all nurses will be informed and educated advocates to advance the research culture. Families and their babies deserve our commitment. When every nurse embraces research culture and recognizes his or

her potential as a link towards the development of new therapies for our vulnerable population, the true nursing impact in facilitating INC's ultimate goal will be possible.

Enthusiastic nursing members can serve as resources to both industry or academic research teams or by leading the research teams themselves by providing input for or creating future protocols. Nursing members' keen bedside perspectives about families and their babies is the foundation as we move forward to build research culture.

### Industry

Mary Short, *Eli Lilly & Co*

The industry members recognize and appreciate the engagement and participation of multiple stakeholders in the current INC work groups and meetings. The multi-stakeholder approach working in partnership is needed to develop the regulatory path forward for research in this vulnerable and physiologically dynamic population. The approach is valued by industry as a successful model of public-private partnership.

Sponsors believe that through INC's efforts the conversation has evolved to identifying what is needed to help industry be successful in developing and evaluating therapies to improve the outcomes for neonates. The needs for a well-defined disease criteria and appropriate neonatal outcomes are being

addressed by the INC work-streams (BPD definition and seizure master protocol). Industry is encouraged that the INC Clinical Pharmacology whitepaper is being considered for development of guidance by regulatory agencies. We look forward to the efforts of the data work stream to inform us of the core data to obtain in future neonatal trials. It is encouraging to see that as work groups finish deliverables, additional projects are initiated towards the INC goals that support industry efforts.

Industry members are concerned about the challenges of enrollment in neonatal trials and the need for more innovative trial designs in this population. We hope work groups can consider the regulatory science issues related to studying such small, complex and developmentally heterogeneous populations. We propose that INC might consider developing a white paper outlining the difficulties in enrollment in NICUs including the issue of small number of infants with many conflicting studies and the restriction of participation limited to one study.

Since the initiation of the consortium, industry members have noted a slight increase in neonatal drug development activity within their companies both related to specific compounds for neonatal indications as well as neonatal parts of studies for drugs in

adults and older children but recognize that legislation, such as *'The Promoting Life Saving New Therapies for Neonates Act'*, would likely enhance the development of therapies for neonates.

### Parents

Jennifer Canvasser, *Preemie Mother & Founder, Micah Smiles Fund & Founder, Necrotizing Enterocolitis Society*



Zachary, Jennifer and Micah Canvasser

When I received my Master's degree in Social Work with a concentration in Community Organizing, I never imagined using it to establish a nonprofit organization in memory of my first-born son, Micah. After years of nonprofit advocacy work focused on children's environmental health at the local, state and federal levels, my twin boys Micah and Zachary were born early at 27 weeks gestation. Zachary is now a thriving preschooler, who asks questions about his twin brother on a daily basis. Micah passed away from complications of necrotizing enterocolitis (NEC) when he and Zachary were 11 months old.

It was an honor to represent the NEC Society and Preemie Parent Alliance (PPA) at the 2016 INC meeting at the EMA. The NEC Society is committed to bringing together diverse stakeholders to reduce the incidence of NEC. The NEC Society is a member of the PPA, a coalition of organizations dedicated to advancing the needs of babies and families in the NICU.

By participating in this global meeting, I joined with physicians, nurses, pharmacists and others who are committed to improving care and treatment for families just like mine. As I shared during my presentations at the EMA, families in the NICU are often overwhelmed with guilt, and feel helpless, traumatized and so very alone as they try to figure out how to parent their fragile baby.

It was a privilege to present in both the "Embracing a Research Culture in the NICU" as well as "NEC" sessions. As a mother who spent nearly a year in the neonatal and pediatric ICUs, and then ultimately lost her son to NEC, these issues are clearly poignant for me personally. Furthermore, as the founder and director of the NEC Society, I strive to represent the hundreds of families globally who have joined the society. These families are desperate for increased awareness, prioritization, and funding for therapies to better prevent and treat NEC.

The INC is in a unique position to drive change, particularly as the group prioritizes and seeks to empower the patient-family perspective. Diverse stakeholders, including the NEC Society and PPA, are eager to partner with the INC because we know that these national and international strategic partnerships foster our efficiency and effectiveness. By working together, we can accomplish objectives that would be unachievable to any one of us working alone.

The NEC Society is thrilled that the INC has voted to dedicate focused time and resources on NEC by establishing a work group. There have not been significant advances in NEC morbidity and mortality in over 30 years; the disease continues to impact thousands of babies annually. As the INC engages key players, including governmental agencies, industry, renowned clinicians, researchers and patient-family advocacy organizations, I am



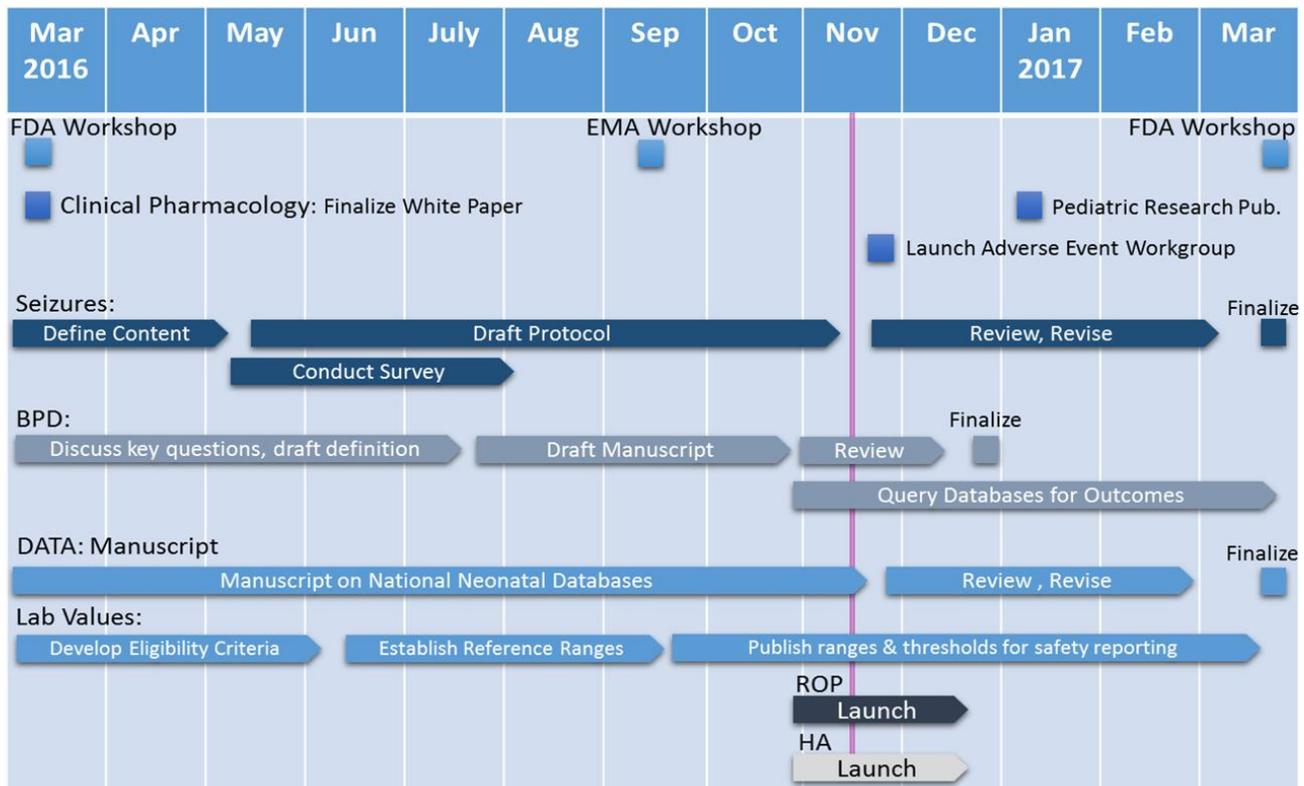
Elijah (Micah and Zachary's brother wearing his INC meeting badge at the EMA)

confident that together we can finally better prevent and treat NEC so that babies like Micah can survive and thrive.

## INC Workgroup Timelines and Deliverables: Turning Stakeholder Collaboration Into Action

There are numerous on-going projects across the INC neonatal seizure, bronchopulmonary dysplasia (BPD), clinical pharmacology and data workgroups. The INC is pleased to launch two new workgroups in November, including: retinopathy of prematurity (ROP) and hemodynamic adaptation (HA).

### Workgroup Timelines and Deliverables



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

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