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International Neonatal Consortium

Second Annual Neonatal Scientific Workshop at the EMA

Welcome

September 12th – 13th, 2016

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Agenda – September 12th, Afternoon

1:00 - 2:15 p.m.	**Session II: INC Workgroup Updates** RON PORTMAN, INC CO-DIRECTOR (NOVARTIS)
2:15 – 3:00 p.m.	**Session III:** *Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome* JOHN VAN DEN ANKER (CHILDREN'S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN'S HOSPITAL) & JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS
3:00 - 3:30 p.m.	COFFEE BREAK
3:30 – 5:00 p.m.	**Session III Panel**
5:00 p.m.	*Concluding Remarks for Day 1* JON DAVIS (TUFTS UNIVERSITY), INC CO-DIRECTOR
6:30 p.m.	NETWORKING DINNER AT THE PEARSON ROOM 16-19 Canada Square, Canary Wharf

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Session II: *Workgroup Updates*

Ron Portman, Chair

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Agenda – INC Workgroup Updates

1:00 – 2:15 p.m.

Session II: *INC Workgroup Updates*

RON PORTMAN, INC CO-DIRECTOR (NOVARTIS)

- New Workgroups
  - Retinopathy of Prematurity (ROP)
  - Hemodynamic Adaptation (HA)

- Clinical Pharmacology:
  BOB WARD (UNIVERSITY OF UTAH)
- Seizures:
  GERALDINE BOYLAN (UNIVERSITY COLLEGE CORK)
- Bronchopulmonary Dysplasia:
  ROBIN STEINHORN (CHILDREN'S NATIONAL HOSPITAL)
- Data:
  TOM DIACOVO (COLUMBIA UNIVERSITY)

INC AND THE NICU

The International Neonatal Consortium concentrates its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of preterm birth.

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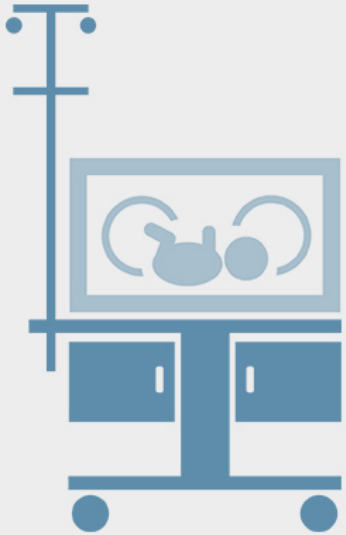

- NEONATAL LUNG INJURY AND CIRCULATORY FAILURE
- PERINATAL/NEONATAL INFECTIONS
- NEONATAL ABSTINENCE SYNDROME (NAS)
- RETINOPATHY OF PREMATURITY (ROP)
- NEONATAL GASTROINTESTINAL INJURY
- NEONATAL BRAIN INJURY
- DRUGS TO PREVENT PRETERM LABOR
- HEMODYNAMIC ADAPTATION (HA)

Implementation of a **Haemodynamic Adaptation** Workgroup: Members

Co-chairs

- Heike Rabe
- Janis Dionne

Group members

- Gene Dempsey
- Keith Barrington
- Varsh Bhatt-Mehta
- Luana Pesco Koplowitz

Regulatory members

- Shari Targum (FDA)
- Dina Apele-Freimane (PDCO)

Additional members can be recruited through HIP and NEO-CIRC consortium partners.

Implementation of a **Haemodynamic Adaptation** Workgroup: Specific Aims & Proposed Methods

The need for an international consensus on what would be an acceptable blood pressure for preterm and term newborns was discussed at the INC meeting in March 2016.

- The consensus could form the basis of inclusion criteria for drug study protocols in the neonatal period.
- The group proposes to look at both, low and high blood pressure thresholds and defining standard methods of measurements in different health care settings (e.g. primary and secondary care). All blood pressure components: systolic, diastolic and mean threshold values, will be determined.

A staged approach has been discussed:

1. Literature review to define appropriate methods of measurement.
2. Literature review to define normal values: low, high, age groups, exclude influence factors (medication etc.)
3. Analyse data from existing networks (HIP, NEO-CIRC, others)
4. Consider prospective data collection based on steps 1-3

Implementation of a **Haemodynamic Adaptation** Workgroup: Timeline and Estimated Resources

Timeline:

Steps 1 and 2 could be completed in about 1 year.

This could be followed by a consensus statement published in a peer reviewed journal.

Resources In the first year:

- Approximately 6 phone conferences
- 1 face to face meeting at INC workshop March 2017

ROP Workgroup Members

Melissa Liew – Novartis, Co-chair

Boubou Hallberg – Astrid Lindgren Children's Hospital, Co-Chair

Adina Tocoian - Shire

Olaf Dammann - Tufts University School of Medicine

Misha Eliasziw – Tufts Medical Center

Neil Marlow – University College London Hospital

Ann Hellström – Linkoping University

Lois Smith – Harvard Children's

Alistair Fielder – City University, London

Wiley Chambers - FDA

Dina Apele-Freimane - PDCO

Jacqueline Carleer - PDCO

Implementation of a **Retinopathy of Prematurity** Workgroup: Members

- Co-chairs – industry & clinical
  - Melissa Liew & Boubou Hallberg
- Industry – drug developers
  - Melissa Liew & Adina Tocoian
- Epidemiology & Statistics
  - Olaf Dammann & Misha Eliasziw
- Neonatology & child development
  - Boubou Hallberg & Neil Marlow
- Ophthalmology
  - Ann Hellström, Lois Smith & Alistair Fielder
- Regulatory
  - Wiley Chambers (FDA)
  - Dina Apele-Freimane (PDCO)
  - Jacqueline Carleer (PDCO)

Specific Aims & Methods - ROP

- **Focus on standards & outcomes**
- **Deliverables**
  - Definition of stages of stages of ROP
  - Clinical trial templates for ROP
    - Endpoints
    - Tools to measure
      - RetCam & others – vessel analysis
      - OCT
    - Time-points for measuring
  - Long-term outcomes for ROP
    - Objective & Subjective (QoL)

Implementation of a **Retinopathy of Prematurity** Workgroup: Timeline and Estimated Resources

Resources:

- In-kind resources – technical expertise provided by:
  - 2 practicing pediatric ophthalmologists , 2 neonatologists, 2 industry drug developers
  - 1 epidemiologist, 1 pediatric clinical pharmacologist
  - A Preclinical expert in animal models for ROP
- Supplied by C-Path
  - Bi-monthly TCs of 1-2h in the next 12 months
  - 2 F2F meetings at bi-annual INC meetings of 2-4h each

An estimated timeline for deliverables

- 12 months: Sep 2016 - Sep 2017

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Session II: *Workgroup Updates*

Clinical Pharmacology, Bob Ward (University of Utah)

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Clinical Pharmacology Working Group

Co-Chairs: Bob Ward
Karel Allegaert
Jeff Barrett

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical Pharmacology Workgroup Members

- Dina Apele-Freimane - Riga Stradins University Hospital, Latvia
- Jack Aranda - University Hospital of Brooklyn
- Danny Benjamin - Duke University (DCRI)
- Edmund Capparelli – UC San Diego
- Edress Darsey – Pfizer
- Walter Kraft – Thomas Jefferson University
- Irja Lutsar – University of Tartu, Estonia & PDCO
- Jeff Ming – Sanofi
- Min Soo Park – Yonsei University, Seoul, South Korea
- Randy Prescilla – Lilly/Boston's Children Hospital
- Catherine Sherwin - University of Utah
- Lily Mulugeta – CDER/FDA
- Ine Skottheim Rusten - Norwegian Medicines Agency & PDCO
- Adina Tocoian – Shire
- Mark Turner – U. Liverpool
- John Van Den Anker – Children's National Health System/U. of Basel Children's Hospital
- Sander Vinks - Cincinnati Children's Hospital Medical Center
- Kelly Wade – Children's Hospital of Philadelphia
- Siri Wang – Norwegian Medicines Agency & PDCO
- Anne Zajicek – NICHD/NIH
- Ron Ariagno - Stanford
- Jon Davis – Tufts U
- Ron Portman – Novartis, & INC co-director

Clinical Pharmacology Working Group

- Diverse skills are represented within the Clinical Pharmacology WG
  - Clinical Neonatology
  - Developmental Biology/Clinical Pharmacology
  - Pharmacogenetics
  - Pharmacometrics
  - Clinical trialists with experience in neonatal studies
  - Regulators: Europe, Japan, U.S., Canada
  - Neonatal nursing
  - Parents and children experienced in advising investigators
  - National Institutes of Health
  - Industry with pediatric development experience
  - Formulations chemistry

Clinical Pharmacology Working Group: Accomplishments

White Paper: It was the Best of Times and the Worst of Times

- White Paper about how to study drugs in the newborn utilized the entire skill set of the WG with help from FDA Ethicist, Skip Nelson
- White Paper is a comprehensive, referenced guide that can be used by investigators and regulators
  - **“Safety, Dosing, and Pharmaceutical Quality for Studies that Evaluate Medicinal Products (including Biological Products) in Neonates”**
  - 76 double spaced pages, 131 references
  - To be available online through Pediatric Research in open source thanks to Sanofi’s funding and through the Critical Path Institute Website
- Pediatric Research agreed to publish the entire document, but only on-line. They required an “Executive Summary” (5000 words, 80 references) for print publication
- Review process was difficult; new function for Ped Res; the final Exec Summary is now at Nature Publishing Group, expected publication in the fall

“Safety, Dosing, and Pharmaceutical Quality for Studies that Evaluate Medicinal Products (including Biological Products) in Neonates”

Primary authors: Robert M. Ward, Daniel Benjamin, Jeffrey S. Barrett, Karel Allegaert, Ronald Portman, Jonathan M. Davis, Mark A. Turner with careful review and input from

The International Neonatal Consortium (INC):

Jack Aranda	Agnes Klein	Randy Prescilla	Alexander Vinks	John van den Anker
Ronald Ariagno	Walter Kraft	Catherine Sherwin	Kelly Wade	Ine Skottheim Rusten
Raafat Bishai	Irja Lutsar	Vikram Sinha	Siri Wang	Dina Apele Freimane
Edress Darsey	Jeffrey Ming	Adina Tocoian	Anne Zajicek	Edmund Capparelli
Nick Hall	Yeruk Mulugeta	Min-Soo Park		Christine Gleason

(Longer names in one column)

Clinical Pharmacology Working Group: New Directions

- With the first deliverable for the INC accomplished, the Clin Pharm WG has proposed several directions to apply their diverse knowledge bases
  1. Formulations that are safe and appropriate for newborns, especially extremely premature newborns
     - Safety of excipients
     - Compatibility with other medications and parenteral nutrition solutions
     - Concentrations too low and require large volumes to administer
     - Concentrations too high and require dilution to administer accurately

Clinical Pharmacology Working Group: New Directions

2. Neonatal Abstinence Syndrome: to respond to the U.S. national epidemic
    - Standardize care delivery: room-in, skin to skin, train staff in interactions with adults who are opioid dependent, revise how to use scoring systems, delay initiation of drug treatment for 24-36 hrs (while SSRIs, nicotine, caffeine are cleared)
    - Focus on feeding, emesis, stooling and consolability more than tremors, sneezing, etc.; what's needed for care at home
    - Develop shorter, more efficient scoring systems
    - Standardize scoring: feed, change, swaddle & don't wake the baby
    - Standardize opioid treatment by protocol-shortens stay
    - Develop non-opioid treatment: clonidine, ondansetron
    - Work with obstetrics about prenatal management: methadone vs buprenorphine; safety of withdrawal during supervised, prenatal visits

Clinical Pharmacology Working Group: New Directions

3. Adverse Event scale for neonatal clinical trials
   - Unique/largely unique neonatal AE's: Intraventricular hemorrhage, apnea of prematurity, NEC, bronchopulmonary dysplasia, anemia of prematurity, ROP
   - Many of these require treatment
   - Many have long lasting adverse effects
   - Premies are similar around the world supporting an international effort with potential for wide spread utilization

   Diverse and useful skills represented in the Working Group

   - Many countries
   - Neonatology, nurses, parents, clinical pharmacology, sponsors, regulators, pharmacometricians

   Karel Allegaert's graduate student, Thomas Salaets, MD working on PhD

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Session II: *Workgroup Updates*

Seizures: Geraldine Boylan, Janet Soul

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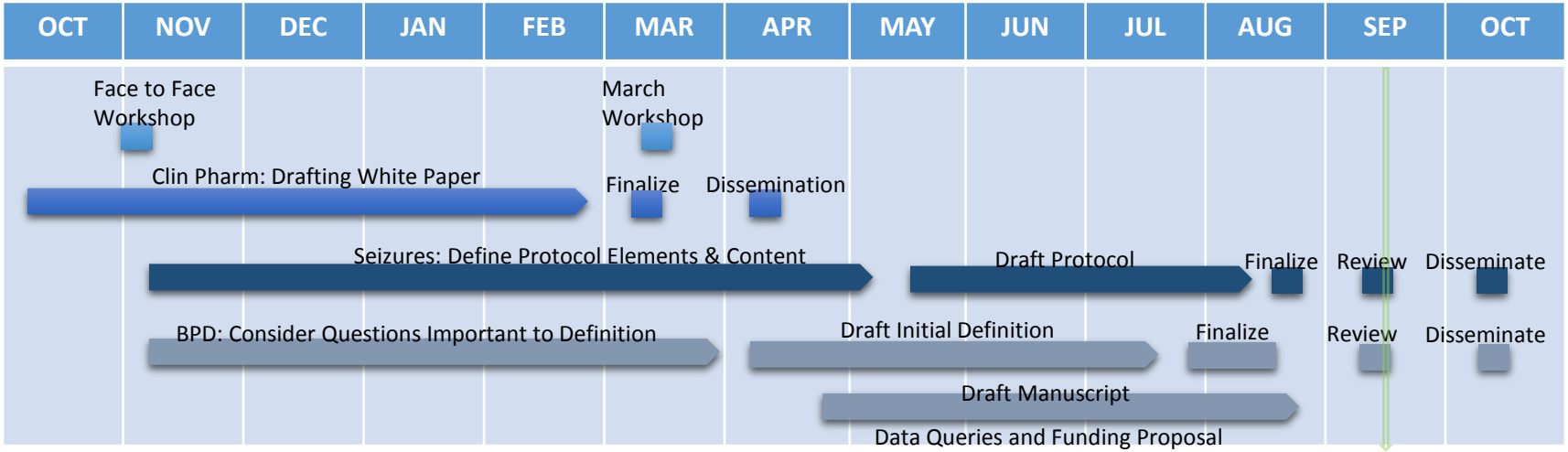
Seizures Workgroup Members

Janet Soul - Harvard University, Co-chair

Ronit Pressler - Great Ormond Street Hospital, Co-chair

- AJ Allen – Lilly
- Marilee C. Allen – Johns Hopkins
- Stephane Auvin – Robert Debré Hospital, Paris
- Varsha Bhatt-Mehta – University of Michigan
- Sylvie Benchetrit – ANSM, France and PDCO
- Geraldine Boylan - University College Cork
- Catherine Chiron – Inserm, France
- Tony Daniels - UCB
- Scott Denne – Indiana U, Riley's Children's Hospital
- Wakako Eklund – NANN
- Fernando Gonzalez - UCSF
- Pierre Gressens - Diderot University Paris
- Cristal Grogan – Preemie Parent Alliance
- Richard Haas - UCSD
- Cecil Hahn – SickKids Research Institute, Canada
- Polly Hardy - Oxford
- Norm Hershkowitz – CDER/FDA
- Kun Jin - FDA
- John Lantos – Children's Mercy Hospital, KCMO
- Neil Marlow – University College London Hospital
- Luc Masson – INJENO
- Jennifer Mayberry – Graham's Foundation
- Susan McCune – CDER/FDA
- Angela Men – OTS/CDER/FDA
- Karen New - COINN
- Skip Nelson – Office of Pediatrics, US FDA
- Heike Rabe - Brighton & Sussex Medical School
- Phil Sheridan – CDER/FDA
- Pam Simpkins – Janssen
- Keira Sorrells – Preemie Parent Alliance
- Brian Tseng – Novartis
- Alexander Vinks – University of Cincinnati
- Karen Walker – U. of Sydney
- Jennifer Ann Zimmer – Lilly
- Sarah Zohar – Cordelier Research Center, Paris
- Jon Davis - Tufts Medical Center & INC co-director
- Mark Turner - University of Liverpool & INC co-director
- Ron Portman – Novartis & INC Co-director
- Lynn Hudson – C-Path & INC Co-director

Workgroup Timelines and Deliverables



- October 1 – March 12: Seizures Workgroup: Defining Master Protocol Elements and Content
- October 1 – March 12: BPD Workgroup: Defining BPD
- October 23: Face-to-face Workshop for Clin Pharm Workgroup to finalize white paper
- October 23: Workgroup report out on proposed deliverables and timelines (Seizures, BPD, Data) at INC Working Dinner)
- February: Clin Pharm Workgroup submits white paper to Coordinating Committee for review
- March: INC submits final clin pharm white paper to FDA, EMA, PMDA
- March 9: Face to Face Workshop, Workgroup meetings for path to finalizing on deliverables

Members of the Protocol Design Subgroup

- **Janet Soul- Harvard University**
- Ronit Pressler – GOSH
- Richard Haas - UCSD
- Pam Simpkins – Janssen
- Mark Turner – University of Liverpool
- Polly Hardy - Oxford
- Catherine Chiron – INSERM, U. Paris Descartes
- Stephane Auvin – Robert Debré Hospital, Paris
- Brian Tseng – Novartis
- Philip H. Sheridan– CDER/FDA
- Norm Hershkowitz – CDER/FDA
- Kun Jin – CDER/FDA
- Tony Daniels – UCB
- Sander Vinks – U. of Cincinnati

Seizures master protocol

International Neonatal Consortium

Seizures Master Protocol

Draft

Document type:	Protocol
Document status:	DRAFT
Release date:	
Number of pages:	

Table of Contents

Protocol Design

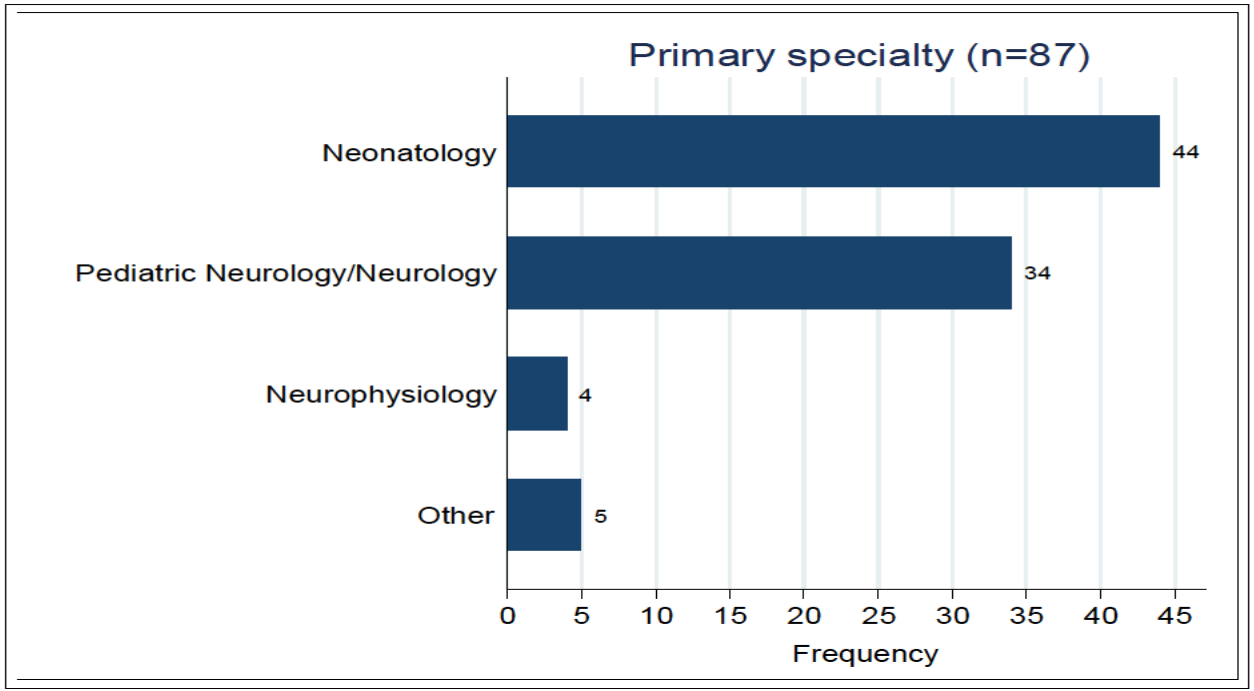
- Comparator Section drafted
- Summary of Statistical Design drafted

Members of the Primary Outcome Measures Subgroup

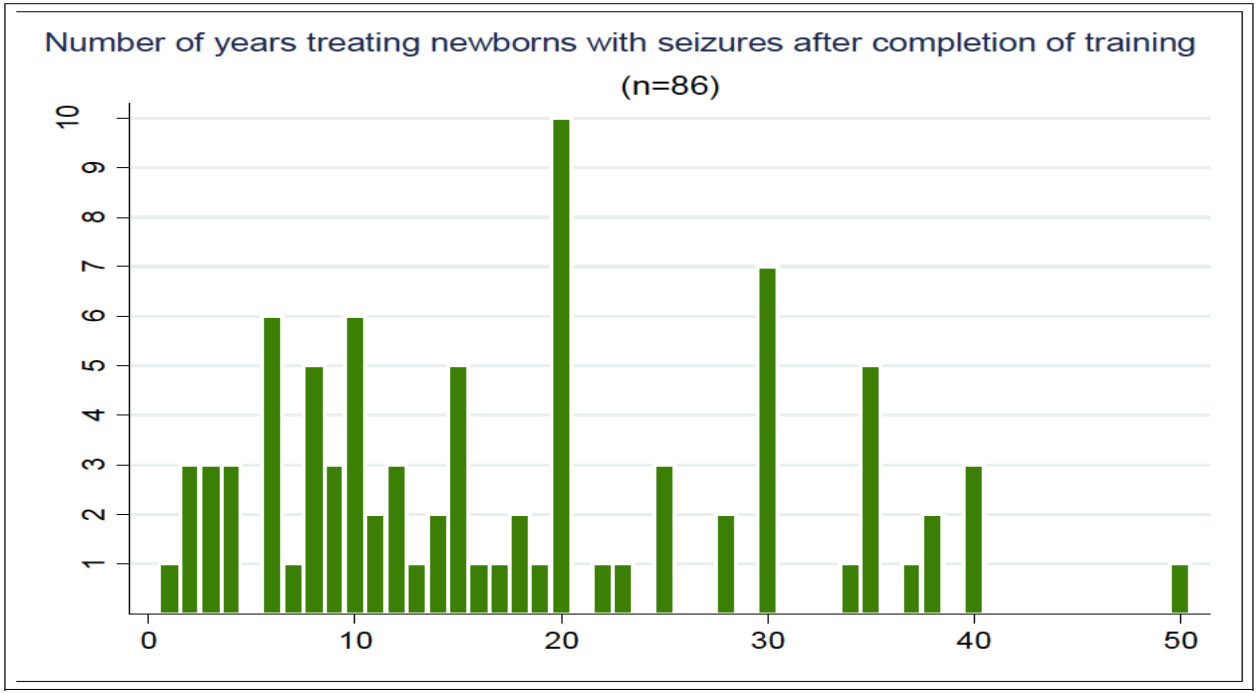
- **Geraldine Boylan – University College Cork**
- Fernando Gonzalez – University of California, San Francisco
- Sylvie Benchetrit – ANSM, France and PDCO
- Marilee C. Allen – Johns Hopkins
- Janet Soul – Harvard University
- Philip H. Sheridan– CDER/FDA
- Norm Hershkowitz – CDER/FDA
- Susan McCune– CDER/FDA
- Cecil Hahn – SickKids Research Institute

Primary Outcomes Survey Results

- Results to date (87 responses)

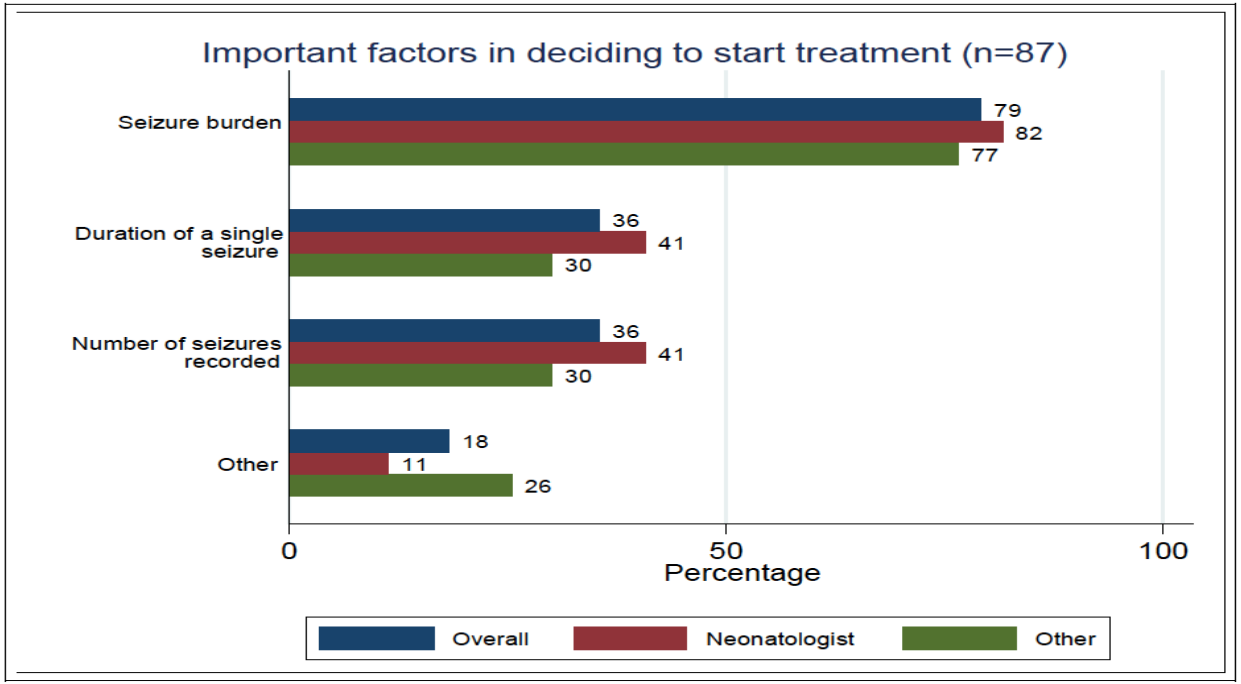


Primary Outcomes Survey Results



Median 15 years

Primary Outcomes Survey Results



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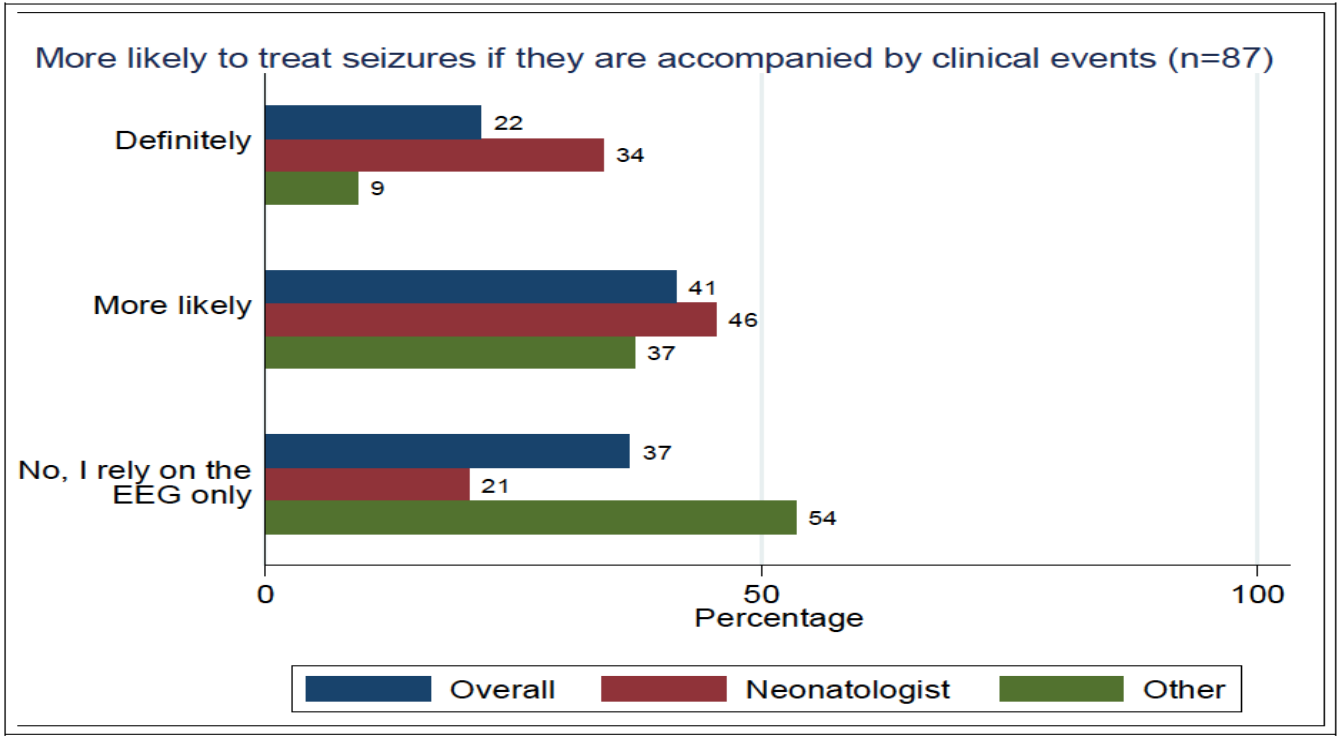

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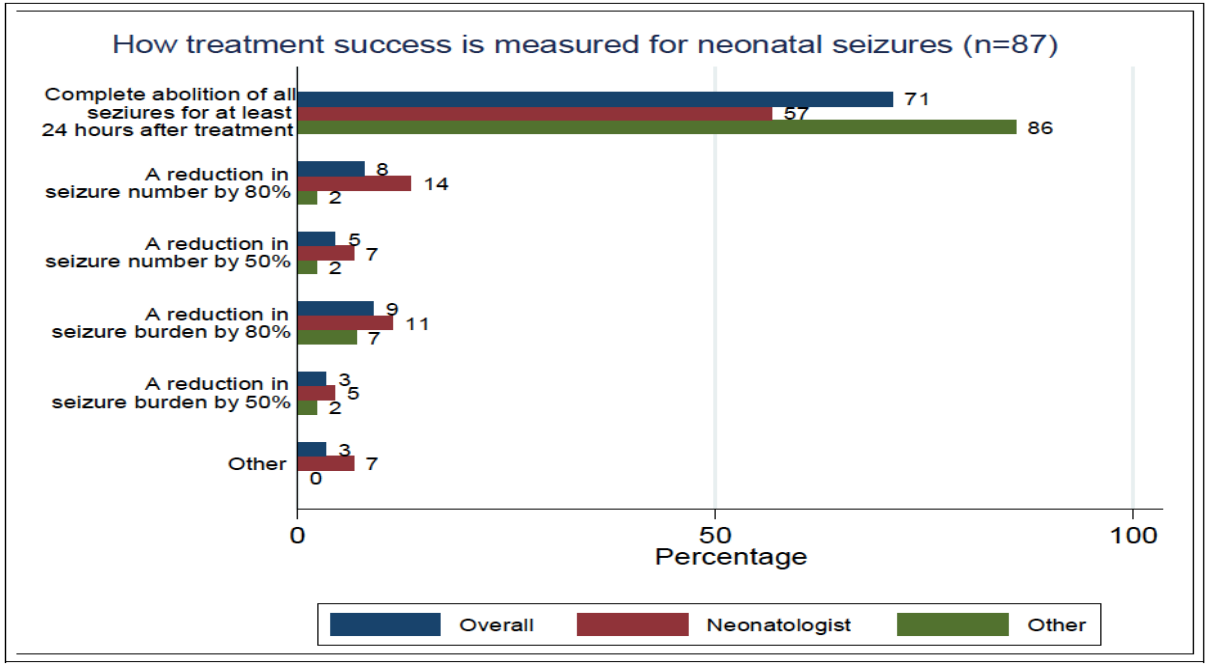

Members of the Secondary Outcome Measures Subgroup

- **Marilee C. Allen – Johns Hopkins**
- Neil Marlow – University College London Hospital
- Pierre Gressens - Diderot University Paris
- Sylvie Benchetrit – ANSM, France and PDCO
- Philip H. Sheridan– CDER/FDA
- Norm Hershkowitz – CDER/FDA
- Susan McCune – CDER/FDA

Secondary Outcomes - Status

Section Drafted

Ongoing discussions with the whole group

- What to assess and how
- When to assess

Members of the Drug Related Issues Subgroup

- **Heike Rabe – Brighton & Sussex Medical School**
- Ron Portman – Novartis
- Marilee Allen – Johns Hopkins
- Angela Men – OTS/CDER/FDA
- Sylvie Benchetrit – EMA PDCO
- Alexander Vinks – University of Cincinnati

Drug-Related Issues

- All Sections Drafted

Members of the Ethics and Parent Involvement Subgroup

- **Ronit Pressler – GOSH**
- Stephane Auvin – Robert Debré Hospital, Paris
- Scott Denne – Indiana University, Riley Children's Hospital
- John Lantos – Children's Mercy Hospital, KCMO
- Luc Masson – INJENO (parents of children with epilepsy, France)
- Jennifer Mayberry – Graham's Foundation
- Skip Nelson – Office of Pediatrics, US FDA
- Karen New – COINN
- Wakako Eklund - NANN

Parent/Ethics - Assignments

1. Review of literature
2. Ethical issues of study design
3. a. Use of placebo
   b. Delayed treatment
   c. Use of prophylactic medication
4. Other issues –
   a. GCP adherence
   b. sample size
   c. volume of blood samples
5. Consent
   a. Methods of consent (continuous consenting, deferred consent)
   b. What to include in patient information sheet
6. Parent involvement in trials

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Thank You

http://c-path.org/programs/inc

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Session II: *Workgroup Updates*

BPD, Robin Steinhorn (Children's National)

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BPD Workgroup Members

- **Robin Steinhorn – Children's National Hospital, Co-chair**
- **Wolfgang Göpel – U-Lübeck/ VOC, Co-chair**
- Steve Abman – University of Colorado
- Ron Ariagno - Stanford
- Judy Aschner - Montefiore
- Roberta Ballard - UCSF
- Eduardo Bancalari - Jackson Medical Center, Miami
- Dirk Bassler – University of Zurich
- Carol Blaisdell – NHLBI/NIH
- Giuseppe Buonocore – University of Siena, Italy
- Jon Davis – Tufts University, INC Co-Chair
- Danièle De Luca - South Paris University Hospitals
- Laura Fabbri - Chiesi
- Anne Greenough – King's College, London
- Ninna Gullberg - Karolinska University Hospital & PDCO
- Helmut Hummler – University of Ulm, Germany
- Alan Jobe - Cincinnati Children's Hospital
- Matt Laughon - UNC
- Susan McCune –FDA/CDER
- Marek Migdal - Children's Memorial Health Institute, Warsaw, Poland
- Christian Speer - University of Wurzburg, Germany
- Linda Storari - Chiesi
- Anthony Durmowicz – FDA/CDER/DPARP
- Adina Tocoian - Shire

Challenges to BPD Prevention Research

- BPD – complex phenotypes (BPD in a 25 week infant is a different disease than that in a 29 week infant)
- Multi-institutional collaborations essential, but introduce tremendous variability in practice and outcomes
- Challenges in balancing risks and benefits of preventive strategies
  - Those premature infants not destined to develop disease will be exposed to experimental therapies with potential adverse effects
  - Adverse effects of drugs may not be evident for months or years (eg, dexamethasone)
- Current endpoints do not necessarily capture those infants who will have long term respiratory morbidity

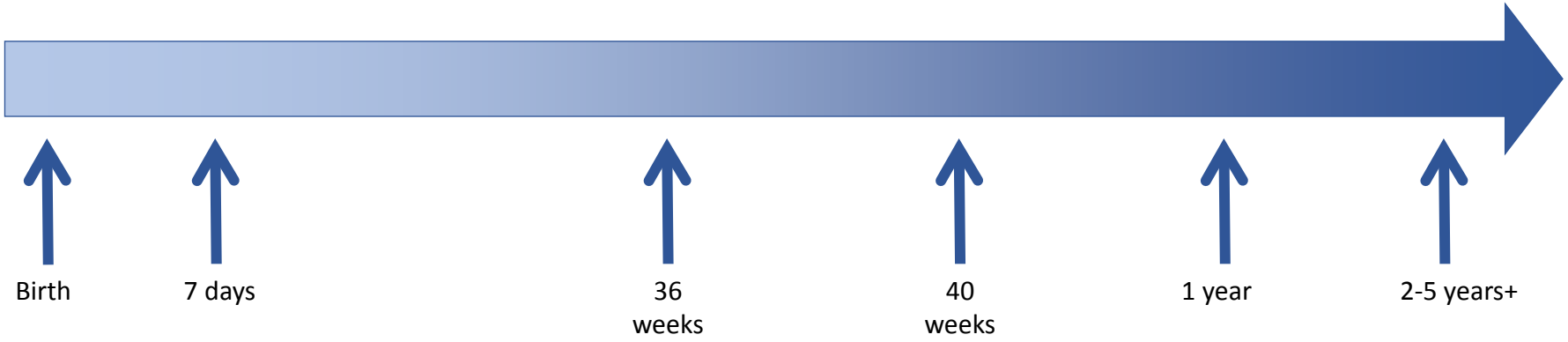
Commonly Used BPD Definitions

Name	Year	Definition	Comments
Northway	1979	Oxygen use at 28 days of life	
Shennan	1988	Oxygen use at 36 weeks PMA	A child on 4 LPM HFNC support and 21% O_2 at 36 weeks would not have BPD
Modified Shennan		Assigns infants discharged in room air before 36 weeks PMA as no BPD	
NIH Consensus	2001	• None (<28 days of oxygen support) • Mild (oxygen or respiratory support at >28 days but on room air at 36 weeks PMA) • Moderate (<30% oxygen at 36 weeks) • Severe (>30% oxygen or positive pressure at 36 weeks PMA)	A child placed on HFNC support for 2-3 days for worsening apnea would have BPD
Walsh "Physiologic"	2003	SpO2 <90% after 60 minute room air challenge at 36 weeks PMA	

Defining BPD at 36 weeks PMA

- Familiar, widely accepted and pragmatic indicator of lung function
- Can usually be assessed during the initial hospitalization, maximizing the opportunities for accurate data capture.
- Residual immaturity of respiratory control is commonplace at 36 weeks PMA
- No consensus on which definition should be used for clinical trials
- Recent systematic review of 47 randomized clinical trials for BPD prevention:
    - Only 31 of the trials provided a discrete BPD definition
        - 71% used oxygen at 36 weeks
        - 6% used the physiologic definition
        - 32% used only oxygen requirement at 28 days

Endpoints Under Evaluation



Risk factors:
SGA
Mechanical ventilation
Oxygen
NRN BPD risk calculator

Outcomes:
Survival
Hospitalizations
ED visits
Medication use
Functional level

Outcomes:
Pulmonary function

Enrollment

Short Term Surrogate Outcomes

Long Term Outcomes

Endpoints Under Evaluation

- 36 week endpoint
  - Does the definition apply to 36+0 weeks only?
  - How do we handle CPAP or HFNC support without O_2?
  - Can we move past a dichotomous definition and develop a “BPD Scale”?
- 40 week endpoint
  - Overcomes some of the confounders of the 36 week endpoint
  - Requires additional data imputation
  - Does this endpoint improve the predictive value for long term outcomes?
- 1 year endpoint
  - Are the measurements objective?
  - Need to control for environmental influences after discharge
  - Is attrition too high?
- Consideration of QOL endpoints – eg, sleep, feeding

BPD Outcomes Analysis

Data Elements	PROP (Judy Aschner, Alan Jobe)	Canadian Neonatal Network (Prakesh Shah)	Colorado-Indiana Cohort (Steve Abman)	German Neonatal Network (Wolfgang Gopel)	German Neonatal Network (Wolfgang Gopel)	UKOS (Anne Greenough) SEE SECOND TAB BELOW	Neonatal Research Network (Rose Higgins, Matt Laughon)	NO-CLD, TOLSURF (Roberta Ballard)
Baseline characteristics		**Neonates born Jan 2010-Sept 2011 (GA <29 W)**		GNN-infants born since Jan 2009 and discharged until Dec 2015, GA < 29 weeks	GNN-infants with 5-year follow-up, GA < 29 weeks		2010-2014	
n	835 enrolled/765 36 wk survivors	2594	575	6659	440			
GA, mean (sd), median (IQR)	26.7 (1.4) [23+0 -28+6] (n=765)	26.2 (1.5), 26 (25, 27)	27 (22-33) wks	26.5 (1.6)	26.6 (1.5)		22-28 weeks	
Weight, mean (SD)	915.8 (232.2) (n=765)	923 (243)	925 (500-1250) g	865 (268)	866 (239)			500-1250 g
% SGA	5.20%	7.90%	155 (27.0%)	12.8%	13.2%			
Race	59.3% W; 35.7% B;3& A; 11.1% H; 2% UK							
36 week endpoint								
n	765							
Death	63/835 (7.5%) [7 withdrawals]	14%	32 (5.6%)	4.8% 323/6659	0			
Hospitalized	682 (89.1%)	50%	538 (93.6%)	82% 5469/6659	85% 375/440			
Oxygen	264 (34.5%) (+95 on RA flow)	24%	396 (68.9%)	21% 1345/6336	19% 82/440			
Positive pressure (CPAP, NC>2LPM)	143 (18.7%)	13%	74 (12.9%)	19% 1188/6336	15% 65/440			
BPD severity assesment	266/359 (80 (30.1% passed)		560 (97.4%) Assessed Mild: 130 (23.2%) Moderate: 177 (31.6%) Severe: 171 (30.5%)					
Pulmonary Hypertension	65/765 (8.5%)		34 (10.1%)					
Mechanical Ventilation	data pending	3.40%	34 (5.9%)					
Respiratory medications	data pending		24%					
40 week endpoint								

Robin Steinhorn:
Of 765 infants assessed at 36 weeks

BPD Outcomes Worksheet

Data Elements	PROP (Judy Aschner, Alan Jobe)	Canadian Neonatal Network (Prakesh Shah)	Colorado-Indiana Cohort (Steve Abman)	German Neonatal Network (Wolfgang Gopel)	German Neonatal Network (Wolfgang Gopel)	UKOS (Anne Greenough) SEE SECOND TAB BELOW	Neonatal Research Network (Rose Higgins, Matt Laughon)	NO-CLD, TOLSURF (Roberta Ballard)
40 week endpoint	**Robin Steinhorn:** Of 765 infants assessed at 36 weeks							
n	744 (426 D?C+315 in Hosp+3 transf w/ data)							
Death	63+3 b/t 36 -40 wk= 66 deaths (n=835)	15%	34 (5.9%)	5.2% 346/6659	0			
Hospitalized	315/835 (37.7%)/315/744 (42.3%)	41%	252 (43.8%)	33.6% 2235/6659	36% 159/440			66%
Oxygen	277/744 (37.2%)	12%	191 (33.2%)	10% 639/6313	9% 41/440			29.2%
Positive pressure	31/765 (4.1%)/110/765 (14.4%)	4%	31 (5.4%)	6.4% 406/6313	3% 13/440			
Pulmonary Hypertension	65/765 (8.5%)		15 (4.5%)					
Mechanical ventilation	22/744 (2.9%)	1.40%	32 (5.6%)					10.4%
Respiratory medications	20% of 741 on respiratory medications		-					
Supp O2 and Meds	10/741							
Meds only/Room Air	50/741							
1 Year CGA endpoint	paper in progress/data pending	**Outcome at 18-24 months CA (n=2015)**						
n								
# hospitalizations (all cause, respiratory)		30% (19% for respiratory reason)	155, 129					
Respiratory medications (inhaled steroid, inhaled bronchodilators, diuretics)		16%	100 (20.0%)					
Home O2 use (O2 or CPAP)		1.70%	70 (14.0%)					
Respiratory Diaries			-					
Growth/Nutrition			-					
Unscheduled ED and/or medical visits			251, 176					

Identification of High Risk Populations

- Early lethal BPD
- Intrauterine growth restriction
- Severe RDS
- Early pulmonary vascular disease
- BPD risk calculator (NRN)
- Genetic markers

International Neonatal Consortium

Second Annual Neonatal Scientific Workshop at the EMA

Session II: *Workgroup Updates*

Data, Tom Diacovo (Columbia University)

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Data Workgroup Members

Kate Costeloe - Queen Mary University, Co-chair

Tom Diacovo - Columbia University, Co-chair

Michael Padula - Children's Hospital of Philadelphia; PEDSnet, Co-chair

Khosrow Adeli – Hospital for Sick Children, Toronto

Gerri Baer – FDA

Simin Baygani – Eli Lilly

Yun Sil Chang – Samsung Medical Center, South Korea

Dominique Haumont - St-Pierre University Hospital

Rose Higgins – NICHD/NIH

Steve Hirschfeld – NICHD/NIH

Lauren Kelly – Mount Sinai Hospital

Satoshi Kusuda – Tokyo Women's Medical University

Thierry Lacaze – CHEO Research Institute, Ottawa

Kei Lui – Australian and New Zealand Neonatal Network (ANZNN)

Susan McCune – CDER/FDA

Neena Modi - Imperial College London

Hide Nakamura – National Research Institute for Child Health and Development, Japan

Martin Offringa – University of Toronto

Prakesh Shah – CNN /U - Toronto

Catherine Sherwin – University of Utah

Mary Short – Eli Lilly

Roger Soll – Vermont Oxford Network

Brian Smith - Duke University (DCRI)

Marta Terrile - Novartis

Charlie Thompson – Pfizer

Mark Turner – University of Liverpool

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Data Workgroup:
Concepts, Terminology, & Data Definitions

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DATA WORKGROUP: Data Elements

AIM:

- Develop a set of data elements for neonates/infants that may be referenced and implemented for future reporting/investigation

- What to follow?
  - ***core set*** of elements to be collected for all newborns
    - demographic
    - maternal/perinatal data
    - major outcome measures
    - adverse events
  - ***complementary set*** of elements that may be employed for specific domains or topics
    - support subject specific domains, such as
      - respiratory interventions for intubated infants
      - enteral medication use for pulmonary hypertension

DATA WORKGROUP: Establishing meaningful definitions

- **Data Definitions:**

  "The increased use of data processing and electronic data interchange heavily relies on accurate, reliable, controllable, and verifiable data recorded in databases. One of the prerequisites for a correct and proper use and interpretation of data is that both users and owners of data have a **common understanding of the meaning and descriptive characteristics (e.g., representation) of that data.** To guarantee this shared view, a number of basic attributes has to be defined."

  -International Standards Organization, 2004. Information Technology Parts 1-6 (2nd Edition) http://www.iso.org/

- achieve data definitions that are *sensitive & specific* enough to capture our concepts of interest
- criteria for these definitions should be reasonably *pragmatic* to implement in a variety of settings
  - May include a description of concept
  - Should be clear and succinct
  - Should contain criteria to differentiating it from other like, but distinct concepts
    - *spontaneous intestinal perforation* vs. *NEC with perforation*
    - different causes of respiratory distress
    - clinical events vs adverse events
  - Use *granular data* when possible *(work towards electronic extraction)*
  - Should aim to align with existing, commonly used precedents when possible (harmonization)

DATA WORKGROUP: Leverage prior efforts

- Select data elements that allow for appropriate designation for cohort criteria and risk stratification
- Sources reviewed include
    - •NHS
    - •iNeo
    - •Neonatal Research Terminology Harmonization
        - •Vermont Oxford Network
        - •NICHD Neonatal Research Network
        - •Children's Hospitals Neonatal Database
    - •Adverse Events [Pediatric Terminology – National Cancer Institute Thesaurus (NCIt)]
- Establish level of granularity for data capture (and reporting) aligned with CDISC Model (SDTM).
    - May develop **concepts** that serve as criteria for other definitions
        - e.g., *oxygen exposure at 36 weeks postmenstrual age*
        - allows for both manual data abstraction and electronic data extraction
        - also provides flexibility for those entities reporting to multiple registries
- Later we can establish which are optional vs. mandatory (may be context specific for a given study)

DATA WORKGROUP: Domains for neonatal concepts

Subject mater experts to select neonatal concepts in selected domains:

- Maternal/Antenatal
  - Maternal conditions relevant to fetus
    - e.g., hypertension, diabetes mellitus, etc..
  - Antenatal diagnoses
- Perinatal
  - Labor
  - Delivery
  - Resuscitation
- Ophthalmologic
- Genetic/Metabolic
- Hematologic/Oncologic
- Infectious
- Neurologic
- Neurodevelopment
- Cardiac
- Respiratory
- Renal/Electrolyte
- Genitourinary
- Gastrointestinal
- Integumentary (Skin)
- Procedures
- Events*

DATA WORKGROUP: Next steps

- Plan for serial calls (e.g., weekly) with subgroup(s) to review lists of concepts and proposed definitions
  - Note source of concept, alignment with other databases
- Allow for group feedback of proposed concepts/definitions
  - identify specific individuals to weigh in on specific topics
- Map concepts to reference terminologies/existing standards
  - achieved with representation in CDISC model
  - may managed/accessible via the NCIt
  - may capture relationships/alignment to existing data sets [as appropriate]

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Data Workgroup: Lab Values

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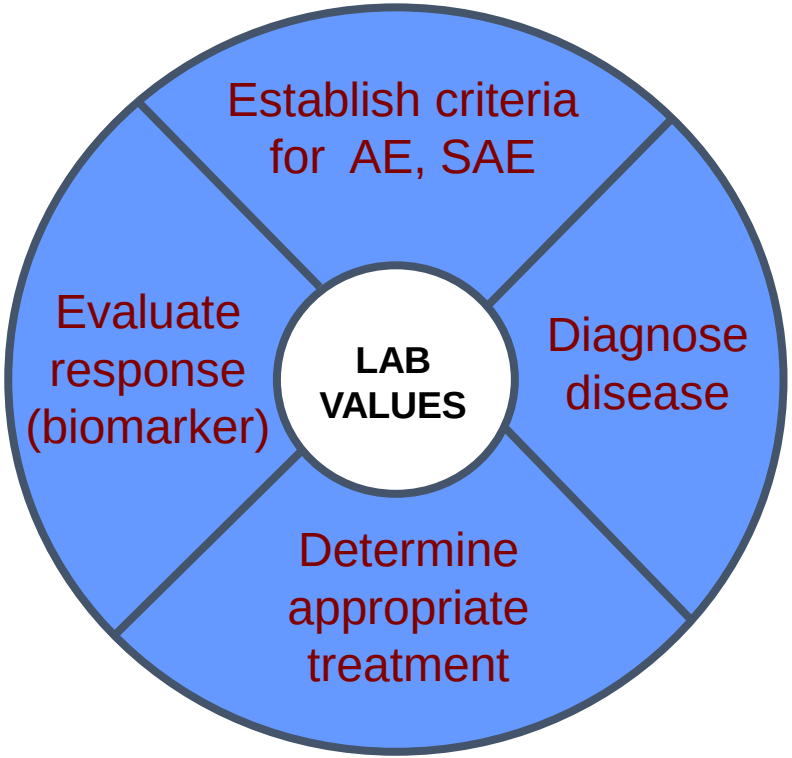
DATA WORKGROUP: LAB VALUES

The quality of clinical trail is critically dependent on accurate interpretation of lab results based on accurate reference intervals or decision limits



Reference ranges:

- Most of the available reference intervals determined decades ago on older/less accurate laboratory instruments/methodologies
- Most neonatal reference intervals incomplete and out of date
- Most available only for Caucasian populations
- No data for many new and emerging disease biomarkers of neonatal disease
- Abnormal values determined by clinicians at each institution / hospital

Reference ranges: Variability based on GA and PMA

	25-27 wk				28-29 wk[a]				30-33 wk[a]			
	µmol/L		mg/dL		µmol/L		mg/dL		µmol/L		mg/dL	
Age (d)	Mean	95 PCTL[a]	Mean	95 PCTL	Mean	95 PCTL	Mean	95 PCTL	Mean	95 PCTL	Mean	95 PCTL
0	69.8	100.8	0.79	1.14	86.6	115.8	0.98	1.31	83.1	107.8	0.94	1.22
0-1	84.0	114.9	0.95	1.30	86.6	115.8	0.98	1.31	84.0	107.8	0.95	1.22
2-3	84.0	114.9	0.95	1.30	80.4	111.0	0.91	1.26	71.6	99.1	0.81	1.12
4-5	81.3	112.8	0.92	1.28	78.7	108.0	0.89	1.22	64.5	90.8	0.73	1.03
6-7	76.9	108.7	0.87	1.23	74.3	103.9	0.84	1.18	58.3	83.9	0.66	0.95
8-9	71.6	103.2	0.81	1.17	66.3	97.0	0.75	1.10	53.0	78.2	0.60	0.88
10-14	66.3	97.3	0.75	1.10	61.0	90.3	0.69	1.02	50.4	74.1	0.57	0.84
15-19	61.0	89.1	0.69	1.01	54.8	81.4	0.62	0.92	43.3	65.9	0.49	0.75
20-24	53.9	79.9	0.61	0.90	46.9	71.8	0.53	0.81	38.9	59.2	0.44	0.67
25-29	46.0	70.2	0.52	0.79	42.4	64.3	0.48	0.73	38.9	56.3	0.44	0.64
30-34	42.4	63.6	0.48	0.72	36.2	57.0	0.41	0.64	30.9	50.2	0.35	0.57
35-39	36.2	56.2	0.41	0.65	35.4	53.6	0.40	0.61	29.2	[b]	0.33	[b]
40-44	37.1	54.8	0.42	0.62	33.6	51.6	0.38	0.58	28.2	[b]	0.32	[b]
45-49	32.7	50.6	0.37	0.57	28.8	b	0.33	b	24.1	[b]	0.27	[b]
50-54	30.1	47.3	0.34	0.54	29.2	b	0.33	b	25.0	[b]	0.28	[b]
55-59	27.4	44.9	0.31	0.51	28.8	b	0.33	b	22.2	[b]	0.25	[b]

[a] PCTL = percentile.

Serum creatinine concentration in very low birth weight infants from birth to 34-36 weeks postmenstrual age

David A. Bateman, William Thomas, Elvira Parravicini, Elena Polesana, Chiara Locatelli, John M. Lorenz

DATA WORKGROUP: LAB VALUES

Reference ranges: Short term approach?

Table 3
Adverse event table laboratory values.

	Adverse event		Serious adverse event	
	Conventional units	International system (si)	Conventional units	International system (SI)
Electrolytes				
Hyponatremia [20]	120–124 mEq/L	120–124 mmol/L	<120 mEq/L	<120 mmol/L
Hypernatremia [21,22]	150–159 mEq/L	150–159 mmol/L	>159 mEq/L	>159 mmol/L
Hypokalemia	2.0–2.5 mEq/L	2.0–2.5 mmol/L	<2.0 mEq/L	<2.0 mmol/L
Hyperkalemia [23]	7–7.9 mEq/L	7.0–7.9 mmol/L	>7.9 mEq/L	>7.9 mmol/L
Bicarbonate: Low	12–14 mEq/L	12–14 mmol/L	<12 mEq/L	<12 mmol/L
Bicarbonate: High	35–45 mEq/L	30–45 mmol/L	>45 mEq/L	>45 mmol/L
Hypocalcemia (ionized) [24]	4.1–4.2 mg/dL	0.7–1.05 mmol/L	<4.1 mg/dL	<0.7 mmol/L
Hypercalcemia (ionized) [24]	5.4–5.7 mg/dL	1.3–1.6 mmol/L	>5.7 mg/dL	>1.6 mmo/L
Renal				
BUN [25]	60–100 mg/dL	21.42–35.7 mmol/L	>100 mg/dL	>35.7 mmol/L
Creatinine [25]	1.5–2.5 mg/dL	132.6–221 μmol/L	>2.5 mg/dL	>221 μmol/L
Endocrine				
Hypoglycemia [26]	25–36 mg/dL	1.4–2 mmol/L	<25 mg/dL	<1.4 mmol/L
Hyperglycemia [27]	250–500 mg/dL	13.9–27.8 mmol/L	>500 mg/dL	>27.8 mmol/L
Gastrointestinal				
Aspartate aminotransferase [28]	200–1000 U/L	3.34–16.7 μkat/L	>1000 U/L	>16.7 μkat/L
Alanine aminotransferase [28]	200–1000 U/L	3.34–16.7 μkat/L	>1000 U/L	>16.7 μkat/L
Alkaline phosphatase [29]	1000–1400 U/L	16.4–23.4 μkat/L	>1400 U/L	>23.4 μkat/L
Conjugated bilirubin [30]	3–10 mg/dL	51.3–171 μmol/L	>10 mg/dL	>171 μmol/L
Gamma-glutamyl transferase [31]	100–125 U/L	1.7–2.1 μkat/L	>125 U/L	>2.1 μkat/L
Hypertriglyceridemia	500–1200 mg/dL	5.7–13.6 mmol/L	>1200 mg/dL	>13.6 mmol/L
Hematologic				
Leukopenia [32]	0.5–2 × 10^3/μL	0.5–2 × 10^9/L	<0.5 × 10^3/μL	<0.5 × 10^9/L
Leukocytosis [32]	30–50 × 10^3/μL	30–50 × 10^9/L	>50 × 10^3/μL	>50 × 10^9/L
Anemia: hemoglobin [33]	7–9 g/dL	70–90 g/L	<7 g/dL	<70 g/L
Anemia: hematocrit [33]	20–26%	0.24–0.26	<20%	<0.24
Polycythemia: hemoglobin [33]	23–24 g/dL	230–240 g/L	>24 g/dL	>240 g/L
Polycythemia: hematocrit [33]	66–70%	0.66–0.7	>70%	>0.7
Thrombocytopenia [34,35]	50–100 × 10^3/μL	50–100 × 10^9/L	<50 × 10^3/μL	<50 × 10^9/L
Thrombocytosis [35]	450–1000 × 10^3/μL	450–1000 × 10^9/L	>1000 × 10^3/μL	>1000 × 10^9/L
Prothrombin time [36]	18–22 s	18–22 s	>22 s	>22 s
Activated partial thromboplastin time [36]	79–101 s	79–101 s	>101 s	>101 s
Lactate [37]	45.1–90.1 mg/dL	5–10 mmol/L	>90.1 mg/dL	>10 mmol/L
Musculoskeletal				
Creatine kinase [38]	470–600 U/L	7.9–10 μkat/L	>600 U/L	>10 μkat/L
Respiratory				
Acidosis: pH [39]	7.10–7.19	7.15–7.19	<7.10	<7.15
Alkalosis: pH [39]	7.50–7.60	7.50–7.60	>7.60	>7.60

All values rounded to the nearest tenth decimal place. All conversions between convention units and international system units performed using *AMA Manual of Style: A Guide for Authors and Editors 10th Edition.* http://www.amamanualofstyle.com/page/si-conversion-calculator.

Optimizing operational efficiencies in early phase trials: The Pediatric Trials Network experience

Amanda England a,1, KellyWade b, P. Brian Smith c,d, Katherine Berezny d, Matthew Laughon a,□, on behalf of the Best Pharmaceuticals for Children Act — Pediatric Trials Network Administrative Core Committee
Contemporary Clinical Trials 47 (2016) 376–382

Previous published studies (2006 to 2011)
AE - 2 SD from mean
SAE – 3SD from mean

Reference ranges: Other approaches

Industry data: lab reference ranges that the FDA has calculated based on submission (Gerri Baer to investigate)

Academic data (Utah and Toronto): generate reference ranges by modified Hoffman method (to be spear-headed by Khosrow Adeli at Sick Kids who runs CALIPER (Clinical lab reference intervals in pediatrics) and Catherine Sherwin at Utah

DATA WORKGROUP: LAB VALUES

Reference ranges: Deliverables

1. Establish search criteria for specific sets of lab reference ranges (inclusion and exclusion criteria)

2. Proof on concept – compare to published studies

3. White paper on approach and rationale for such ref ranges

Future:

*Establish whether reference intervals differ between major ethnic groups

*Establish a comprehensive, age, gender, disease–specific neonatal lab database

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Data Workgroup: White Paper

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DATA WORKGROUP: First white paper

- **TITLE:** Standardising Neonatal Data to Accelerate Clinical Research
- **TARGET READERSHIP:** Staff on neonatal units whether or not active researchers and those involved with dataset management
- **OBJECTIVE:**
  - To inform those responsible for collecting data into existing datasets and those establishing new datasets about the INC
  - To highlight the need for further data standardisation and the potential gains
  - To give a simple outline of plans to take work forward and a vision for future development of aggregated data extracted from the electronic clinical record.
- Currently in second draft

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Thank you!

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Agenda – Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome

2:15 – 3:00 p.m.	**Session III:** *Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome* JOHN VAN DEN ANKER (CHILDREN'S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN'S HOSPITAL) & JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS *The Opioid Epidemic and Neonatal Abstinence Syndrome* STEPHEN PATRICK (VANDERBILT UNIVERSITY) *The Use of Narcotics for Sedation or Analgesia* JACOB ARANDA (UNIVERSITY HOSPITAL – BROOKLYN)
3:00 – 3:30 p.m.	COFFEE BREAK
3:30 – 5:00 p.m.	SESSION III PANEL