INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Workgroup Updates
Chair: Ron Portman

CRITICAL PATH INSTITUTE

Mission

Accelerating the development of safe and effective therapies for neonates.

The consortium will 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.

INC Priority Projects

- Process used to identify and select INC's first four projects
  - (BPD, Seizures, Clin-Pharm, Data)
  - Disease/Condition WGs, Functional WG's
  - Public workshop to identify greatest needs (October 2014, FDA)
  - Pre-workshop priority-setting exercise and detailed discussions at the May 2015 workshop at EMA.
  - Voting by entire workshop group to narrow down priorities; followed by voting at the first Coordinating Committee meeting.

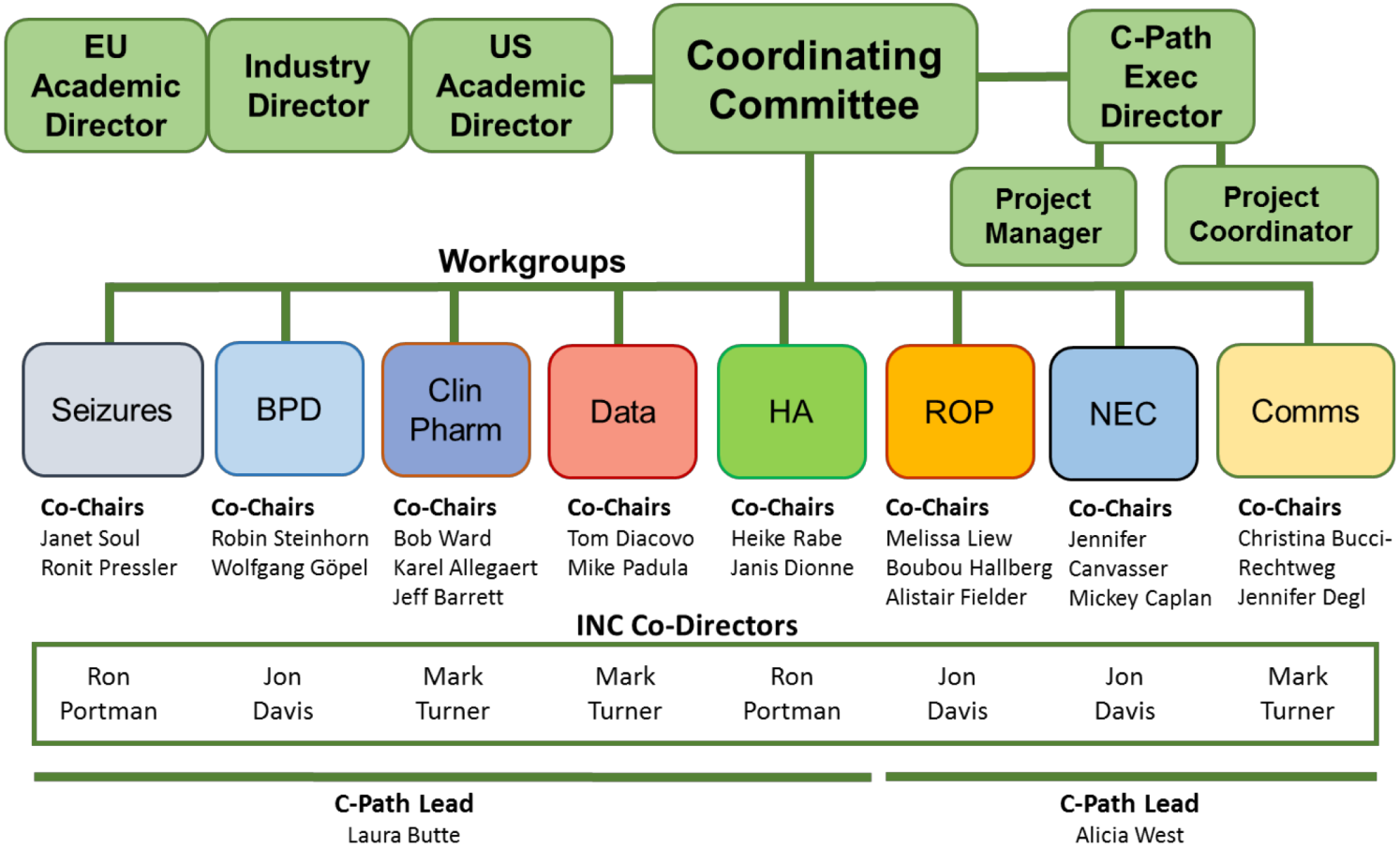
- Considerations for taking on additional projects
  - Alignment with INC mission
  - Budget/resources needed
  - Members volunteering to drive the project

Agenda – Workgroup Updates – Ron Portman

- Workgroup Overview & Governance Structure (Ron Portman)
- Seizures and ROP Progress (Ron Portman)
- NEC Update (Ron Portman)

- Communications (Jennifer Degl)
- Hemodynamic Adaptation (Heike Rabe)
- Data (Michael Padula)
- Bronchopulmonary Dysplasia (Robin Steinhorn, Wolfgang Göpel)
- Clinical Pharmacology (Karel Allegaert)

INC Governance Structure



INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Seizures Workgroup

Ron Portman for
Co-Chairs:
Ronit Pressler and Janet Soul

CRITICAL PATH
INSTITUTE

Seizures Workgroup Members

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
- Teresa Buracchio – FDA/CDER
- Catherine Chiron – Inserm, France
- Tony Daniels - UCB
- Edress Darsey - Pfizer
- Scott Denne – Indiana U, Riley's Children's Hospital
- Dinah Duarte - Infarmed
- 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
- Masahiro Hayakawa – Nagoya University Hospital
- Kun Jin - FDA
- John Lantos – Children's Mercy Hospital, KCMO
- Neil Marlow – University College London Hospital
- Barry Mangum – Paidion Research, Inc.
- Luc Masson – INJENO
- Jennifer Mayberry – Graham's Foundation
- Susan McCune – FDA/OC
- 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 – U. of Liverpool & INC co-director
- Ron Portman – Novartis & INC Co-director
- Lynn Hudson – C-Path & INC Co-director

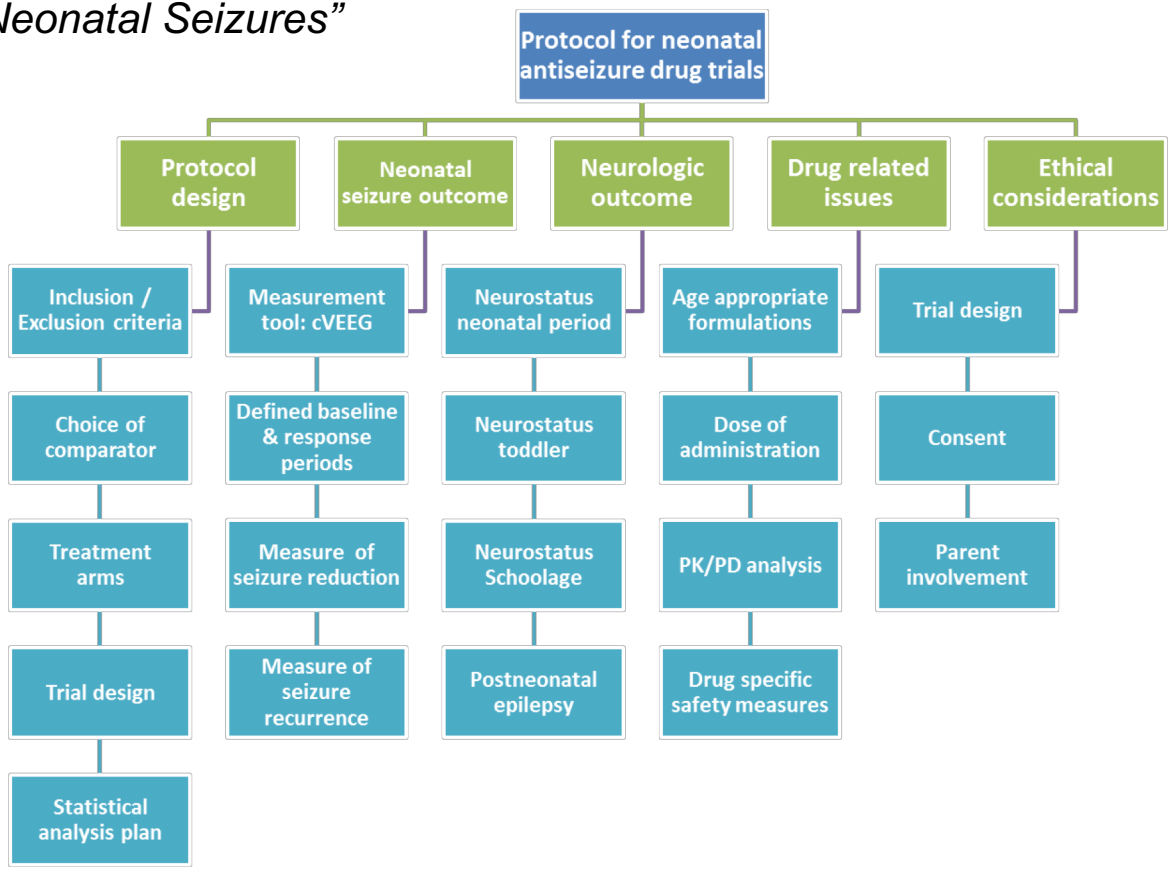
Neonatal Seizure Selection Rationale

- Most commonly effects FT neonates where there is a relative knowledge of drug metabolism compared to the premature infant.
- Diagnosis is both clinical and with a biomarker of EEG – relatively standard and equipment available globally.
- Acute treatment exists and is reasonably standard with phenobarbital; various secondary drugs used such as levetiracetam (Keppra) and topiramate although none studied in neonate in rigorous regulatory fashion. Many drugs exist to be used and studied; few new drugs being developed.
- Treatment outcomes include short term – stopping the seizure and recurrent seizures; preventing epilepsy and long term neurocognitive development.
- Excellent situation to develop master protocols that can be utilized for a number of drugs and studies
- What's next?

Seizures Overview

The Seizure Workgroup wrote a paper titled "*Recommendations for the Design of Therapeutic Trials for Neonatal Seizures*"

Submitted to Pediatric Research
April 2, 2018



INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Retinopathy of Prematurity Working Group

Ron Portman for

Co-Chairs:

Melissa Liew and Boubou Hallberg

CRITICAL PATH INSTITUTE

Retinopathy of Prematurity Workgroup Members

- **Melissa Liew – Novartis Pharmaceuticals, Co-Chair**
- **Boubou Hallberg - Karolinska Institutet and University Hospital, Co-Chair**

- Dina Apele Freimane - Riga Stradins University Hospital, Latvia (PDCO)
- Jacqueline Carleer – Belgium Federal Agency for Medicines and Health Products (PDCO)
- Wiley Chambers - US Food and Drug Administration
- Jane Moseley – European Medicines Agency
- Misha Eliasziw - Tufts Medical Center
- Alistair Fielder - City University, London
- Ann Hellström – University of Gothenburg, Sweden
- Neil Marlow- University College London Hospital
- Ron Portman – Novartis Pharmaceuticals
- Jon Davis – Tufts Medical Center
- Jack Aranda – University Hospital of Brooklyn
- Lois Smith – Harvard University
- Andreas Stahl - University Medical Center Freiburg
- Adina Tocoian - Shire
- David Wallace - Duke University
- Brian Darlow - Christchurch School of Medicine

ROP Overview

The *ROP Workgroup has* drafted and submitted a white paper – March 28, 2018 - that covers

- Proposed ROP descriptors
- ROP activity scale
- Structural and functional efficacy endpoints and
- Long-term safety outcomes for clinical trials of ROP

- Several clinical trials for new drugs in progress: results will enrich the available data and allow for further enhancement of ROP diagnostic and response criteria

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

NEC Working Group

Ron Portman for

Co-Chairs:
Jennifer Canvasser and Mickey Caplan

CRITICAL PATH INSTITUTE

NEC Workgroup Members

- **Jennifer Canvasser- NEC Society and PPA, Co-Chair**
- **Mickey Caplan- University of Chicago, Co-Chair**
- Marilee Allen - John Hopkins Medical Center
- Gerri Baer – US Food and Drug Administration
- Gail Besner – Nationwide Children's Hospital
- Hala Chaaban - University of Oklahoma
- Walt Chwals - Tufts Medical Center
- Robert Clay - Highbury Regulatory Science
- Eamonn Connolly - IBT
- Jon Davis – Tufts Medical Center, INC Co-Director
- Jennifer Duchon - Tufts Medical Center
- Wakako Eklund – NANN
- Joanne Ferguson – NEC Society
- Samir Gadepalli - University of Michigan
- Sheila Gephart - University of Arizona
- Misty Good - Washington University
- Phillip Gordon - Consultant
- Cristal Grogan – NICU Helping Hands / Preemie Parent Alliance
- Minesh Khashu - Poole Hospital NHS
- Jae Kim - UC San Diego
- Andrea Lotze - US Food and Drug Administration
- Alexandra Mangili – Shire
- Troy Markel _ Indianan University Health
- Laura Martin - Graham's Foundation
- Steven McElroy – University of Iowa
- Paolo Manzoni - Saint Anna Hospital, Torino
- Tokuo Miyazawa - Showa University, Japan
- Neena Modi - Imperial College, London
- Josef Neu - University of Florida Gainesville
- Gary Noel - Johnson and Johnson
- Ravi Patel - Emory
- Ron Portman - Novartis, INC Co-Director
- Simone Rosito – PGG Institute
- Ann Schwartz – US Food and Drug Administration
- Brian Scottoline – Oregon Health & Science University
- Suna Seo – US Food and Drug Administration
- Karl Sylvester - Stanford University
- William Treem – Johnson & Johnson
- Erin Umberger - NEC Society
- Mark Underwood - UC Davis
- Tracy Warren – Astarte Medical Partners
- Lynn Hudson – Critical Path Institute
- Alicia West - Critical Path Institute

NEC

The *NEC Workgroup* is drafting a framework for defining NEC, identifying biomarkers, reviewing biobanking needs and standards, describing modifiable risk factors, including feeding approaches, and detailing regulatory considerations involved in clinical trials of supplemental probiotics and other therapies.

White Paper:

1) Defining (re-defining) NEC (Mark Underwood, Mickey Caplan Steve McElroy, Phillip Gordon)
2) Recommendations and needs of identifying new and/or reliable biomarkers that predict, prognosticate, and follow treatment for NEC (Karl Sylvester, Brian Scottoline, Walt Chwals)
3) Supplemental probiotics: regulatory considerations and state of clinical trials (Neena Modi, Ravi Patel, Paolo Manzoni)
4) Modifiable risk factors, including feeding approaches (Mickey Caplan, Mark Underwood, Jae Kim, Sheila Gephart)
5) Biobanking: needs and standards (Misty Good, Hala Chaaban)
6) Opportunities for abdominal US and additional radiologic evaluation/interpretation in NEC diagnosis and prognostication (Jae Kim, Brian Scottoline, Walt Chwals)

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Communications Workgroup

Co-Chairs:
Christina Bucci-Rechtweg and Jennifer Degl

CRITICAL PATH INSTITUTE

Workgroup Members

- **Christina Bucci-Rechtweg- Novartis, Co-Chair**
- **Jennifer Degl- Preemie Parent Alliance, Co- Chair**
- Sandra Beauman – Consultant
- Wakako Eklund – NANN
- Yamile Jackson - Nurture By Design
- Carole Kenner – COINN
- Mehali Patel – Bliss
- Mary Short – Eli Lilly
- Nicole Thiele - EFCNI
- Mark Turner - University of Liverpool
- Scott Winiecki – US Food and Drug Administration

Communications Workgroup Update

Deliverable

Development of parallel multi-stakeholder survey to identify communication practices in NICUs in regards to neonatal research and research practice

Aims

- To facilitate the engagement of neonatal staff and parents in discussions on neonatal clinical trials
- To increase parental consent and participation in neonatal clinical research

Objectives

- To evaluate current communication practices in NICUs across the globe
- To identify communication challenges in NICUs that impede successful implementation of clinical research
- To provide physicians, nurses, and research professionals with a range of recommended methods used to practice improved communication between all stakeholders involved in neonatal clinical research

Communications Workgroup Update

Timeline	Key Activities	Status
Jun - Aug	Key survey topics identified & defined; Finalization of deliverable prospectus; Identification of INC/ *ad hoc* contributors	
Aug - Sept	6 Topic WGs - focused survey content development (off-line)	
Oct - Dec	3 3-hr & 1 1-hr working Webinars (last session 14 Dec)	
Jan - Mar	Identification of beta-testing sites (Across all 3 target stakeholder groups & regions); Agree and finalize technology for survey roll-out	
Mar - Apr	Beta-testing (Across all 3 target stakeholder groups & regions)	
Apr 11	Finalize questionnaire (*During working session at Apr INC F2F*)	
May	Launch questionnaire	

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Hemodynamic Adaptation Workgroup

Co-Chairs:

Heike Rabe and Janis Dionne

CRITICAL PATH INSTITUTE

Hemodynamic Adaptation Workgroup Members

- **Heike Rabe - Brighton & Sussex Medical School, Co-Chair**
- **Janis Dionne - BC Children's Hospital, Co-Chair**
- Dina Apele-Freimane - PDCO
- Keith Barrington – University of Montreal
- Beau Batton - Southern Illinois University SOM
- Simin Baygani - Lilly
- Varsha Bhatt-Mehta - University of Michigan
- Stephen Bremner – Brighton & Sussex Medical School
- Yan Chen - N. Clinical School Sydney, Australia
- Gene Dempsey - University College Cork, Ireland
- Ebru Ergenekon – Gazi University, Turkey
- Hiroko Iwami – Osaka City General Hospital, Japan
- Agnes Klein – Health Canada
- Matt Laughon – University of North Carolina
- Vasum Peiris - FDA
- Luana Pesco Koplowitz – DUCK FLATS Pharma
- Doug Silverstein - FDA
- Shari Targum – FDA
- Bob Ward – University of Utah
- Jon Davis – Tufts University
- Ron Portman – Novartis
- Mark Turner – University of Liverpool
- Lynn Hudson – Critical Path Institute

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 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

HA Group: Structured Literature Review

1. What are the observed ranges of blood pressure by gestational ages, at birth or post-menstrual age, birth weight, current weight and postnatal age in babies who have not received any blood-pressure modifying treatments, including volume/fluid expansion, inotropes, steroids, blood products?
   - *Antenatal steroids and magnesium sulphate for the mothers should be considered.*
2. What other factors influence blood pressure and how?
   - (*e.g. Gender, Ethnicity if data available; a) Maternal factors e.g. medication; b) Perinatal factors e.g. chorioamnionitis; c) infant factors e.g. IUGR, PDA*)
3. What are the recommended measurement methods and devices?
   - *include a characterization of each method and any limitations to each method, and required validation/verification*.)

HA Progress: Systematic review

- Systematic review protocol written according to PRISMA
  - Registered on PROSPERO
- Structured search done
  - Ca 3500 papers found, all years, all languages
  - Selected down to 350 papers covering questions 1 to 3
  - Group focusses on question 3 first
  - 110 papers, data extraction started

HA Progress: Systematic Review

- EXCEL files for data extraction drafted and tested
- Statistical Analysis Plan drafted and refined in face to face working group meeting
- Focus on *measurement methods and devices* first
- Dissemination plans
- Q2 next: *What other factors influence blood pressure and how?*

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Data Workgroup

Co-Chairs:
Tom Diacovo and Mike Padula

CRITICAL PATH INSTITUTE

Data Workgroup Members

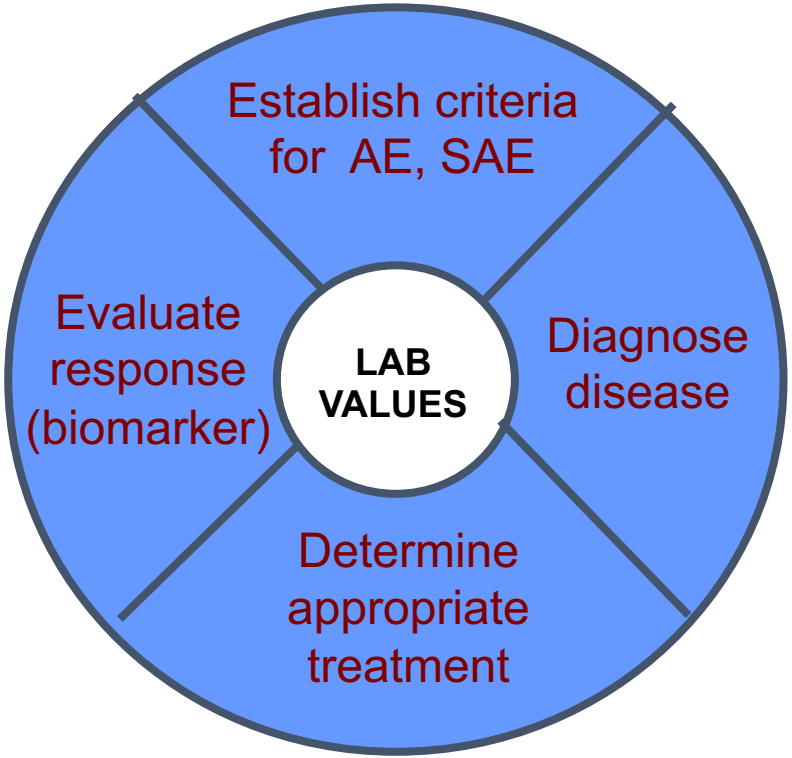
- **Tom Diacovo - Columbia University, Co-chair**
- **Michael Padula - Children's Hospital of Philadelphia; PEDSnet – Co-chair**
- Khosrow Adeli – Hospital for Sick Children, Toronto
- Gerri Baer – FDA
- Simin Baygani – Eli Lilly
- Yun Sil Chang – Samsung Medical Center, South Korea
- George Chang – National Cancer Institute/ Enterprise Vocabulary Services
- Kate Costeloe - Queen Mary University, Co-chair
- Jon Davis – Tufts University
- Laura Fabbri - Chiesi
- Dominique Haumont - St-Pierre University Hospital
- Victoria Higgins – Hospital for Sick Children, Toronto
- Shinya Hirano – Osaka Medical Center & Research Institute for Maternal and Child Health
- Takehiko Hiroma – Nagano Children's Hospital
- Steven Hirschfeld – Uniformed Services Univ.
- 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 – FDA/OC
- Neena Modi - Imperial College London
- Isabella Montagna - Chiesi
- Hide Nakamura – National Research Institute for Child Health and Development, Japan
- Martin Offringa – University of Toronto
- Ron Portman – Novartis
- Prakesh Shah – CNN /U - Toronto
- Catherine Sherwin – University of Utah
- Mary Short – Eli Lilly
- Brian Smith - Duke University (DCRI)
- Roger Soll – Vermont Oxford Network
- Marta Terrile - Novartis
- Charlie Thompson – Pfizer
- Nam Tran – UC Davis
- Mark Turner – University of Liverpool
- Toshimitsu Yanagisawa – Shinsu Univ SOM
- Lynn Hudson – Critical Path Institute

International Neonatal Consortium

Data Workgroup: Lab Values

DATA WORKGROUP: LAB VALUES

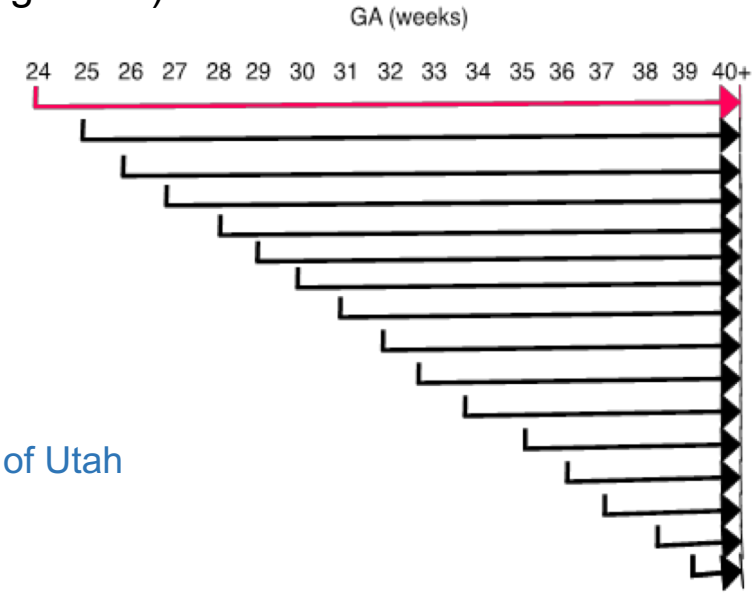
The quality of clinical trail is critically dependent on accurate interpretation of lab results based on accurate reference intervals or decision limits



Lab Values Group - Goal

- To **develop reference ranges** for the most common lab values collected in the NICU, relevant to almost any neonatal study, then branch out into more disease specific lab values.

- **Retrospective study first and then prospective study** (a walk through time)



Catherine Sherwin - University of Utah
Nam Tran – UC Davis

Context for Lab Values: Required Fields

- Lab values
- Lab technique (LOINC Codes)
- Gestational Age
- Chronologic Age (Date of Birth)
- Sex

required for inclusion

- Race
- Ethnicity
- Diagnoses/diseases

captured if available

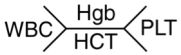
Certain diagnoses that affect organ function:

- -Acute kidney injury
- -Hypoxic Ischemic Encephalopathy
- -Perinatal depression
- -Various congenital anomalies (e.g., posterior urethral valves)
- -Certain genetic disorders

possible exclusion criteria

Key Lab Data Elements for Drug Trials

Complete Blood Count



Hematology	Chemistry
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (red blood cells)	Blood urea nitrogen
Mean cell volume	Creatinine
Leukocytes (white blood cells)	Calcium
Neutrophils, bands, myelocytes, metamyelocytes, etc..	Glucose
Lymphocytes	Chloride
Monocytes	CO2
Eosinophils	Bilirubin (conjugated/unconjugated)
Basophils	AST, ALT, Alk Phos, GGT
Reticulocytes	Total protein, albumin
Platelets	Lactate Dehydrogenase

Electrolyte Panel

Hepatic Panel

DATA WORKGROUP: LAB VALUES

Reference ranges: Deliverables

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

in progress 2. Proof of 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

International Neonatal Consortium

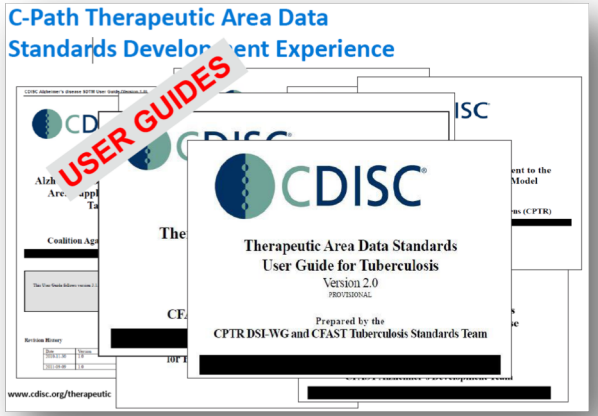
Data Workgroup: Data Concepts

What are we looking to create?

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

- Propose a ***core set*** of elements to be collected for all newborns (infants)
  - demographic
  - major outcome measures
  - maternal/perinatal data
  - adverse events

- Agree on ***domain-specific*** elements (modules) to employed for specific topics
  - *If you are going to collect details about "X"…here are lists of concensus data elements and definitions*



Core Data Set …which concepts…where *should* they exisit in the SDTM

- **Demographic**
  - Birth date
  - Chronologic Age
  - Sex
  - Ethnicity
  - Maternal Age
  - Gravity/Parity
  - Pregnancy gestation assessment (Estimated Date of Delivery)
    - method of determination (optional)
  - Conditions relevant to fetal/maternal health
  - Maternal Ethnicity
  - *Maternal Socioeconomic status*
  - *Maternal Education*

Demographics (DM) domain

BRTHDTC	Date/Time of Birth	Date/time of birth of the subject in ISO 8601 character format.
ETHNIC	Ethnicity	The ethnicity of the subject. Sponsors should refer to "Collection of Race and Ethnicity Data in Clinical Trials" (FDA, September 2005) for guidance.

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition	NCI Preferred Term
C66790		No	Ethnic Group	ETHNIC	Ethnic Group	A social group characterized by a distinctive social and cultural tradition maintained from generation to generation, a common history and origin and a sense of identification with the group; members of the group have distinctive features in their way of life, shared experiences and often a common genetic heritage; these features may be reflected in their experience of health and disease. (NCI)	CDISC SDTM Ethnic Group Terminology
C17459	C66790		Ethnic Group	HISPANIC OR LATINO		A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, regardless of race. (NCI)	Hispanic or Latino
C41222	C66790		Ethnic Group	NOT HISPANIC OR LATINO		A person not of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. An arbitrary ethnic classification. (NCI)	Not Hispanic or Latino
C43234	C66790		Ethnic Group	NOT REPORTED	Not reported	Not provided or available.	Not Stated
C17998	C66790		Ethnic Group	UNKNOWN	U; Unknown	Not known, not observed, not recorded, or refused. (NCI)	Unknown

APEX domain
APSU domain

SC domain

DATA WORKGROUP: Toward a common model for neonatal trials...

- VLBW QI network concepts
- Terminology harmonization efforts
- Published study outcomes
- Case Report Forms (CRFs)*
- Other Workgroup input

more CRFs welcomed!

VON

Case Report Form

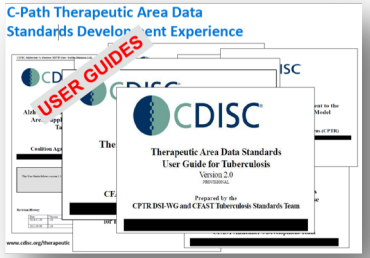
iNeo

neoEPOCH

NIH NATIONAL CANCER INSTITUTE Enterprise Vocabulary Services

NRNT

Core Outcomes In Neonatology



User Guide
for trials involving
Neonates/Infants

…funding…

Core Data Set

+

domain specific fields

maternal/ antenatal

neurologic

hemodynamic

genetic

heme

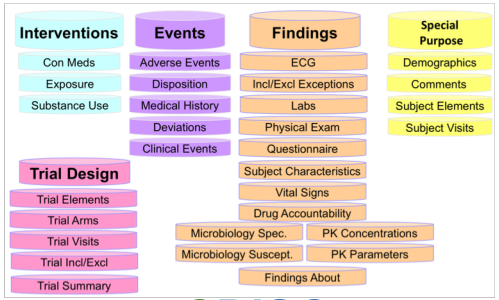
respiratory

adverse events

endocrinologic

ophthalmologic

renal/electrolyte



CDISC

Study Data Tabulation Model (SDTM)

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Bronchopulmonary Dysplasia Workgroup

Co-Chairs:

Robin Steinhorn and Wolfgang Göpel

CRITICAL PATH INSTITUTE

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 – Albert Einstein College of Medicine
- Gerri Baer - FDA
- Roberta Ballard - UCSF
- Eduardo Bancalari - Jackson Medical Center, Miami
- Dirk Bassler – University of Zurich
- Giuseppe Buonocore – University of Siena, Italy
- Danièle De Luca - South Paris University Hospitals
- Laura Fabbri – Chiesi
- Anne Greenough – King's College, London
- Ninna Gullberg - Karolinska University Hospital & PDCO
- Anna Maria Hibbs – Case Western Reserve University SOM
- Helmut Hummler – University of Ulm, Germany
- Alan Jobe - Cincinnati Children's Hospital
- Roberta Keller - UCSF Benioff Children's Hospital
- Matt Laughon - UNC
- Alexandra Mangili - Shire
- Susan McCune – FDA/OC
- Courtney McGuire - FDA
- Marek Migdal - Children's Memorial Health Institute, Warsaw, Poland
- Tomohiko Nakamura – Nagano Children's Hospital
- Michael O'Connell - Pfizer
- Aprile Pilon – Therabron
- Rashmin Savani – UT Southwestern
- Prakesh Shah - CNN/U - Toronto
- Roger Soll - Vermont Oxford Network
- Linda Storari - Chiesi
- Merran Thomson – Neonatal Consultant
- Bob Ward – University of Utah
- Jon Davis – Tufts University
- Ron Portman - Novartis
- Mark Turner – U. of Liverpool
- Lynn Hudson – Critical Path Institute

BPD Workgroup Progress Report

White paper published in Journal of Pediatrics

Traditional BPD definitions (binary, based on O2 use at 36 weeks PMA) no longer sufficient for regulatory purposes

Continued work to define chronic respiratory morbidity at 1 year as a COA

Work on defining and testing surrogate clinical outcomes:

- PIRS Score at term equivalent (Aschner, Davis and others)
- O2 saturation shift (Pillow)

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Clinical Pharmacology Workgroup

Co-Chairs:

Bob Ward, Karel Allegaert

CRITICAL PATH INSTITUTE

Clinical Pharmacology Workgroup Members

Karel Allegaert - University of Leuven, Co-chair
Bob Ward - University of Utah, Co-chair
Jeff Barrett - Sanofi, Co-chair

- Dina Apele-Freimane - Riga Stradins University Hospital, Latvia
- Jack Aranda - University Hospital of Brooklyn
- Ron Ariagno – Stanford
- Gerri Baer - FDA
- Ralph Bax - EMA
- Danny Benjamin - Duke University (DCRI)
- Edmund Capparelli – UC San Diego
- Edress Darsey – Pfizer
- Roberto De Lisa – EMA
- Laura Fabbri –Chiesi
- Ralf Herold - Bayer
- Isamu Hokuto – St. Marianna University
- Walter Kraft – Thomas Jefferson University
- Irja Lutsar – University of Tartu, Estonia & PDCO
- Alexandra Mangili – Shire
- Neil Marlow - University College London Hospital
- Susan McCune – FDA/OC
- Christopher McPherson – St. Louis Children's Hospital, Wash U. SOM
- Jeff Ming – Sanofi
- Lily Mulugeta – CDER/FDA
- Min Soo Park – Yonsei University, Seoul, South Korea
- Thomas Salaets – University of Leuven
- Catherine Sherwin - University of Utah
- Mary Short - Lilly
- Ine Skottheim Rusten - Norwegian Medicines Agency & PDCO
- 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
- Jian Wang - FDA
- Jon Davis – Tufts U & INC Co-Director
- Ron Portman – Novartis & INC Co-Director
- Mark Turner – University of Liverpool & INC Co-Director
- Lynn Hudson - C-Path & INC Co-director

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

WG update: Clin Pharm

Current status of neonatal AE severity grading

CRITICAL PATH INSTITUTE

Approach to a neonatal scale: adapted Delphi methodology

STEP 1:
Define generic criteria applicable to neonates

Web survey 1:
Dec 2016 – Jan 2017

First open questions to guide the draft criteria for neonatal severity.

Input from 55 respondents received.

Web survey 2:
Feb 2017 – Mar 2017

Questionnaire on a proposal based on the responses of web survey 1.

Input from 36 respondents received.

Group discussion:
27th of March 2017

Discussion on the proposal and comments received in web survey 2.
Finalising generic criteria.

32 participants registered.

Input received from academia, industry, people working for regulatory authorities, nursing organisations and parental representatives.

Generic criteria

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Life threatening	Death
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behavior*, no change in baseline care or monitoring indicated	Moderate; resulting in minor changes of baseline age-appropriate behavior*, requiring minor changes in baseline care or monitoring	Severe; resulting in major changes of baseline age-appropriate behavior* and/or non-life threatening changes in basal physiological processes**, requiring major change in baseline care or monitoring***	Life-threatening; Resulting in life-threatening changes in basal physiological processes**	Death related to AE
*Age-appropriate behavior refers to oral feeding behavior, voluntary movements and activity, crying pattern, social interactions and perception of pain. **Basal physiological processes refer to oxygenation, ventilation, tissue perfusion, metabolic stability and organ functioning. ***Examples of major change in baseline care to be defined…				

Approach to a neonatal scale: adapted Delphi methodology

STEP 1:
Define generic criteria applicable to neonates

Web survey 1:
Dec 2016 – Jan 2017

First open questions to guide the draft criteria for neonatal severity.

Input from 55 respondents received.

Web survey 2:
Feb 2017 – Mar 2017

Questionnaire on a proposal based on the responses of web survey 1.

Input from 36 respondents received.

Group discussion:
27th of March 2017

Discussion on the proposal and comments received in web survey 2. Finalising generic criteria.

32 participants registered.

Validation of generic scale

19 retrospective case descriptions were graded. Based on interobserver agreement results the generic criteria were adapted.
12 graders

Input received from academia, industry, people working for regulatory authorities, nursing organisations and parental representatives.

Validation results

19 written case reports (provided by U Liverpool)

12 observers (academia, nursing, industry, regulatory)

overall ICC = 0,39

	grade 1	grade 2	grade 3	grade 4	%agreement
AKI gentamicin	0	3	***9***	0	0,590909
neutropenia diuretics	2	***5***	5	0	0,318182
pyrexia, acyclovir	5	***7***	0	0	0,469697
pyrexia, prostin	***8***	4	0	0	0,515152
thrombocytopenia, antibiotics	5	***7***	0	0	0,469697
tachycardia, eye drops	***8***	4	0	0	0,515152
apnea, vaccination	0	3	***6***	3	0,318182
apnea, eye drops	0	4	***5***	3	0,287879
vomit, eye drops	***10***	2	0	0	0,69697
acidosis, NaCl	3	1	***8***	0	0,469697
thrombocytopenia, linezolid	1	3	***8***	0	0,469697
desat/brady, eye drops	0	4	***4***	4	0,272727
thrombopenia, penicillin	***7***	4	1	0	0,409091
apnea, prostin	1	***9***	1	1	0,545455
urinary retention, midazolam/curare	1	***8***	3	0	0,469697
cerebral hemorrhage, dobutamine	5	***1***	***6***	0	0,378788
hypertension, inotropes	3	***4***	4	1	0,227273
watery stool, antibiotics	***6***	***5***	1	0	0,378788
tachycardia, curare	5	***4***	3	0	0,287879

median grade

Bench marking: CTCAE & SAVES-2

Symptoms	Full sample ($N = 393$)	
	ICC	95% CI
Constipation	0.48	0.36; 0.58
Diarrhea	0.58	0.49; 0.66
Dyspnea	0.69	0.62; 0.75
Fatigue	0.50	0.39; 0.59
Nausea	0.52	0.41; 0.60
Neuropathy	0.71	0.65; 0.76
Vomiting	0.46	0.34; 0.56

Atkinson, Qual Life Res 2012

TABLE 5. SAVES-V2 inter- and intraobserver agreement in the S

Parameter	Interobserver Agreement (95% CI)
No. in group	34
Presence of an AE	97%
AE severity*	0.75 (0.73–0.76)
No. of AEs	0.70 (0.62–0.76)
Specific type of AE	0.80 (0.79–0.82)
Impact of AE on LOS	0.39 (0.21–0.53)

* Primary outcome measure.

Rampersaud, J Neurosurg Spine 2016

Adaptations to generic scale

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Life threatening	Death
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behavior*; no change in baseline care or monitoring indicated	Moderate; resulting in minor changes of baseline age-appropriate behavior*; requiring minor changes in baseline care or monitoring***	Severe; resulting in major changes of baseline age-appropriate behavior* or non-life threatening changes in basal physiological processes**; requiring major change in baseline care or monitoring****	Life-threatening; Resulting in life-threatening changes in basal physiological processes**; **requiring urgent major change in baseline care**	Death related to AE
*Age-appropriate behavior refers to oral feeding behavior, voluntary movements and activity, crying pattern, social interactions and perception of pain. **Basal physiological processes refer to oxygenation, ventilation, tissue perfusion, metabolic stability and organ functioning. ***Minor care changes constitute: brief, local, non-invasive or symptomatic treatments ***Major care changes constitute: surgery, addition of long term treatment, upscaling care level				

Approach to a neonatal scale: adapted Delphi methodology

STEP 2:
Apply the generic scale to specific neonatal AE's

Draft preparation:
March 2018

Thomas Salaets drafted specific criteria based on the generic criteria, CTCAE grading, expert feedback, ...

Focus group discussion:
11th of April 2018

Applied criteria discussed and modified in thematic focus groups, with feedback to the whole group

43 participants registered

Neonatal AE severity scale v1.0

Apnea Definition C26698|no MedDRA term: *Cessation of air flow.* ***Worsening from baseline that occurs following an intervention***				
Self-limiting apnea	Apnea requiring stimulation	Apnea requiring stimulation or FiO_2 increase; reoccurrences requiring respiratory stimulants or other major care changes	Life-threatening respiratory and/or hemodynamic compromise; ventilation required	Death

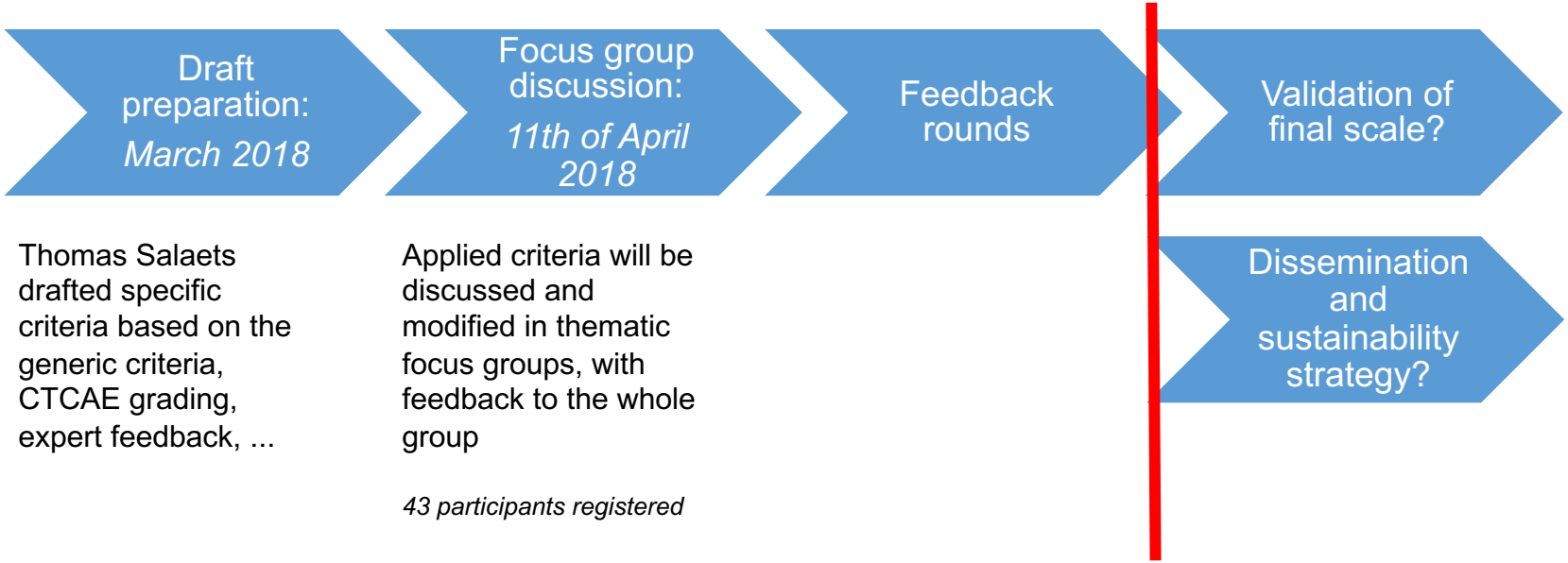
Culture proven sepsis Definition C3364|10040049: *A systemic inflammatory response to an infection (EVS term not specifically neonatal).*				
	Blood culture positive with mild or ambiguous signs or symptoms; anti-infectives initiated	Blood culture positive with signs or symptoms; support treatment escalated or initiated	Life-threatening consequences (e. g. state of shock, DIC); urgent major care change required	Death

Neonatal adverse events

Neurological	Respiratory	Cardio-vascular	Gastro-intestinal	General + Infectious	Lab values
seizures	apnea	hypotension	NEC	rash	anemia
IVH	RDS	hypertension	SIP	infusion site extravasation	leukopenia
HIE	PPHN	tachycardia	diarrhea	fever	thrombopenia
ROP	pulmonary hemorhage	bradycardia	vomiting	suspected sepsis	hypoglycemia
irritability	respiratory deterioration		feeding intolerance	proven sepsis	hyperglycemia
			GI bleeding		bilirubine increase
			constipation		creatinin increase

Approach to a neonatal scale: adapted Delphi methodology

STEP 2:
Apply the generic scale to specific neonatal AE's

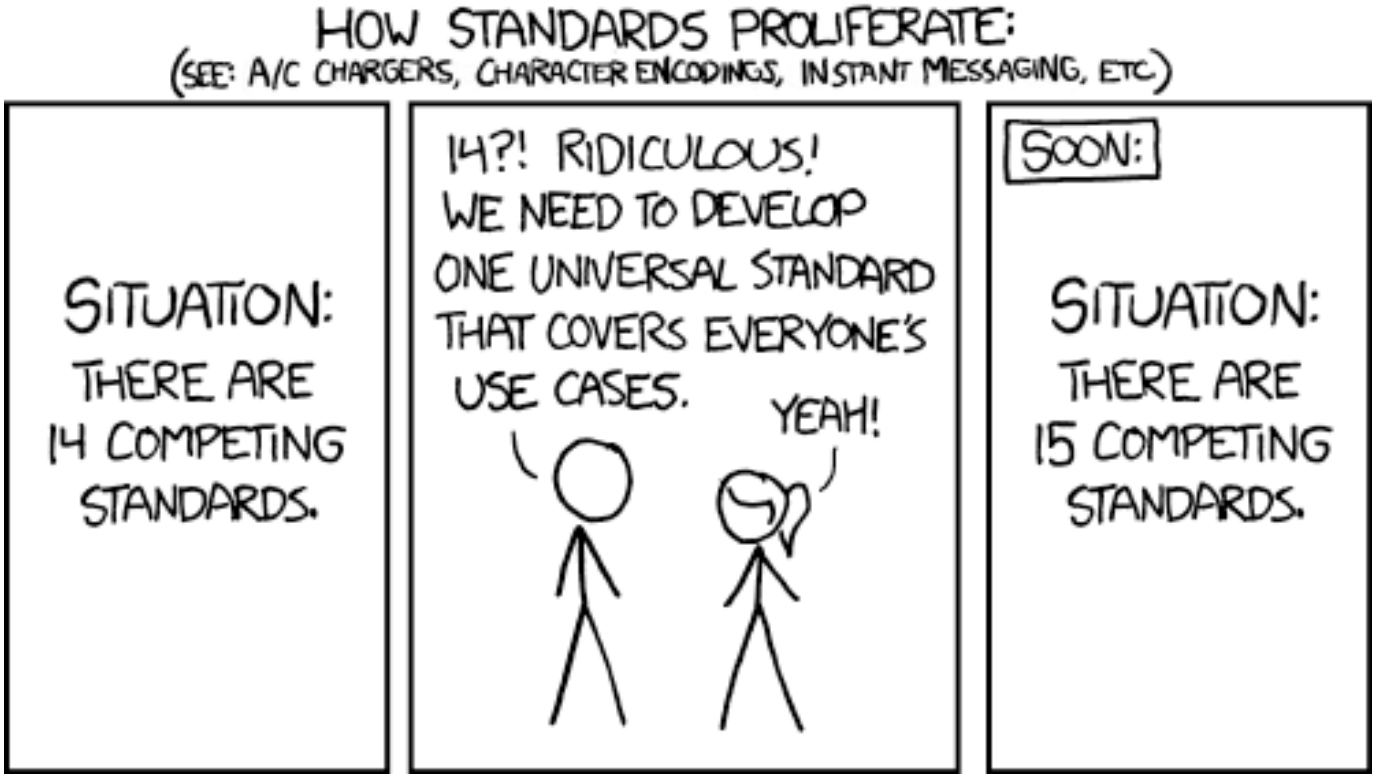


Thomas Salaets drafted specific criteria based on the generic criteria, CTCAE grading, expert feedback, ...

Applied criteria will be discussed and modified in thematic focus groups, with feedback to the whole group

43 participants registered

Dissemination and sustainability?



PhD Comics

INC
CRITICAL PATH INSTITUTE

International Neonatal Consortium

THANK YOU

CRITICAL PATH INSTITUTE