Applying Digital Technologies to Developing Endpoints for Neonatal Trials

Mark Turner and PRAKESH SHAH – Co-Chairs

May 2, 2019
Applying Digital Technologies to Endpoints

1:30 p.m. - 3:00 p.m. Applying Digital Technologies to Developing Endpoints for Neonatal Trials

MARK TURNER AND PRAKESH SHAH, Co-chairs

• ELIN HAF DAVIES (Aparito)
• JOSEPH FRASSICA (Philips)
• LEONARD SACKS (CDER/FDA)
• DOUG SILVERSTEIN (CDRH/FDA)
• CHRIS MCKINLAY (U-Auckland)
• WES ONLAND (Emma Children’s Hospital AMC, Amsterdam)
Technology: an appetite for immortality or a threat to extinction (of neonatologist)?

Prakesh S Shah
Interim Chief, Department of Pediatrics, Mount Sinai Hospital, University of Toronto
Director, Canadian Neonatal Network and International Network for Evaluation of outcomes in Neonates (iNeo)
Objective/Structure of the Session

• Objectives:
  • To review principles of approval of technology for routine use in healthcare
  • To understand challenges associated with adoption of new technology
  • To review evolution of two common potentially problem solving technology for newborns
  • To learn to embrace massive technological shifts coming our way

• Structure
  • Opening remarks by Prakesh Shah: “Technology: an appetite for immortality or a threat to extinction (of neonatologist)?”
  • Talk: What are the processes for approval of technology at FDA or other agencies?
  • Talk by Elin: Patient monitoring made different, Digital Biomarkers for Clinical Trials
  • Talk by Joseph Frassica:
  • Talk by Chris McKinlay: Neonatal Continuous Glucose Monitoring
  • Talk by Wes: Research of Automated Oxygen Devices the CLIO system
  • Discussion/questions
  • Concluding remarks and next steps by Mark Turner
This is Apple tree, ok. But where are the trees of Samsung, Lenovo and HP...?
Using Health Information Technology to Improve Safety in Neonatal Care

Group 1
- CPOE
- CDS
- Bar coding
- Smart pumps

Group 2
- Error detection
- Telemedicine
- Communication
- Monitoring and care processes

Kristin R. Melton, MD\textsuperscript{a,*}, Yizhao Ni, PhD\textsuperscript{b}, Heather L. Tubbs-Cooley, PhD, RN\textsuperscript{c}, Kathleen E. Walsh, MD, MSc\textsuperscript{d}
Technology adoption by households
Technology adoption cycle

- Innovators: 2.5%
- Early Adopters: 13.5%
- Early Majority: 34%
- Late Majority: 34%
- Holdouts: 16%
Design Framework for a Data Mart in the Neonatal Intensive Care Unit

FIG. 1: Architecture framework for an automated system for data collection, storage, and analysis for a NICU
Blockchain Technology – Promising Use Cases for Healthcare Industry

**Patient Generated Data**
- Stores different types of health data (e.g., images, genomics, and lab reports).
- Consists structured and unstructured data.
- Information is encrypted and digitally signed.

**Clinical Data and Health Records**
- Consists a complete indexed history, patient’s unique identifier, and an encrypted link to health record.
- Each record is time stamped.
- All patient records (historical) are together and stay with the patient.
- Patient has control over the permissions on whom to share with.

**Blockchain**
- Distributed patient consent for research/clinical trials enables data sharing, audit trials, and clinical safety analyses.

**Data lakes**
- Providers use health application to access health data.

**Health Analytics & IoMT**
- Providers uses predefined smart contracts.

**Payers**
- Patients use mobile devices to assign access permission to data and to provide public key.

**Pharma/Research**
- Blockchain network consensus enables disintermediation to automate claim adjudication and payment processing with predefined smart contracts.

Source: www.healthit.gov, Frost & Sullivan
Convincing staff to use new technology
Binodal, wireless epidermal electronic systems with in-sensor analytics for neonatal intensive care

So, let’s begin...

To review principles of approval of technology for routine use in healthcare

To understand challenges associated with adoption of new technology

To review evolution of two common potentially problem solving technology for newborns – Oxygen control and Sugar monitoring

To learn to embrace massive technological shifts coming our way
Patient monitoring made different, Digital Biomarkers for Clinical Trials

Elin Haf Davies (Aparito)
Introducing Aparito

- Aparito formed in 2014, is a technology-enabled clinical research company
- Developed a propriety technology solution (CARBON) that enables the capture of Patient Generated Data (PGD)
- Europe based (offices based in UK and Holland)
- Currently raised a total of £2.3M and revenue generating

Dr Elin Haf Davies
Founder and CEO

Experienced clinician with 22+ experience within rare disease and regulatory (EMA). Elin founded Aparito in to address the current gaps and challenges in clinical trials and routine care

Dr Ian Radford
CTO

After completing a PhD in Artificial Intelligence, Ian has spent 30+ years in software engineering and AI within pharma and finance.

Cecile Ollivier
COO

10 years + experience in paediatric Global Clinical Research. Co-authored recent EMA extrapolation framework, which Cecile has been recognised for within the EU and Globally.

Liam Eves
CCO

Liam has spend the last 12+ years growing life sciences companies. His last position was COO for a life sciences company which he took public on LSE:AIM and raised a total of £100m.
Experience to date

- Approaching **1.5 million** Patient Generated Data points collected
- **Eight** diseases studied
- International experience and reach
- Proven platform and team
- Only technology-enabled clinical research company in the rare disease space
The drug development paradigm is rapidly changing in view of bottlenecks to safe drug access for patients with high unmet needs (especially neonates).
Collecting patient data in a Clinical Trial: The past, present & future

**What the Doctor sees ...**

- **Patient A**
- **Patient B**

Current problems in clinical trials:
- Clinical trial complexity
- Participation burden and missed engagement
- Cost
- Clinical capacity

**‘Episodic snapshots’**

Currently: We only see data at clinical visits

Currently:
- 49 percent of patient activity happens outside of the hospital or clinic. Beyond the scope of the traditional health record. (HR)

**‘Disease in motion’**

The future: Monitoring patients at home 24/7/365

Benefits:
- Patient Centric
- Cost reduction (17%)
- Better patient centric study design
- Improved patient access to studies, incl. diverse population
- Rapid recruitment and improved retention
- Greater real world

**What the Patient experiences ...**

- **Patient A**
- **Patient B**

Benefits:

- Patient Centric
- Cost reduction (17%)
- Better patient centric study design
- Improved patient access to studies, incl. diverse population
- Rapid recruitment and improved retention
- Greater real world

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Source: S. Elvidge, “Importance of Patient Retention Strategies,” Life Science Leader
How we see the Clinical Trial Process adapting

1. **Crawl.... Traditional approach**
   - Pharma continues its current approach to clinical trials, using clinical sites and capturing data using paper and pens.

2. **Walk... Hybrid Model**
   - Companies will leverage technology to gather data. The market adoption however won't be huge. This will take time resulting in a hospital and tech clinical trial model.

3. **Run... Virtual Model**
   - Companies will have adopted technology and virtual clinical trials as a standard way of conducting trials. They will also leverage the huge data set generated to find insights using AI.

**Healthcare Trends**
- ePatient
- More engaged participants with increased expectations
- Digital health has become a thing
- Cheaper technology
- IoT’s
- Precision medicine

**Barriers to Entry**
- Expert regulatory knowledge
- Expert technologists in the Clinical Trial space
- Clinical trial expertise
- Commercial expertise in the Pharma sector
Technology Enabled Clinical Trials

Designed to overcome clinical, regulatory and user roadblocks

- Vastly improved understanding of diseases
- Better, cheaper & faster drug development
- More participants & engagement
- Increased chance of regulatory approval
- Higher patient empowerment & quality of life
- Lives Saved & Improved

Patient Generated Outcome Data
- Continuous Data
- Digitalised Monitoring Process
- Remote Disease Monitoring
- Real Time Data
- Real Time Flags
- Passive Data Capture
- Paperless Data Capture
- Medication Prompts

Passive Data Capture
- Remote Disease Monitoring
- Real Time Data
- Real Time Flags
- Continuous Data
- Digitalised Monitoring Process
- Patient Generated Outcome Data
- Continuous Data
- Digitalised Monitoring Process
- Patient Generated Outcome Data
CARBON application

Designed to overcome clinical, regulatory and user roadblocks

Wearables
Collects data in real-time and uploads it by Bluetooth

Mobile app
Collects information from the patient’s perspective

Dashboard
Authorised clinical staff can review individual or cohort data in real-time
Clinical dashboard – Combining data for meaningful insights
Methodology to Optimise Drug Development for neonates

**EMA Extrapolation Framework**

**Reflection paper on the use of extrapolation in the development of medicines for paediatrics**

- Draft agreed by Biostatistics Working Party: September 2017
- Draft agreed by Modelling and simulation group: September 2017
- Draft agreed by PKWP: September 2017
- Draft agreed by Scientific Advice Working Party: September 2017
- Draft Adopted by PRAC: 29 September 2017
- Draft Adopted by PDCO: 12 October 2017
- Draft Adopted by CHMP: 12 October 2017
- Start of public consultation: 13 October 2017
- End of consultation (deadline for comments): 14 January 2018

Comments should be provided using this template. The completed comments form should be sent to extrapolation@ema.europa.eu.

**Keywords**: Paediatrics, extrapolation, medicine development, biostatistics, modelling and simulation

**EMA concept paper on neonates**

Term and preterm neonates represent the most vulnerable subgroup of the paediatric population with the highest rate of unauthorised or off-label used medicines across the entire paediatric population.

Greater importance of study design, identifying standard measures and timelines: choice of response variables, assessment time points and observation duration and intervals.

- PK/PD extrapolation, modeling and simulation approaches has evolved.

**Regulatory Tools**
**for a Structured Approach**
**to Increase Predictability in decision making**
Points to consider when designing studies for neonates

| Factors associated to changes in organ function | Brain, liver, renal system, lung, GI system |
| Factors associated to changes in growth body weight and size, organ weight, tissue composition (plasma proteins, water and fat composition) | Enzyme activity, alveolar parameters, neural tube differentiation, … |
| Extrapolation parameters | Disease, Pharmacology, Clinical response |
| Extrapolation Challenges | Physical growth, organs maturation, transporters and enzymes ontogeny create size -> age-dependent variability in PK parameter. **Safety can’t be extrapolated** |

**Extrapolation and data analytics opportunities**
- Extrapolation unlikely to be possible particularly for preterm neonates
- But modelling and simulation principles for rational interpretation of the available evidence and to guide study design/dosages.

Digital tools can help generate robust and reliable data that could ultimately increase confidence in the use of modelling and simulation.
Developing Endpoints fit for regulatory purposes

1. Identify existing knowledge and gaps in knowledge
   - Natural history of the disease or condition
     - Onset/Duration/Resolution
     - Diagnosis
     - Pathophysiology
     - Range of manifestations
   - Patient subpopulations
     - By severity
     - By onset
     - By comorbidities
     - By phenotype
   - Health care environment
     - Treatment alternatives
     - Clinical care standards
     - Health care system perspective
   - Patient/caregiver perspectives
     - Definition of treatment benefit
     - Benefit-risk tradeoffs
     - Impact of disease

2. Identify research questions and uncertainties
   - Define context of use (COU) for clinical trial:
     - Disease/Condition entry criteria
     - Clinical trial design
     - Endpoint positioning
   - Select clinical outcome assessment (COA) type:
     - Patient-Reported Outcome (PRO)
     - Observer-Reported Outcome (OBSRO)
     - Clinician-Reported Outcome (ClinRO)
     - Performance Outcome (motor, sensory, cognition)

3. Select appropriate endpoints and study design
   - Search for existing COO measuring COI in COU:
     - Measure exists
     - Measure exists but needs to be modified
     - No measure exists
     - Measure under development
   - Begin COA development:
     - Document content validity (qualitative or mixed methods research)
     - Evaluate cross-sectional measurement properties (reliability and construct validity)
     - Create user manual
     - Consider submitting to FDA for COA qualification for use in exploratory studies
   - Complete COA development:
     - Document longitudinal measurement properties
     - Construct validity, ability to detect change
     - Document guidelines for interpretation of treatment benefit and relationship to claim
     - Update user manual
     - Submit to FDA for COA qualification as effectiveness endpoint to support claims

Extrapolation framework
Patient Generated Data

Patient-generated data (PGD):

- Created, recorded, or gathered by or from patients
- Health related events / symptoms (videos, photos, voice, text)
- Medication adherence
- Biometric data (wearable devices)
- ePatient Reported Outcomes (PROs)

Patient-generated data (PGD) ≠ clinical settings:

- Patients, not providers, are responsible for capturing or recording these data.
- Patients decide what data to share, and with which health care providers / researcher to do so.
- (e.g. physical activity using wearable devices, medication adherence and ePRO using a mobile app.)

PGD most easily captured digitally in today’s world. Digital Biomarker becoming an important concept.
But how do we decide?

Not everything that counts can be counted, and not everything that can be counted counts.

Albert Einstein
Demonstration

- GREAT OPPORTUNITY FOR PAIN (CRYING), FONTANELLE, SEIZURES, RESPIRATORY AND LONG-TERM DEVELOPMENTAL OUTCOMES (AoL)
Joe Frassica (Philips)
Use of Digital Health Technologies in clinical trials - regulatory perspective

Leonard Sacks
Office of Medical Policy
CDER, FDA
Digital technologies- opportunities in clinical trials

• Continuous measurements
• Pharmaco-dynamic information
• Real world information
• Rare events
• Remote data acquisition
• Patient convenience and inclusiveness
• Objective measurement
• Pediatrics and cognitively impaired patients
Use in Neonates

- Use in neonates is particularly exciting as they cannot tell us how they feel, reliance on caregivers
- Some of the things we can measure
  - Apnea, seizures, sleeping, crying, movement, glucose, oxygen.
- Types of tools: Invisibles, video-cameras, mattress sensors, wearables
Types of endpoints where Mobile Technology Tools may play a role

• Clinical laboratory measurements
  • Continuous glucose monitoring, pulse oximetry

• Physiological measurements
  • Heart rate and rhythm, breathing and lung function, seizures, syncope, temperature, weight

• Performance assays
  • Stamina, strength, coordination, abnormal movements, sleep, cognition
Device clearance by CDRH

• To date, our experience is with medical devices in the care of patients.
• Depending on the device and the way it is being used, CDRH clearance may or may not be needed when the device is used in a clinical trial
• (not all cleared devices will be acceptable for use clinical trials and not all devices used in trials will require approval or clearance)
One or more of the following steps may be needed to support use in a clinical trial

• Verification
• Validation
• Justification
• Fitness for use
• Safety
• DCTs and remote data acquisition
• Part 11
Verification of the tool

• Verification- ensure that the mobile technology tool engineering specifications are suitable for the intended use (non-clinical laboratory testing)

• Accuracy and precision (inter- and intra- device variability) of the physical measurements made by the tool (e.g. acceleration, temperature, pressure, time)

• Suitable range of measurements, sampling frequency, battery life etc.
Validation of the measurement

• Can the tool be relied on to measure the clinical or pathological characteristic of interest (e.g. steps, breaths, heartbeats, arrhythmias, seizures)?

• Measurement errors must be avoided: Inaccurate measurements inflate the type 1 error (false positives) in non-inferiority studies and the type 2 error (false negatives) in superiority studies.

• Generally, we can compare measurements made by the tool to measurements made by observation or by other techniques already accepted in the research environment.

• Characterize intra- and inter- device variability.

• Depending on the circumstances it might be necessary to test the Mobile Technology Tool in patients with the disease.

• For some commercial devices this type of information might be available from manufacturers or published literature.
Justification of the endpoint

• When the tool is simply used as an alternative way to measure a validated disease outcome (e.g. blood pressure, FEV1), it can be substituted for the traditional measurement.

• When the endpoint is new:
  • Compare with a traditional endpoint (e.g., EEG with seizure diary, continuous glucose monitoring with HBA1C, polysomnography with sleep diary (perhaps in a pilot study or in an adaptive trial)).
  • Compare with a clinical outcome e.g., caregiver’s reported outcome, clinical event.
  • When no traditional endpoints exist, the clinical significance and/or clinical value of the new measurement would have to be justified. This would involve clinical review divisions, clinical outcome staff, caregivers, patients and others.
Components of the endpoint

• What?
  • The physical characteristic is being measured e.g. glucose, sleep, seizures

• When?
  • The window of observation

• How?
  • The formula used to translated the measurement into a response for each patient
    • mean value, peak value, area under the curve, number of events, time to event, change from baseline
Clinical relevance of the endpoint

• How well does the endpoint reflect how the patient feels, functions or survives?
• Is the timing of the measurement appropriate?
• Are the characteristics being measured relevant to patients and clinicians?
• Is the magnitude of the response to treatment meaningful to patients and clinicians?
Risk to subjects using the Mobile Technology Tool

• Physical risks from the mobile technology tool e.g., occluding blood supply, penetrating skin, producing local allergic response
• Risk of erroneous measurements resulting in excessive, deficient or inappropriate treatment
• Risk mitigation plans to respond to abnormal measurements (e.g., hypoglycemia, arrhythmia, apnea)
Considerations to ensure the Mobile Technology Tool is suitable for a planned clinical trial

• Study Population
  Physical characteristics of the population

• Usability of the technology.
  Comfort of wearable
  Training of care givers and study personnel

• Study design
  Duration of use
  Circumstances when caregivers can review biosensor data

• Support
  Manufacturers able to address software updates, replacement device, electricity, internet speed, wireless access, battery life
Part 11 regulations

• Part 11- Access controls, location of source data, audit trails, record retention, validation of mobile technologies, training
• Does not address the sensitivity and specificity of the mobile technology (e.g., wearable biosensors, mobile apps, or portable devices) to measure what it is designed to measure
Communicating with FDA

- Critical Path Innovation Meeting
  - Opportunity to discuss projected use of mobile technology tool
- Drug Development Tool qualification
- Review division pre-IND meeting
  - Opportunity to discuss planned use of the mobile technology tool in a proposed drug-specific study

Resources:

- Part 11 draft guidance
  [https://www.fda.gov/downloads/drugs/guidancecompliance/communication/ucm563785.pdf](https://www.fda.gov/downloads/drugs/guidancecompliance/communication/ucm563785.pdf)
- Critical Path Innovation Meeting
- Drug Development Tool website
  [https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/](https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/)
Conclusions

• Many potential opportunities using mobile technology tools
• Need to understand the accuracy and precision of measurements
• Need to development clinically meaningful endpoints
• Avoidance of risks
• A time for innovative thinking
Digital Health: The FDA Device Perspective

Doug Silverstein
FDA
Center for Devices and Radiological Health
Renal Devices Branch
Definitions of Digital Health

- The convergence of computing power, connectivity, sensors, and software used in healthcare
- Technologies designed to be used with traditional medical products with the aim to improve healthcare outcomes for individuals
- “The cultural transformation of how disruptive technologies that provide digital and objective data leads to an equal level doctor-patient relationship with shared decision-making and the democratization of care.” (The Medical Futurist, 2017)

Source: www.fda.gov/digitalhealth
Uses for Digital Health

• Used as a medical product;
• Incorporated into a medical product (include a pharmacologic product);
• Used to develop a medical product;
• Used to study a medical product;
• Used as a companion or adjunct to a medical product, including diagnostics and therapeutics.
Examples of Digital Health Products

• Mobile health/Medical apps (mHealth)
• Software as a Medical Device (SaMD)
• Health Information Technology (IT)
• Wearable devices
• Telehealth/Telemedicine
• Personalized medicine

Source: https://www.fda.gov/MedicalDevices/DigitalHealth/default.htm
What are the Goals of Digital Health Technologies?

• Reduce inefficiencies
• Improve access
• Reduce costs
• Increase quality
• Personalize medicine (i.e., precision medicine)

Source: https://www.fda.gov/MedicalDevices/DigitalHealth/default.htm
## Regulatory Categories for Digital Health Products

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>REGULATED BY FDA?</th>
<th>PURPOSE</th>
<th>INTENDED USER</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile Medical Apps</td>
<td>Maybe/Enforcement Discretion</td>
<td>Software run on a mobile platform (e.g., smartphone) or web</td>
<td>General public</td>
<td>Provides nutritional information and tracks intake for patients with high blood pressure</td>
</tr>
<tr>
<td>Software as Medical Device (SaMD)</td>
<td>Maybe, depending on purpose and clinical condition</td>
<td>Software used for medical purpose(s) without being part of the hardware medical device but used in conjunction with the hardware</td>
<td>Various</td>
<td>Software on a digital camera to take images of a lesion; Software that collects data from an implanted cardiac pacemaker</td>
</tr>
<tr>
<td>Clinical Decision Support Software (CDSS)</td>
<td>Maybe/Enforcement Discretion</td>
<td>Lab/other clinical data intended to help make data-driven medical decisions</td>
<td>Clinicians</td>
<td>Alerts for drugs prescribing (e.g., drug-drug interactions, allergy warnings)</td>
</tr>
<tr>
<td>Patient-Decision Software (PDS)</td>
<td>Maybe/Enforcement Discretion</td>
<td>Support or provide recommendations about disease diagnosis/prevention/treatment</td>
<td>Patients/Caregivers</td>
<td>Weight management app</td>
</tr>
</tbody>
</table>

Sources: [https://www.fda.gov/MedicalDevices/DigitalHealth/default.htm](https://www.fda.gov/MedicalDevices/DigitalHealth/default.htm); FDA Guidance Document- Software as a Medical Device (SAMD): Clinical Evaluation
Not all Mobile Apps are Medical Devices-Examples

- Medical dictionaries
- Electronic copies of medical textbooks or literature articles such as the Physician’s Desk Reference (PDR) or Diagnostic and Statistical Manual of Mental Disorders (DSM)
- Library of clinical descriptions for diseases and conditions
- Encyclopedia of first-aid or emergency care information
- Medical abbreviations and definitions
- Translations of medical terms across multiple languages

Source: Mobile Medical Applications-Guidance for Industry and Food and Drug Administration Staff
# Clinical Evidence Steps for Digital Health Products

<table>
<thead>
<tr>
<th>STEP</th>
<th>QUESTION POSED</th>
<th>SOLUTION</th>
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| Valid Clinical Association              | Is the output of the product based on scientific validity—a concept or conclusion that is generally well-accepted and which corresponds to a clinical condition? | • Proof of concept, such as:  
  o Literature  
  o Society guidelines  
  o New evidence |
| Analytical/Technical Evaluation         | Is the product able to accurately, reliably, and precisely generate the output? | • Bench (performance) studies (e.g., quality management)  
  • Pre-clinical (animal) studies |
| Clinical Validation and Evaluation      | Does the product generate an output that is clinically meaningful, predictable, reliable, and associated with the target (intended) population? | • Clinical data, such as:  
  o Randomized, controlled  
  o Single arm  
  o Real world evidence  
  o Continuous learning (allows for device iteration) |

Source: FDA Guidance Document-Software as a Medical Device (SAMD): Clinical Evaluation
Clinical Trial Requirements-Sources of Clinical Data

• Existing data from studies conducted for the same intended use (real-world evidence/data);
• Existing data from studies conducted for a different intended use (extrapolation); or
• Generating new clinical data for a specific intended use (prospective trial).

*Source:* FDA Guidance Document-Software as a Medical Device (SaMD): Clinical Evaluation
Clinical Trial Requirements-CITI

• **Outcomes**: Focus on endpoints and measures that are meaningful to patients. The product should generate an output that is more meaningful and/or more informative to patients than existing products.

• **Subjects**: Optimize participant inclusion with consideration of diversity and to maximize access.

• Technology Characteristics/Human Factors: Consider the acceptability, usability, and tolerability of the technology and plan to test the technology at various sites and with multiple users.

Clinical Trial Transformation Initiative (CITI): A public-private partnership to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials.

*Source: Clinical Trial Transformation Initiative- https://www.ctti-clinicaltrials.org/briefing-room/tools*
## Clinical Trial Requirements - Categories of SaMD

<table>
<thead>
<tr>
<th>State of Healthcare Situation or Condition</th>
<th>Significance of information provided by SaMD to the healthcare decision</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Treat or Diagnose</td>
</tr>
<tr>
<td>Critical</td>
<td>IV</td>
</tr>
<tr>
<td>Serious</td>
<td>III</td>
</tr>
<tr>
<td>Non-Serious</td>
<td>II</td>
</tr>
</tbody>
</table>

Levels: I (lowest impact on health to IV (highest impact on health)

Drive clinical management: Information used to form the basis of a diagnosis or treatment plan

*Source:* FDA Guidance Document-
Software as a Medical Device (SaMD): Clinical Evaluation
Research of Automated Oxygen Devices

the CLIO system

Wes Onland
Emma Children’s Hospital Amsterdam UMC
Amsterdam, the Netherlands
Oxygen friend or foe
Without oxygen, no music
Oxygen treatment in preterms

Optimal target range?

- Mortality to discharge NNT 34
- Necrotising enterocolitis NNT 37
- Oxygen@ 36 wks PMA NNT 20
- Severe ROP NNT 34

Askie et al., Cochrane Library 2017
Oxygen treatment in neonates

Achieved vs intended SpO\textsubscript{2} target

Hagadorn et al. *Pediatrics* 2006
Closed loop principle

Pulse Oximeter

Spo₂

mFiO₂

Neonatal Nurse

cFiO₂

Computer Algorithm

FIO₂

Mechanical Ventilator

FiO₂
Closed-loop control of inspired oxygen
Studies in neonates

• >10 cross-over studies from 1979-2017
• $\text{PaO}_2$ catheter (<1990) or $\text{SpO}_2$ (>1990)
• All preterm infants
• $\text{O}_2$-dependent with or without frequent AOP
• Comparing closed-loop to manual control
• Main end point: time spent within the target range
Closed-loop control of inspired oxygen

Time spent within target range

Closed-loop control of inspired oxygen

Time above $\text{SpO}_2$ target
Closed-loop control of inspired oxygen
Prolonged desaturations (<80%, > 1 min)

Closed-loop control of inspired oxygen

Summary

• Closed-loop oxygen control is feasible
• It improves % -time within target SpO₂ by reducing time above the target
• It reduces time spend in hypoxia and hyperoxia
• Feasible at different SpO₂ targets and modes of support
• It reduces the hands-on time nurses
Looking beyond feasibility

What target range (TR) gives the best (most optimal) performance of the CLIO?

86-94% vs 88-92% vs 89-91%

Results OPTICLIO study

Compared to manual

• Similar results previous studies (more time spent within TR, less hypoxia/hyperoxia)

Narrowing the target ranges

• %-time within target SpO₂ similar in all TR ranges
• %-time in hypoxia reduced when narrowing
• %-time in hyperoxia reduced when narrowing
• However, number of episodes in hyperoxia increased using narrow TR

Questions/Topics for Discussion

Where are we now?

- Short term outcomes are promising but why not routine care?

- Increasing commercially available devices with unknown algorithms

- Is there a difference in approval process of technology for monitoring vs technology for therapeutics (nanotechnology drug delivery system)?

- What outcomes do we need (BPD, ROP, long term neurodevelopmental outcomes?)

- What would a futuristic NICU look like?

- How INC can facilitate bringing developers and approvers together?
these systems. Moreover, none of the studies investigated if automated control of FiO₂ can actually improve outcome in preterm infants. We conclude that further large-scale studies are warranted to assess the actual clinical relevance of these devices and to decide if they should become the standard of care.

The vast majority (95%) of very preterm infants receive oxygen-therapy monitored by oxygen pulse saturation (SpO₂). However, they spend a significant percentage of time out of the SpO₂ target with a high risk of severe complications such as bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP). Recently, systems allowing the automated control of inspired oxygen (FiO₂) for patient delivery to maintain target SpO₂ has been become commercially available. We reviewed literature and individuated sixteen studies on the effectiveness of automated control of FiO₂ in preterm infants. These studies demonstrate that automated devices are significantly more effective than manual control in maintaining target SpO₂ and in preventing hyperoxia, while they seem to be less effective in preventing hypoxia. The studies were very heterogeneous for design, population size, duration, and device used, and this precludes firm conclusions regarding effectiveness and best setting of these systems. Moreover, none of the studies investigated if automated control of FiO₂ can actually improve outcome in preterm infants. We conclude that further large-scale studies are warranted to assess the actual clinical relevance of these devices and to decide if they should become the standard of care.
Oxygen treatment in preterms

Benefits
- Mortality to discharge NNT 34
- Necrotising enterocolitis NNT 37

Harms
- Oxygen@ 36 wks PMA NNT 20
- Severe ROP NNT 34

Askie et al., Cochrane Library 2017
• NICHD trial

• European trial
Where are we now?

• Short term outcomes are promising but why not routine care?

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• What outcomes do we need (BPD, ROP, long term neurodevelopmental outcomes?)

• What would a futuristic NICU look like?

• How INC can facilitate bringing developers and approvers together?
**SPOC - SpO2 Controller**

Together with Ulm University Hospital, Prof. Stephan Greif has developed an automatic FIO2 control system for stabilizing SpO2 oxygen saturation at the patient. 

This oxygen saturation controller "SPOC" is now available for use with ventilators with SPOF or SPOC. In combination with SPOF, the existing SpO2 monitoring can be avoided. Ventilation units can be equipped with this new technology swiftly and cost efficiently.

SPOC helps to:
- Avoid hypoxia, thus reducing oxidative stress.
- Avoid hypoxia, reducing damage to brain tissue and brain hemorrhages.
- Reduce SpO2 variation.
- Increase the period within the SpO2 target range.
- Reduce the number of manual interventions from care staff.

**Studies??**
Questions/Topics for Discussion

Where are we now?

• Short term outcomes are promising but why not routine care?

• Increasing commercially available devices with unknown algorithms

• Is there a difference in approval process of technology for monitoring vs technology for therapeutics (nanotechnology drug delivery system)?

• What outcomes do we need (BPD, ROP, long term neurodevelopmental outcomes?)

• What would a futuristic NICU look like?

• How INC can facilitate bringing developers and approvers together?
Questions/Topics for Discussion

Where are we now?

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• Is there a difference in approval process of technology for monitoring vs technology for therapeutics (nanotechnology drug delivery system)?

• What outcomes do we need (BPD, ROP, long term neurodevelopmental outcomes?)

• What would a futuristic NICU look like?

• How INC can facilitate bringing developers and approvers together?
High frequency recording EPD
Collaboration?
Thank You

http://c-path.org/programs/inc
Coffee break
Neonatal Continuous Glucose Monitoring

Dr Chris McKinlay
University of Auckland
c.mckinlay@auckland.ac.nz
Outline: Neonatal CGM

- What is CGM?
- Why use in neonates?
- Is it accurate?
- Biomarkers for neurodevelopmental risk
- Next steps

Focus on late preterm and term neonates
# What is CGM?

Device that provides frequent glucose measurement (<15 min) without capillary blood sampling

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Biosensor</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Inline blood draw, electrochemical sensor</td>
<td>ViaMedical (GlucoScout)</td>
</tr>
<tr>
<td></td>
<td>Fluorescent tipped fibreoptic probe</td>
<td>In developed</td>
</tr>
<tr>
<td></td>
<td>Transcutaneous NIR spectroscopy</td>
<td>In developed</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Glucose binding protein (± iontophoresis)</td>
<td>In development</td>
</tr>
<tr>
<td>Interstitial</td>
<td>Amperometric needle electrode (subcutaneous tissue glucose)</td>
<td>Dexcom (G4,5,6): from 3 years Medtronic (Enlite or Guardian): from 7 years Professional (blinded) and real-time modes</td>
</tr>
</tbody>
</table>

![Image of CGM device](image_url)

- 13 mm
- 8.75 mm
- <0.4 mm thick
Why use CGM in Neonates?

Clinical objectives

- Improve neurodevelopmental outcome by
  - Optimising glycaemic control
  - Reducing heel pricks (pain stress)
- Closed-loop systems for dextrose and insulin delivery

Research objectives

- Understand pathophysiology & treatment effects (retrospective)
- Biomarkers for optimising treatment (real-time)
- Biomarkers as surrogate outcome (?)

Amperometric Needle Electrode Sensors

- **Blood Glucose (mM)**
  - **Current (nA)**

**Calibration**

- **Gold wire conducts current, processed and averaged ~5 min**
- **Peroxidase releases electrons**
- **Glucose oxidase oxidises glucose to form hydrogen peroxide**
- **Semipermeable membrane filters glucose and protects sensor**

**Sensor glucose falsely low**

Continuously shifting regression line
Inaccurate calibration point has ongoing effect
CGM accuracy limited by accuracy of calibration device
Commercial Real-time Interstitial CGM Devices

- Provide IG and trend value
- Not “general” glucose sensors
- Designed for type 1 diabetes
- Output limited to 2.2 to 22 mmol/L
- Factory set guards aim to keep BG >4.4 mmol/L
Limitations of CGM in Neonates

- Fewer sites for sensor (usually thigh)
- Wetting phase may be longer (? 4-6 hours)
- Drugs can interfere with electrochemical reaction, e.g., paracetamol
- Potential for large random errors (imprecision)
  - Increased sensor noise at low glucose concentrations
  - Tissue effects: hydration, temperature, pressure
- Few data on systematic errors (trueness)
  - Drift
  - Physiological lag
Modest point accuracy – worse at low glucose concentrations, better with more frequent calibration

Trend accuracy not assessed

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensor</th>
<th>Population</th>
<th>Reference / Calibration</th>
<th>Point accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris 2010*</td>
<td>Medtronic CGMS Gold</td>
<td>≥32 weeks NICU (N=102)</td>
<td>Gas analyser All BG</td>
<td>&lt;3 mM (186 pairs): bias -0.2 mM, 95% LOA ±1 mM</td>
</tr>
<tr>
<td>Beardsall 2013</td>
<td>Medtronic CGMS Gold</td>
<td>VLBW (N=188)</td>
<td>Various, glucometer All BG</td>
<td>MARD 8.8% 2.2-2.6 mM (584 pairs): in 50% ARD &gt;10% Hypoglycaemia: sensitivity 17%, specificity 100%</td>
</tr>
<tr>
<td>Wackernagel 2016</td>
<td>Medtronic Enlite</td>
<td>≥35 weeks NICU (N=102)</td>
<td>Glucometer q12h</td>
<td>MARD 17% (171 pairs, few &lt;3 mM)</td>
</tr>
<tr>
<td>Tiberi 2016</td>
<td>Medtronic Enlite</td>
<td>27-36 weeks (N=20)</td>
<td>Glucometer q12h</td>
<td>in 26% ARD &gt;20%; bias -0.4, 95% LOA -2.1, 1.3 mM (449 pairs few &lt;3 mM)</td>
</tr>
</tbody>
</table>

*Shifting internal algorithm used to calculate sensor glucose <2.2 mM
MARD = mean absolute relative difference
Is Neonatal CGM Accurate?

CGM is primarily a tool to help decide when to do a blood glucose measurement.
Retrospective Sensor Re-calibration

CHYLD Longitudinal Study: 477/604 (79%) children born at risk of neonatal hypoglycaemia assessed at 4.5 years
- 38% infant of diabetic; 34% preterm; 15% SGA; 13% LGA/other
- Half of infants developed hypoglycaemia
- 79% masked CGM, data commencing from 2.5-6 hours

**Blood glucose episodes**

<table>
<thead>
<tr>
<th>Severity</th>
<th>No./Total No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosensory impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>75/195 (38.5)</td>
<td>.07</td>
</tr>
<tr>
<td>Mild hypoglycemia</td>
<td>53/167 (31.7)</td>
<td></td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>51/111 (46.0)</td>
<td></td>
</tr>
<tr>
<td>Visual-motor difficulty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>3/194 (1.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Mild hypoglycemia</td>
<td>5/167 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>8/110 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>9/190 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Mild hypoglycemia</td>
<td>12/165 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>17/108 (15.7)</td>
<td></td>
</tr>
</tbody>
</table>

---

**Frequency**

<table>
<thead>
<tr>
<th>Hypoglycemia category</th>
<th>No./Total No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosensory impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>75/195 (38.5)</td>
<td>.78</td>
</tr>
<tr>
<td>1-2 Episodes</td>
<td>83/225 (36.9)</td>
<td></td>
</tr>
<tr>
<td>≥3 Episodes</td>
<td>21/53 (39.6)</td>
<td></td>
</tr>
<tr>
<td>Visual-motor difficulty</td>
<td></td>
<td>.05</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>3/194 (1.6)</td>
<td></td>
</tr>
<tr>
<td>1-2 Episodes</td>
<td>9/224 (4.0)</td>
<td></td>
</tr>
<tr>
<td>≥3 Episodes</td>
<td>41/53 (7.6)</td>
<td></td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>9/190 (4.7)</td>
<td></td>
</tr>
<tr>
<td>1-2 Episodes</td>
<td>24/222 (10.8)</td>
<td></td>
</tr>
<tr>
<td>≥3 Episodes</td>
<td>5/51 (9.8)</td>
<td></td>
</tr>
</tbody>
</table>
Hypoglycaemic CGM metrics NOT associated with outcome:
- Hypoglycaemic index (average discursion below thresholds)
- Negative glucose increment (area below thresholds)
- Glucose miles (length of CGM curve)

Main predictor of risk appears to be “episodes” (dose-response)
- Among at-risk babies with normal BG, 22% had undetected hypoglycaemic episodes on CGM
- Undetected episodes (≥10 min) associated with a 4-fold increased risk of executive function difficulties

McKinlay: JAMA Pediatr 2017;171(10):1-12
Biomarkers for Neurodevelopmental Risk: Glucose Stability

Neurosensory Impairment 2 years

**Interstitial Glucose**
- Percent of time outside central band during the first 48 hr
  - (Q1–5: 0, 23, 41, 57, 74%)
  - \( \Delta IG = 2.9 \) (95% CI, 0.5–5.2) \( P = 0.02 \), \( IG^{*t} P = 0.94 \)

Neurosensory Impairment 4.5 years

**IG % of time outside central band <48 h (n = 369)***
- 5 Quintile
- 4 Quintile
- 3 Quintile [Referent]
- 2 Quintile
- 1 Quintile

Biomarkers for Neurodevelopmental Risk: Glucose Stability

Relationship between neurosensory impairment and IG 6 hours post onset of hypoglycaemia (adjusted for baseline BG, N=139)

Odds ratio (95% CI)

4.2-6.0 h

0.4-2.3 h
Novel Biomarkers: State Change

Novel Biomarkers: State Change

Novel Biomarkers: Stochastic Modelling

- IG value related to expected probability function derived from previous CGM behaviour
- Values outside confidence limits indicate unusual behaviour
e.g., sensor error, fluid or feed change, illness etc

Next Steps...What We Need...

• Neonatal-specific CGM system
  • Option of masked recording, guards, trend, or real-time IG
  • Output <2.2 mmol/L

• Optimise calibration
  • Standard for acceptable calibration devices(s)
  • Identify optimal calibration frequency and conditions

• Flexible guards for “out of range”...ability to combine with third party software
  • Probability score based on trend and current value
  • Ideally incorporating insulin sensitivity modelling

• Specific guards for change after hypoglycaemia

• Clinical trials of CGM to
  • Target blood testing: reduce heel pricks while decreasing frequency of episodes
  • optimise treatment of hypoglycaemic episode (?)

• At this stage, the endpoint still has to be long-term neurocognitive function
New Zealand Team

Jane Harding  
Deb Harris  
Greg Gamble  
J Geoff Chase
Systematic Errors

Drift
- Changing properties of the probe surface over time, e.g., biofilm
- Different sensor current for same interstitial glucose concentration

Lag
- Time delay between plasma and interstitial compartments when glucose is changing rapidly ($\geq 30$ min)
- Increasing positive error when glucose is falling and negative error when glucose is rising
- Accurate calibration requires stable glucose in range

Induced hypoglycaemia in preterm lambs (N=15)

95% LOA 2, -1 mM -2, -6 mM

Harris: Neonatology 2009;95(4):271-8
Physiological Lag

Increasing negative error when glucose is rising

Increasing positive error when glucose is falling

CGM performs best when glucose is stable in range

Novel Biomarkers: State Change

**CHYLD Study CGM First 48 hours**  
N=366

<table>
<thead>
<tr>
<th>Number of state changes</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21%</td>
</tr>
<tr>
<td>1</td>
<td>55%</td>
</tr>
<tr>
<td>2</td>
<td>16%</td>
</tr>
<tr>
<td>3</td>
<td>8%</td>
</tr>
<tr>
<td>≥4</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Direction of state change (all)**  
N=407

<table>
<thead>
<tr>
<th>Increase</th>
<th>60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease</td>
<td>40%</td>
</tr>
</tbody>
</table>

**Median (IQR) ΔIG (mmol/L)**  
0.6 (0.4, 0.9)

**Maximum ΔIG (mmol/L)**  
2.8
The International Neonatal Consortium

Jonathan Davis, Lynn Hudson, Ron Portman, Mark Turner, - Directors

May 1-3, 2019
1:30 - 3:00 p.m. Applying Digital Technologies to Developing Endpoints for Neonatal Trials
MARK TURNER (U. LIVERPOOL AND INC CO-DIRECTOR) AND PRAKESH SHAH (UNIVERSITY OF TORONTO), co-chairs

3:00 – 3:30 p.m. COFFEE BREAK

3:30 – 4:45 p.m. INC Workstream Updates
RONALD PORTMAN (Novartis, INC Co-Director), chair

4:45 p.m. Closing Remarks – JON DAVIS (TUFTS U AND INC CO-DIRECTOR)

5:00 p.m. FULL WORKSHOP ADJOURNS
INC WorkStream Updates

Ron Portman
Dated – Monday April 22, 2019

Dear Dr. Soul,

Congratulations on your accepted paper in *Pediatric Research!* The Editors in Chief are excited to notify you that your paper has been selected for highlight in the Editor’s Focus for the June 2019 print issue.

https://doi.org/10.1038/s41390-018-0242-2

We encourage you to let your department chair know that your paper has been selected for highlight and publicize your article. Congratulations again and thank you for your contributions to *Pediatric Research!*

Best Regards,

Lauren Overbey
Managing Editor
Pediatric Research
LAUNCH 1ST ANNUAL WORKSHOP

2015

- Global Efforts to Accelerate Newborn Therapy Development. *SOATT Newsletter*, 2015

2017


2018


2020

- Observed Ranges of Blood Pressure Measurements in Neonates (Planned)
- Factors that Influence Blood Pressure in neonates and infants (Planned)
- Retrospective Validation of the Neonatal Adverse Event Severity Scale
- Prospective Validation of the Neonatal Adverse Event Severity Scale (Planned)
- NICU Stakeholder Survey Results and Key Messages (In Development)
- Proper Method of Blood Pressure Measurement is Critical in Neonates and Infants: A Systematic Review and Analysis (In Development)
- Standardizing Safety Assessment and Reporting for Trials (Submitted to INC Coordinating Committee)
- Development of a Neonatal Adverse Event Severity Scale (Submitted, Archives of Disease in Childhood)
- Long Term Neurodevelopmental Outcome Following Trials of Medicinal Products in Neonates (In Review, Pediatric Research)
- Therapies to Prevent or Treat Retinopathy of Prematurity (In Press JAMA Ophthalmology)
Hemodynamic Adaptation

Simin Baygani (Eli Lilly) and Stephen Bremner (Brighton Sussex Medical School)

May 3, 2019
Hemodynamic Adaptation Workgroup Members

• Heike Rabe - Brighton & Sussex Medical School, Co-Chair
• Janis Dionne - BC Children’s Hospital, Co-Chair
• Dina Apele-Freimane - PDCO
• Beau Batton - Southern Illinois University SOM
• *Simin Baygani - Lilly
• Varsha Bhatt-Mehta - University of Michigan
• *Stephen Bremner - Brighton & Sussex Medical School
• Gene Dempsey - University College Cork, Ireland
• Ebru Ergenekon - Gazi University
• Hiroko Iwami - Osaka City General Hospital, Japan
• Agnes Klein - Health Canada
• Luana Pesco Koplowitz - DUCK FLATS Pharma
• Doug Silverstein - FDA
• Bob Ward - University of Utah
• Lynn Hudson - Critical Path Institute, INC Co-Director
• Ron Portman - Novartis, INC Co-Director
• Mark Turner - University of Liverpool, INC Co-Director

Early contributors, no longer active: Martin Kluckow, Yan Chen, Huihui Luo, Claudwynne Faulkner
Research Questions

- Question 1: What are the observed ranges of blood pressure (BP) by gestational ages, weight, and postnatal age in babies who have not received any modifying treatments?

- Question 2: What other factors influence BP and how? (Criteria 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)

- Question 3: What are the recommended measurement methods? (to include a characterization of each method and any limitations to each method.)
Question 3: What are the recommended measurement methods?
• Measuring BP in neonates & infants critically important but technically challenging
• BP reflects perfusion, fluid status, cardiac & endocrine function, illness
• Limited literature to guide clinicians & researchers on measurement technique
• Current practice informed by literature often decades old, when technology & neonatal populations were different
• Need to analyze the literature, synthesize appropriate data into recommendations, & outline further research needs
Flow Diagram of Article Numbers

OVID Medline 1946 to present
2115 Citation(s)

OVID Embase 1974 to 2017 Week 03
3056 Citation(s)

Cochrane Library Releases January 2015 to January 2017
128 Citation(s)

3606 Non-Duplicate Citations Screened

Inclusion/Exclusion Criteria Applied
2985 Articles Excluded After Title/Abstract Screen

602 Articles Retrieved

Inclusion/Exclusion Criteria Applied
388 Articles Excluded After Full Text Screen
5 Articles Excluded During Data Extraction

201 Articles Included
Universal standard for BP device validation published: collaboration of Association for the Advancement of Medical Instrumentation, European Society of Hypertension & International Organization for Standardization

Recommend > 85 participants for a validation study

Special populations (e.g. neonates), > 35 participants; many published neonatal studies would not fulfill this criterion

BP device considered acceptable if mean BP difference is ≤ 5 mmHg with SD ≤ 8mmHg

By this criterion, 5-13 mmHg differences in BP readings in neonates with expected values in the 30-50 mmHg range would imply a difference of 10-40% of BP. Such large differences unacceptable for clinical care & research
Cuff Size
Optimal BP Cuff Size

RECOMMENDATION
(based on 4 papers):

cuff width to arm circumference ratio of
~0.5 should be used for non-invasive BP
measurements obtained by oscillography
Location of Measurement
RECOMMENDATIONS

• Upper arm BPs are the recommended location for oscillometric BP measurements.

• Calf BP may be considered only in the earliest days of life or if there is a contra-indication to arm BP measurements.

• Right upper arm is preferred to left in case of coarctation of the thoracic aorta.
Measurement Method
Found 20 papers comparing different methods of BP measurement

Most of these were concerned with non-invasive (oscillometric) versus the reference standard i.e. invasive (radial or umbilical)

In a small number of papers, non-invasive methods (or similar devices) were compared to one another and one compared invasive with non-invasive at different sites

Several studies reported mean BP only

36 comparisons MBP, 20 each of DBP, SBP.

Studies were generally small; 11/20 were in fewer than 35 neonates

Bias is defined as the mean of the differences between paired BP measurements using each method, in most entries on the following plots: direct (intra-arterial) – indirect (non-invasive).

HA Workgroup agreed that acceptable bias in BP measurement would be ±5 mmHg with a standard deviation of 5 mmHg. These define 95% limits of agreement at -14.8 & 4.8 mm Hg when the bias is negative, -4.7 & 14.8 mmHg when bias is positive.
Sample figure

Figure 1: Mean BP

- Papadopoulos, 1999, HP
- O'Shea, 2009, Dnapmap
- Ribeiro, 2011, Crit, IL, Dop-Osc
- Zhou, 2016, nore
- Takol, 2012, MAP<30
- Ribeiro, 2011, Dop-Osc
- Long, 1985
- Zhou, 2016, hypo
- Pichler, 1988, Dina-HP
- O'Shea, 2009, Dash
- Konig, 2011, RA>1000g
- Papadopoulos, 1999, Dnapmap
- O'Shea, 2009
- Baker, 1984, upper
- Papadopoulos, 1999, SpaceLabs
- Konig, 2011, RA>1000g
- Wareham, 1997
- Baker, 1984, lower
- Nelson, 2002
- Shimokaze, 2015
- Konig, 2011, RA<751g
- Meyer, 2010, 1010-1490g
- Meyer, 2010, 495-995g
- O'Shea, 2009, Marquatta
- Takol, 2012
- Lalan, 2014, IAC
- Langbaum, 1994
- Meyer, 2010, 1590-2550g
- Liu, 1998
- Konig, 2011, RA<751g
- Vassilinov, 2006
- Konig, 2011, RA<751g
- Lalan, 2014, radial
- Dasnadi, 2015
- Troy, 2009

Mean of Direct-Indirect MBP (mm Hg)

-45 -40 -35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30 35 40 45
• Majority of published literature does not provide confidence that non-invasive (mainly oscillometric) BP measurements give readings that are close to the reference standard.

• The 95% limits of agreement are far apart and represent an unacceptable and significantly large interval within the range of neonatal BPs.
Proper Method of BP Measurement is Critical in Neonates and Infants: A Systematic Review and Analysis

Janis M. Dionne MD1, Stephen A. Bremner2, Simin K. Baygani3, Beau Batton MD4, Ebru Ergenekon5, Varsha Bhatt-Mehta6, Gene Dempsey7, Martin Kluckow8, Luana Pesco Koplowitz9, Dina Apele-Freimane10, Hiroko Iwami11, Agnes Klein12, Mark Turner13 and Heike Rabe MD2 on behalf of the International Neonatal Consortium14
Question 2:
Which maternal, perinatal and infant factors affect BP?
What other factors influence BP and how?

Criteria 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, cord management
Question 2 Flowchart

- OVID Medline: 1946 – Present, 2115 Citations
- OVID Embase: 1974 – 2017, 3056 Citations
- Cochrane Library: 2015 – 2017, 128 Citations

3606 records after duplicates removed

3606 records screened by title and abstract

2985 records excluded due to language, irrelevance to all questions

621 full-text articles assessed for eligibility

598 full-text articles excluded due to irrelevance to sub-question

23 articles included for data extraction

8 full-text articles excluded due to lack of extractable data

15 studies included in review
Question 2: Maternal Factors

- **Sociodemographic factors**
  - Age (5 studies, variable results, 2 studies report increased BP with maternal age > 40 y)
  - Race (3 studies report a variable correlation of higher BP in babies of African decent)
  - Socio-economic class (1/3 studies report a higher BP for babies of mothers of low socio-economic class)

- **Maternal Health**
  - Body Mass Index (1 study BMI > 30)
  - Maternal BP (conflicting results, 2 studies report on higher BP for preterm or term babies, especially with pre-eclampsia)
  - Maternal diabetes (1 study preterm infants had higher BP)

- **Maternal Medication and Smoking**
  - Medications (to be determined)
  - Smoking (2 studies, no. of daily cigarettes 15/d)
Question 1: What are the observed ranges of BP?
Progress and plans

• Shell tables drafted and layout tested with 7 articles

• Initial discussion identified gestational age and birthweight as main covariables

• Iterative process of data extraction and presentation
• Mike Padula (Chair) - Children’s Hospital of Philadelphia; PEDSnet
• Maria Bocchi - Chiesi
• Laura Fabbri - Chiesi
• Isabella Montagna - Chiesi
• George Chang - NCI-EVS
• Theresa Quinn - NCI-EVS
• Dominique Haumont - St-Pierre University Hospital
• Bill Hess - FDA
• Tsai, Yijing (CoCo) - FDA
• Phong Do - FDA
• Steve Hirschfeld - NIH
• Devon Kuehn - Paidion Research, Inc.

• Neena Modi - Imperial College London
• Prakesh Shah - Canadian Neonatal Network/University of Toronto
• Mary Short - Eli Lilly
• Roger Soll (VON) - Vermont Oxford Network
• Mark Turner - University of Liverpool
• Laura Butte - C-Path
• Diane Corey - C-Path
• Lynn Hudson - C-Path
Terminology Workgroup Aims

• To develop a set of terms and concepts to support clinical investigation involving therapies for neonates and infants

• Establish a common meaning for these concepts of interest (e.g., diagnoses, conditions, or findings)

• Define the criteria necessary to confirm their presence while differentiating them from other similar but distinct concepts
  • prevent misclassification

• Provide suggested lists of terms/concepts with their supporting granular criteria for data collection (not just a binary “Yes”/“No”)
  • Facilitate secondary use of data for meta-analyses, future study design, severity stratification, and to establish relationship with other “Real World” sources

• While the primary purpose is to support clinical trials, we will also evaluate how the selected concepts and criteria align with existing precedents from clinical trials and quality improvement registries
Lessons from Past...Guiding Future Direction

The Johns Hopkins University Evidence-based Practice Center systematic review of the effect of inhaled nitric oxide on the severity of bronchopulmonary dysplasia in the randomized controlled trials was compromised by the wide variation in bronchopulmonary dysplasia definitions and other study parameters. The Johns Hopkins University Evidence-based Practice Center analysis concluded that insufficient data are available to perform a meta-analysis for any measure of severity due to the lack of uniformity in definitions and study measures used. There is insufficient

Trial 1 used A+B
Trial 2 used A alone
Trial 3 used A+C

[X] Oxygen support at 36 weeks PMA
[ ] Failed oxygen challenge
[ ] characteristic X-ray findings
Supporting future neonatal trials...Establishing commonly defined terms

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

*Thank you (more welcomed)

Recently Concept Review

Core Neonatal Terminology Set + domain specific terms

- maternal/antenatal
- neurologic
- hemodynamic
- respiratory
- adverse events
- genetic
- endocrinologic
- heme
- ophthalmologic
- renal/electrolyte

Establish a library of INC terms for use in trials
AGENDA (8am – 12pm)
• Introduction/Background
• Desired goals and deliverables
  • Establish relationship to other initiatives
• Review of progress to-date
• COFFEE BREAK
• Plan action items & schedule
• Promotion of initiative
• Conclusion

**We very much welcome input from other subgroups and subject matter experts to leverage your existing and ongoing work**
Adverse Event Severity Scale

Karel Allegaert, Thomas Salaets (University of Leuven)

May 3, 2019
Background

Assessing AE’s

- Assess severity
- Determine seriousness
- Determine causality
- Determine expectedness
- Observe and recognize AE
- Assess seriousness regulatory definition
- Assess causality regulatory guidance
- Notify IRB and regulators of SUSAR
Clinical signs and symptoms: baby given first immunisations on 14/02/17 approximately 14:30pm. At 23:00 there is first documentation of frequent desaturations down to 20%, bradycardias and apnoeas which required bagging. Further documentation of these episodes continues throughout the night requiring bagging and vigorous stimulation. Documented with these concerns is acknowledgement that baby had immunisations recently and consultant on ward round on 15/02 confirms this association is likely. There was also a rise in CRP during this time period- baby was screened but cultures were negative at 24 and 36 hours. These episodes continue on 15/02 then seem to settle over 16th and 17th of Feb. Baby was given 5 days of antibiotics just in case imms were masking further problem.

Mild? Moderate? Severe? Life-threatening?

<table>
<thead>
<tr>
<th>Score</th>
<th>Study A</th>
<th>Study B</th>
<th>Study C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
<td>—</td>
<td>Missing or unknown</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
<td>Mild</td>
<td>Very mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>Severe</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Very severe</td>
<td>Not assessed or missing</td>
<td>Serious</td>
</tr>
<tr>
<td>5</td>
<td>Not assessed</td>
<td>—</td>
<td>Very serious</td>
</tr>
<tr>
<td>6</td>
<td>—</td>
<td>—</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>9</td>
<td>Unknown</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

## Work flow

<table>
<thead>
<tr>
<th>PHASE 1: GENERIC SEVERITY CRITERIA</th>
<th>PHASE 2: SPECIFIC SEVERITY CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey 1</td>
<td>Meeting 2</td>
</tr>
<tr>
<td>Dec 2016 – Jan 2017</td>
<td>11th of April 2018</td>
</tr>
<tr>
<td>Survey 2</td>
<td>Survey 3</td>
</tr>
<tr>
<td>Feb 2017 – Mar 2017</td>
<td>June 2018</td>
</tr>
<tr>
<td>Meeting 1</td>
<td></td>
</tr>
<tr>
<td>27th of March 2017</td>
<td></td>
</tr>
<tr>
<td>Pilot validation</td>
<td></td>
</tr>
<tr>
<td>Dec 2017 – Jan 2018</td>
<td></td>
</tr>
<tr>
<td>Anonymous stakeholder survey</td>
<td>Anonymous stakeholder survey</td>
</tr>
<tr>
<td>to identify the aspects of an AE</td>
<td>to review the draft specific</td>
</tr>
<tr>
<td>determining severity, to gauge</td>
<td>severity criteria for 35 AE’s</td>
</tr>
<tr>
<td>ideas about a general framework</td>
<td></td>
</tr>
<tr>
<td>and to gather a priority list for</td>
<td></td>
</tr>
<tr>
<td>AE’s to be included</td>
<td></td>
</tr>
<tr>
<td>Anonymous stakeholder survey</td>
<td>Half day face to face</td>
</tr>
<tr>
<td>to review a proposal for generic</td>
<td>meeting in thematic working groups</td>
</tr>
<tr>
<td>severity criteria based on and</td>
<td>to draft specific severity criteria</td>
</tr>
<tr>
<td>embedded in the results of the</td>
<td>for common neonatal adverse events</td>
</tr>
<tr>
<td>first survey.</td>
<td>on the priority list.</td>
</tr>
<tr>
<td>Multiple observers graded 19 AE</td>
<td></td>
</tr>
<tr>
<td>case reports based on the</td>
<td></td>
</tr>
<tr>
<td>consensus generic severity</td>
<td></td>
</tr>
<tr>
<td>criteria in order to check face</td>
<td></td>
</tr>
<tr>
<td>validity and measure inter</td>
<td></td>
</tr>
<tr>
<td>observer agreement.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**WHAT**

- **Anonymous stakeholder survey** to identify the aspects of an AE determining severity, to gauge ideas about a general framework and to gather a priority list for AE’s to be included.
- **Anonymous stakeholder survey** to review a proposal for generic severity criteria based on and embedded in the results of the first survey.
- **Full day face to face meeting** to discuss and modify the proposed generic severity criteria.
- **Multiple observers graded 19 AE case reports** based on the consensus generic severity criteria in order to check face validity and measure interobserver agreement.
- **Half day face to face meeting in thematic working groups** to draft specific severity criteria for common neonatal adverse events on the priority list.
- **Anonymous stakeholder survey** to review the drafted specific severity criteria.

**WHO**

- **55 respondents**
  - C, I, N, P, R*
- **36 respondents**
  - C, I, N, P, R*
- **32 participants**
  - C, I, N, R*
- **12 observers**
  - C, I, N, R*
- **43 participants**
  - C, I, R*
- **51 respondents**
  - C, I, R*

**OUTCOME**

- **Identification of immediate functional consequences, treatment, supportive measures, hospitalization and long term outcome as determinants of AE severity. Priority list for neonatal AE’s to be included in severity scale v1.0.**
- **71.8% agreement with the proposed generic severity criteria. Comments to improve the generic severity criteria.**
- **Consensus on generic severity criteria.**
- **Overall χ² = 0.23. Modifications made to determinants with low interobserver agreement.**
- **Draft specific severity criteria for 35 typical and common neonatal AE’s.**
- **≥80% agreement on the criteria for 23/35 AE’s. Improvement of criteria based on feedback.**

**Milestone:** Final generic severity criteria

**Milestone:** Final specific severity criteria for 35 AE’s
# INC NAESS v1.0

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Life threatening</td>
<td>Death</td>
</tr>
<tr>
<td>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</td>
<td>Moderate; resulting in minor changes of baseline age-appropriate behavior*; requiring minor changes in baseline care or monitoring***</td>
<td>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****</td>
<td>Life-threatening; Resulting in life-threatening changes in basal physiological processes**; requiring urgent major change in baseline care</td>
<td>Death related to AE</td>
</tr>
</tbody>
</table>

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### AEs in INC neonatal AE severity scale

<table>
<thead>
<tr>
<th>Neurological</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Convulsion</td>
<td>Infantile Apnea</td>
</tr>
<tr>
<td>Neonatal Epileptic Seizure</td>
<td>Neonatal Respiratory Insufficiency</td>
</tr>
<tr>
<td>Neonatal Intraventricular Hemorrhage</td>
<td>Neonatal Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>Retinopathy of Prematurity</td>
<td>Neonatal Pulmonary Hemorrhage</td>
</tr>
<tr>
<td>Hypoxic Ischemic Encephalopathy</td>
<td>Persistent Pulmonary Hypertension of the Newborn</td>
</tr>
<tr>
<td>Periventricular Leukomalacia</td>
<td>Neonatal Pneumothorax</td>
</tr>
<tr>
<td>Infant Irritability</td>
<td>Bronchopulmonary Dysplasia</td>
</tr>
<tr>
<td>Infant Sedation</td>
<td></td>
</tr>
</tbody>
</table>

### Cardiovascular

<table>
<thead>
<tr>
<th></th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Hypotension</td>
<td>Neonatal Diarrhea</td>
</tr>
<tr>
<td>Neonatal Hypertension</td>
<td>Infantile Vomiting</td>
</tr>
<tr>
<td>Neonatal Sinus Tachycardia</td>
<td>Feeding Intolerance</td>
</tr>
<tr>
<td>Neonatal Sinus Bradycardia</td>
<td>Neonatal Gastrointestinal Bleeding</td>
</tr>
<tr>
<td>Neonatal Tachyarrhythmia</td>
<td>Neonatal Spontaneous Intestinal Perforation</td>
</tr>
<tr>
<td>Neonatal Bradyarrhythmia</td>
<td>Neonatal Constipation</td>
</tr>
<tr>
<td>Neonatal Edema</td>
<td></td>
</tr>
<tr>
<td>Neonatal Sinus Bradycardia</td>
<td></td>
</tr>
</tbody>
</table>

### Gastrointestinal

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Culture Positive Sepsis</td>
<td>Neonatal Rash</td>
</tr>
<tr>
<td>Neonatal Culture Negative Sepsis</td>
<td>Neonatal Administration Site Complication</td>
</tr>
</tbody>
</table>

---

*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 asymptomatic treatments

****Major care changes constitute: surgery, addition of long-term treatment, upscaling care level

If the different factors of this scale result in conflicting severity grades, **the highest grade** should be reported.
**Work flow: integration with MedDRA and NCI-Thesaurus**

<table>
<thead>
<tr>
<th>Phase 1: Generic Severity Criteria</th>
<th>Phase 2: Specific Severity Criteria</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survey 1</strong>&lt;br&gt;Dec 2016 – Jan 2017</td>
<td><strong>Meeting 1</strong>&lt;br&gt;27th of March 2017</td>
<td><strong>Integration in terminology</strong>&lt;br&gt;September 2018</td>
</tr>
<tr>
<td>Anonymous stakeholder survey to identify the aspects of an AE determining severity, to gauge ideas about a general framework and to gather a priority list for AE’s to be included</td>
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<td>Anonymous stakeholder survey to review the drafted specific severity criteria.</td>
</tr>
<tr>
<td><strong>Survey 2</strong>&lt;br&gt;Feb 2017 – Mar 2017</td>
<td><strong>Pilot validation</strong>&lt;br&gt;Dec 2017 – Jan 2018</td>
<td><strong>Survey 3</strong>&lt;br&gt;June 2018</td>
</tr>
<tr>
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<td><strong>INC, NCI-EVS and MedDRA</strong></td>
</tr>
<tr>
<td><strong>Meeting 2</strong>&lt;br&gt;11th of April 2018</td>
<td><strong>Anonymous stakeholder survey</strong>&lt;br&gt;to review the drafted specific severity criteria.</td>
<td>All 35 AE’s linked to MedDRA terms, all AE’s and severity grades available on NCI-EVS with a definition.</td>
</tr>
<tr>
<td><strong>PHASE 3</strong></td>
<td><strong>Milestone: Final specific severity criteria for 35 AE’s</strong></td>
<td><strong>Milestone: Publicly available AE severity criteria</strong></td>
</tr>
<tr>
<td><strong>WHAT</strong></td>
<td><strong>Identification of immediate functional consequences, treatment, supportive measures, hospitalization and long term outcome as determinants of AE severity. Priority list for neonatal AE’s to be included in severity scale v1.0.</strong></td>
<td><strong>Milestone: Final generic severity criteria</strong></td>
</tr>
<tr>
<td><strong>WHO</strong></td>
<td><strong>36 respondents C, I, N, P, R</strong>&lt;br&gt;71.8% agreement with the proposed generic severity criteria. Comments to improve the generic severity criteria.**</td>
<td><strong>INC, NCI-EVS and MedDRA</strong></td>
</tr>
<tr>
<td><strong>OUTCOME</strong></td>
<td><strong>32 participants C, I, N, R</strong>&lt;br&gt;Consensus on generic severity criteria.**</td>
<td><strong>Milestone: Publicly available AE severity criteria</strong></td>
</tr>
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<td><strong>Milestone: Final specific severity criteria for 35 AE’s</strong></td>
</tr>
</tbody>
</table>
Integration with MedDRA and NCI-Thesaurus Terminology

NCIt

MedDRA v22 (March 2019)

Congenital and neonatal arrhythmias (SMQ)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>SMQ Code</th>
<th>SMQ Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1577</td>
<td>Narrow A</td>
<td>Arrhythmia neonatal</td>
<td>10003124</td>
</tr>
<tr>
<td>1578</td>
<td>Narrow A</td>
<td>Arrhythmogenic right ventricular dys</td>
<td>10058093</td>
</tr>
<tr>
<td>1579</td>
<td>Narrow A</td>
<td>Atrophic ventricular node dispersion</td>
<td>10077893</td>
</tr>
<tr>
<td>1680</td>
<td>Narrow A</td>
<td>Brugada syndrome</td>
<td>10059027</td>
</tr>
<tr>
<td>1681</td>
<td>Narrow A</td>
<td>Foetal arrhythmia</td>
<td>10016847</td>
</tr>
</tbody>
</table>
INC NAESS v1.0 is publicly available
Terminology: published on NCI - Thesaurus

https://evs.nci.nih.gov/ftp1/INC/Adverse_Events_Terminology/

For download:
https://evs.nci.nih.gov/ftp1/INC/

User friendly interface:
Manuscript submitted

DEVELOPMENT OF A NEONATAL ADVERSE EVENT SEVERITY SCALE

Thomas Salaets, MD, Mark A. Turner, MD, PhD, Mary Short, MSN, Robert M. Ward, MD, Isamu Hokuto, MD, Ronald Ariasno, MD, Agnes Klein, MD, Sandra Beauman, MSN, Kelly Wade, MD, PhD, Merran Thomson, MBChB, Eve Roberts, MD, PhD, Judy Harrison, MD, Theresa Quinn, RN, BS, Gerri Baer, MD, Jonathan M. Davis, MD, Karel Allegaert, MD, PhD for the International Neonatal Consortium

AFFILIATIONS:
1 Department of Development and Regeneration, KU Leuven, Leuven, Belgium
2 Institute of Translational Medicine, University of Liverpool, Liverpool, UK
3 Eli Lilly & Co, Indianapolis, Indiana

Submitted to Archives of Disease in Childhood on 11th of April
Ongoing work

- Validation: assess interobserver variability
  - Prospective validation:
    - protocol ready: discussion tomorrow
    - 5 centers participating: Kansas City, Liverpool, Leuven, Rotterdam, Canadian center

- Retrospective validation: recruiting volunteers
- INC NAESS v2.0: lab values and other AE’s to be included
Standardizing Safety Reporting

(Gerri Baer – FDA, Jon Davis – Tufts University)

May 3, 2019
Communications

Christina Bucci-Rechtweg (Novartis), Jennifer DeGl (Speaking for Moms and Babies, Inc.)

May 3, 2019
Background

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
Comms WG activities since close of survey

- Survey closed 23-November-2018

- Data exported from Survey Monkey and analyzed
- 3 Comms WG Meetings to review survey results
- FINAL Results study deck developed (127 slides) for C-Path
- 3 Comms WG Meetings (in addition to offline work) to develop ‘Key Messages Supporting Data’ document
- Initiation of ‘Call to Action’ activities – brainstorming activity completed
- 2 Coordinating Committee status updates (12-Dec-18, 15-Mar-19) provided
Sample Results - Demography

**Neonatologists**
(n = 52)
- United States (38.5%)
- Canada (1.9%)
- EU/EEA (38.5%)
- Switzerland (1.9%)
- Japan (9.6%)
- Other {Argentina, Mexico, Ecuador, Australia} (9.6%)

**Nurses**
(n = 188)
- United States (78.7%)
- Canada (3.2%)
- EU/EEA (9.6%)
- Japan (3.2%)
- Other {New Zealand, Middle East, Australia, Africa, Southeast Asia, Thailand} (5.3%)

**Parents**
(n = 83)
- United States (66.3%)
- Canada (2.4%)
- EU/EEA (21.7%)
- Brazil (4.8%)
- Japan (1.2%)
- Other {Argentina, Taiwan, Australia} (3.61%)
The medications currently available in the NICU are sufficient to meet the medical needs of sick newborns (% respondents)

Neonatologists
N = 38

Nurses
N = 141

Parents
N = 60

<table>
<thead>
<tr>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
<th>Unsure</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.2%</td>
<td>13.2%</td>
<td>5.3%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>30.5%</td>
<td>20.6%</td>
<td>36.2%</td>
<td>5%</td>
<td>2.1%</td>
<td>0%</td>
</tr>
<tr>
<td>13.3%</td>
<td>16.7%</td>
<td>35%</td>
<td>11.7%</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Legend:
- Strongly Disagree
- Disagree
- Neutral
- Agree
- Strongly Agree
- Unsure
Next Steps (1)

- Results publication(s)

1. Agreed publication plan - Journal supplement or series
   - Proposed – methodology paper, primary results paper, ‘Call to Action’ paper, stakeholder targeted papers
   - Target journal(s) discussed – to socialize proposal with selected editors
2. Continue ‘Key Messages & Supportive Results’ development in addition to mapping the ‘Proposed Actions’ to build foundation for ‘Call to Action’
3. Identification of writing leads for primary results paper sections
   - Proposed plan to present results for each of the 5 survey sub-topics (each lead by a writing lead)
4. Proposed timeline for development of 1) methodology and 2) primary results papers for submission – end of year 2019
Next Steps (2)

- Additional proposals
  - Webcast to INC membership of survey results (Summer/Fall 2019)
  - Identification of objectives and targeted messages for stakeholder targeted papers
Next Steps (3)

- Call for new INC Comms WG contributors

Interested parties, please contact:

- Sarah Spieth (sspieth@c-path.org)
- Christina Bucci-Rechtweg (christina.buccirechtweg@novartis.com)
- Jennifer Degl (jenniferdegl@gmail.com)
THANK YOU
The International Neonatal Consortium

Lynn Hudson – Executive Director
Jonathan Davis, Ron Portman, Mark Turner – Co-Directors

May 1 – 3, 2019
Pain Session
Opioids and Pain

• The US has a lot of people in pain – we write 80% of the world’s opioid prescriptions
• Need to safely reduce the number of prescriptions, number of pills – people are sharing
• Neonates can respond to noxious stimuli, but changes significantly >34 weeks gestation
• A variety of pain scales being used; minimal/no standards, subjective, variable, non-specific
• Physiologic indicators non-specific; EEG, MRI, salivary biomarkers (cortisol, catechols)
• What are the best outcome measures (meticulous data collections)?
• Can’t extrapolate from adults – need PK, safety, efficacy data
• A variety of clinical trials have been conducted – “add-on” are most common
• Dosage related to genetics, developmental changes, physiologic stability/instability
• Neopain – MS was not beneficial in ventilated preterm neonates, some GA with more WMI
• MS dosing likely too high – modeling can help reduce dosage by 66-75%
• POPPI stopped due to increased SAEs (apnea, hypoxemia, bradycardia, more respiratory support)
• Alternatives – paracetomol, ibuprofen, dexmedetomidine, sweet-ease (discuss with regulators)
Opioids and NAS

- Definitions of NAS needs further study/delineation (what are the neonates actually withdrawing from)
- Highly variable approaches to NAS (non-pharm/pharm)
- Significant uncertainty on who to treat, when to treat, how to treat, how to wean, the best agents to use
- NAS assessment tools – streamlined, less subjective, and more accurate/specific (voice analyzers, salivary biomarkers)
- Current outcomes are focused on clinical care; need better short and long-term outcomes (with standard/validated instruments) that are more patient centered
Opioids and NAS

- Common data elements, data dictionaries, interoperability, RWD
- Data important to parents, clinicians, regulators, researchers, policy makers
- Reducing stress in neonates, parents, caregivers
- SUPPORT – EDUCATION - TREATMENT
- Concerns over safety of formulations
- Concerns over infrastructure/equipoise
- Genetic/epigenetic analyses may be important
- Validated screening, assessment, and precision medicine approaches to optimize care
Digital Technologies

• The right device for the right patient at the right time…
• Need for prospective safety data
• Practicality collecting large scale data – storage, multiple sources
• Innovative approaches
• Registries, don’t “re-invent” data
• Machine learning, Artificial Intelligence – what new data/endpoints can be captured
• Matching physiologic data with medical records
• Genomic data – highly complicated and not able to de-identify
• Predictive variables and algorithms
• Communication with regulators in advance
Digital Technologies

- Mobile technologies
- Making devices compatible with neonates (smaller and faster)
- Essential to evaluate and validate
- Reliable data across multiple institutions – change the research paradigm completely
- Continuous glucose monitoring and automated oxygen control systems – unique challenges for neonates
- What should the outcome measures be for these types of clinical devices/trials?
  1. Advocate for big databases
  2. Describe the state of the art
Thank You