Second Annual Neonatal Scientific Workshop

Welcome

March 7th – 8th, 2016
FDA White Oak Campus, Silver Spring, MD
Agenda – March 7th, Morning

9:00 am  Welcome – Jon Davis (INC Co-Director, Tufts U.)

9:10 am  Regulatory Science for Neonates – Rob Califf (US Food and Drug Administration)

9:30 am – 12:30 pm

Retinopathy of Prematurity (ROP): Overview of the Needs and Regulatory Science Strategies for Improving Neonatal Outcomes
Mark Turner (INC Co-Director, U-Liverpool), Chair
Second Annual Neonatal Scientific Workshop at the FDA

Jon Davis, INC Co-director
Tufts Medical Center
Jonathan Davis, MD
Vice-Chair of Pediatrics
Chief of Newborn Medicine
Tufts Medical Center
Professor of Pediatrics
Tufts University

Chair, Neonatal Advisory Committee
Office of the Commissioner, FDA
Co-Director, International Neonatal Consortium (INC)
Coordinating Committee, Pediatric Trials Consortium
Newborn Intensive Care

- 6% of the 4,000,000 births each year in the US require NICU admission.
- Prematurity rates worst of any developed country.
- Total cost of prematurity >$29 billion each year.
- Only small improvements in survival and outcome in the last 20 years.
- >90% of drugs used in the NICU are not FDA approved; the last approved drug that increased survival was surfactant in 1991.
History of Pediatric Initiatives

...but 55% of Medicines Still Do Not Have Data in Labels to Guide Appropriate Use in Children

- AAP Guidelines Issued
- PPRU launch
- ICH E11 Guidelines
- EU Pediatric Regulation "carrot & stick"
- US FDAMA Renews "carrot"
- US BPCA Renews "carrot"
- US FDAAA Makes "carrot & stick" permanent!
- PPRU sunset

Key initiatives

Proportion of medicines in PDR with information on children

- Yes 78%
- No 22%

Discussion Only 3/31/2016
How About Neonatal Studies?

Studies must be clinically relevant

- Of 406 medicines that were studied in the pediatric population in order to achieve 6 months of exclusivity, only 28 (or 7%) had been studied in neonates.

- Of those 28 drugs, the majority are not used regularly in this vulnerable population.

We Have a Dream

- Every newborn admitted to the NICU will enroll in a study protocol to optimize outcomes (similar to cancer).
- The definitions for our most important outcomes will be the same worldwide.
- We will collect standardized data on all infants, and the databases will be shared, harmonized, and readily searchable.
- We will be able to easily examine survival and outcome based on region of the world and adopt best practices.
- We will have established normal laboratory values based on birthweight, gestational age and postnatal age.
We Have a Dream

- All drugs in the NICU will be approved for use in our population – sufficient safety and efficacy data exists.
- Drug formulations will be designed for neonates and any additives will be safe and not affect efficacy.
- Regulators, investigators, funding agencies, industry and parent groups will collaborate to develop the best master protocols with agents that are “regulatory ready”.
- High quality and ethical trials conducted in multiple countries simultaneously - well qualified investigators and sustainable infrastructure.
- Novel therapeutics for neonates – faster, cheaper, better.
The International Neonatal Consortium will concentrate its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of pre-term birth.
Members Spanning the Globe

New Methods to Assess Therapies for Neonates

Neonatal Nurses
- NANN
- COINN

Companies
- AstraZeneca
- Bristol-Myers Squibb
- Chiesi
- Janssen R&D
- Eli Lilly & Co.
- Novartis
- Pfizer
- Sanofi
- Shire
- TriNetX

Families/Advocacy
- Graham’s Foundation
- March of Dimes
Accomplishments to Date

- Initial meetings at FDA & EMA to launch the consortium.
- High priority working groups – Seizures, BPD, Clinical Pharmacology, Big Data.
- Active involvement and participation by many highly motivated and qualified people from around the globe.
- Multiple impactful publications.
- Clinical Pharmacology white paper to help inform regulators on the conduct of clinical trials in neonates.
- Tremendous support by the Critical Path Institute.
- We have the capacity to do more – ROP, Infections, Hemodynamics, and NAS.
- Leveraging efforts of other initiatives: the Pediatrics Trial Consortium.
About the Pediatric Trials Consortium

- Involves 32 diverse global stakeholders organizations from:
  - Academia
  - Patient advocacy
  - Government scientific and regulatory agencies
  - Biopharmaceutical companies

- Focused on pediatric product development & clinical trials
- Launched October 2015
- Overseen by Coordinating Committee (with 3 Subcommittees)
- 5 Work Streams focused on key areas
- Slated to complete work by the end of 2016
- One of 12 of Critical Path Institute consortia
PTC Advice & Guidance:
• Strategic plan & options
• Optimal leadership
• Operating plan & options
• Financial projections
• Legal Assessment

Critical Path Obtains:
• EIN #
• Tax-exempt status

Non-Profit:
• Hires leadership
• Refines strategic & operations plans
• Recalculates financial projections
• Completes legal assessments
• Builds administrative core
• Begins operations: First Patient In

Deliverables
INC: Advancing Maternal - Child Health

Sustainable Infrastructure
Cooperative Groups

Knowledgeable Investigators
Efficient Regulatory Processes
Retinopathy of Prematurity (ROP): Overview of the Needs and Regulatory Science Strategies for Improving Neonatal Outcomes

Mark Turner
INC Co-Director, U-Liverpool, Chair
Introduction

Mark Turner
Senior Lecturer / Consultant Neonatologist
University of Liverpool / Liverpool Women’s NHS Foundation Trust

- Co-Director INC
- Member, Co-ordinating Committee PTC
  - Lead Operations WG, Co-lead Interoperability WG
- Chair, European Network of Paediatric Research at the European Medicines Agency (EnprEMA)
- Co-Scientific Coordinator, Global Research in Paediatrics (GRIP)
- Lead, European Paediatric Clinical Trials Research Infrastructure
- International Lead, NIHR Clinical Research Network: Children
  - Informal support to networks in Spain, Austria, Switzerland, Japan, South Korea, Ireland
- Chair, NIHR CRN Children Neonatal Clinical Studies Group
Overview Slides

This meeting is important because it will contribute to:

• A shared understanding of complexities of drug development in neonates
  • Move towards solutions

So we need to start with shared understanding of the context of the meeting
Regulatory Science: context

• Regulatory Science
  • Regulatory Engineering
    • Regulatory Logic
      • Regulatory Reality
Regulatory Science: context

- Regulatory Science
- Regulatory Engineering
- Regulatory Logic
- Regulatory Reality
The FDA definition:

“Regulatory Science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products”

• Science is generalizable (and transparent about methods and assumptions; reproducible etc.)

• Comparability is important
Generalisable aspects of Regulatory Science

Formal Generalisation, e.g. Biomarker Qualification.
• This is rigorous and attractive and CPath does this well
• It is not going to be easy in neonates – lack of data, difficulty adding data points to meet evidentiary standards

Informal Generalisation
• Shared justification, shared definitions
• Agreements about useful modules of protocols that can be shared between companies
Formal Generalisation

Hint of Biomarker Qualification

• Well-defined context of use
• Well-justified choices about biomarker
  • Thresholds
  • Management of intra- and inter-individual variability
• Replicability
• Reference standards
• Cross-validation
• Analysis plan
  • Ante hoc hypotheses
  • Multiplicity adjustments
  • Missing data
Informal Generalisation

This is what the workgroups have been doing

- How to extend this?
- What is the value of this approach?
- Depends on current status of the condition
  - Cf. STEMI and decompensated heart failure
  - Cf. Framingham study and Neonatal hypotension

Types of informal generalisation

- Scoping
- Definitions
- Protocols
- Validation
Regulatory Engineering

• Applying general principles and specific data to a specific project

• This is what we all do during the development, review, and implementation of PSPs, PIPs, protocols etc. and during the review of applications for label change / marketing authorisation
The reasoning behind successful Regulatory Engineering

- Regulatory Logic = using data to allow the marketing of a product; regulators need to be careful for legal reasons but also because it is very difficult to change things after a label is granted

- This is partly expressed in guidelines and other documents from the Agencies

- This is partly a cultural thing, which depends on correct interpretation of the official documents (which often use jargon, that is words have specific meanings that are not always similar to common meanings) but also on a shared understanding that is not written down

- Some of the cultural aspects of regulatory logic will always be opaque to the clinical community because of knowledge that the Agencies have about disasters
Modes of thinking: clinical investigators

- "Basic science"
  - Underpinning
  - Mechanisms
  - Epidemiology
- Clinical pharmacology
  - PK / PD, dose
- Evidence-based medicine
  - Pragmatic

- Each mode of thinking has a place but is separate from regulatory logic
Regulatory Reality

• Many constraints
• Multiple steps to authorisation / label:
  • PIPs, PSPs are only part of the journey
• Disagreements between companies and regulators
  • Within companies and regulators
• Time
• Detail
Regulatory Science: context

- Regulatory Science
  - Regulatory Engineering
    - Regulatory Logic
  - Regulatory Reality
One Community
A Mixed Community
## Agenda – ROP Session

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tbody>
<tr>
<td>9:30 am</td>
<td>Challenges in Conducting Clinical Trials to Treat ROP &amp; Strategies for Overcoming those Challenges Olaf Dammann (Tufts Medical Center)</td>
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<td>10:00 am</td>
<td>ROP Panel</td>
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<td>Melissa Liew (Novartis), Adina Tocoian (Shire)</td>
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<td>10:20 am</td>
<td>COFFEE BREAK</td>
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<td>10:50 am</td>
<td>ROP Panel (continued)</td>
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<td></td>
<td>Alistair Fielder (City University London)</td>
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<td>Ann Hellstrom (University of Gothenburg)</td>
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<td>Neil Marlow (University College London)</td>
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<td>Wiley Chambers (US Food and Drug Admin.)</td>
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<td>Reiko Shimizu (Pharmaceutical and Medical Devices Agency, Japan)</td>
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<td>Ralph Bax (European Medicines Agency)</td>
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<tr>
<td>12:15 pm</td>
<td>Voting on Priority Projects for ROP</td>
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<td>12:30 pm</td>
<td>LUNCH</td>
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Standardisation of Key Elements in Trials For the Prevention and Treatment of ROP

Olaf Dammann, Tufts University, Boston, U.S.A.
Mark Turner, University of Liverpool, U.K.
Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010

ROP incidence <32 wks: 22 – 37%

Global numbers 2010
- Any ROP: 187,000
- Progression towards pot. vis. imp.: 54,000
- Severe visual imp. or blindness: 20,000
- Mild or moderate visual impairment: 12,000
One Goal

Reduce ROP-related visual impairment
Two Approaches

Prevention

Treatment
Three Issues

- Biomarkers
- Timepoints
- Simulation
Why Focus on Systemic Inflammation?

1. Associated with risk increase
2. Experimental evidence
3. ROP process: window of opportunity
# Neonatal Bacteremia and ROP

<table>
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<tr>
<th>Late Bacteremia</th>
<th>ROP</th>
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<tr>
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<td>Stage 3-5</td>
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<tr>
<td>Presumed</td>
<td>Univariable</td>
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<td>Multivariable*</td>
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<tr>
<td>Definite</td>
<td>Univariable</td>
</tr>
<tr>
<td></td>
<td>Multivariable*</td>
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</table>

*Washburn et al, Arch Ophthalmology 2011*
Neonatal systemic inflammation in rats alters retinal vessel development and simulates pathologic features of retinopathy of prematurity

Hye Kyoung Hong, Hyun Ju Lee, Jung Hwa Ko, Ji Hyun Park, Ji Yeon Park, Chang Won Choi, Chang-Hwan Yoon, Seong Joon Ahn, Kyu Hyung Park, Se Joon Woo and Joo Youn Oh

LPS 100 μl (0.25 mg/kg) on P1, 3, and 5

- Delayed vascular growth
- Reduced capillary density
- Aberrant vessel tufts in the periphery
- Inflammatory cell infiltration
- Increased level of pro-inflammatory cytokines and apoptosis
Three Issues

Biomarkers

Timepoints

Simulation
Sustained Inflammation and ROP

Newborns <28wks GA with systemically elevated markers of inflammation are at two-fold increased risk for ROP compared to their peers w/o e.m.i.

ELGAN Study, unpublished
Questions for Industry and Regulators

• Can they be reduced to one measurement?
  – Which methods to select one measurement would be acceptable?

• What if these effects cannot be reduced to a single measurement?
  – How would a systems approach fit with drug development?
Questions for Industry and Regulators

• Are these enrichment biomarkers?
  – How would we find out in a way which is useful / acceptable?
  – Could they be “de-richment” variables – could prophylactic treatment be stopped if there is no inflammation?
  – What sort of strategies are needed to examine this possibility?

• What do we need to know about inter- and intra-individual variability?
The clustering of disorders in infants born before the 28th week of gestation

Alan Leviton (alan.leviton@childrens.harvard.edu)\(^1\), Olaf Dammann\(^2\), Stephen Engelke\(^3\), Elizabeth Allred\(^1\), Karl CK Kuban\(^4\), T Michael O’Shea\(^5\), Nigel Paneth\(^6\), for the ELGAN study investigators*

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<th>Retina</th>
<th>Lung</th>
<th>(Bacteremia)</th>
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<tr>
<td></td>
<td>ROP(^f)</td>
<td>BPD(^f)</td>
<td>Early(^§)</td>
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<tr>
<td>Bowel</td>
<td>3.1 (1.7, 5.8)</td>
<td>3.7 (1.9, 7.1)</td>
<td>0.8 (0.2, 2.7)</td>
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<tr>
<td>Brain</td>
<td>1.1 (0.8, 1.6)</td>
<td>1.0 (0.6, 1.7)</td>
<td>1.2 (0.7, 2.3)</td>
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<tr>
<td>Retina</td>
<td>2.6 (1.7, 3.9)</td>
<td>1.7 (1.1, 2.8)</td>
<td>1.4 (1.1, 1.9)</td>
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<tr>
<td>Lung</td>
<td>62/34</td>
<td></td>
<td>0.5 (0.2, 1.3)</td>
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<td>Blood early</td>
<td>35/23.3</td>
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<td>2.1 (1.3, 3.3)</td>
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<tr>
<td>Blood late</td>
<td>118/92.6</td>
<td>5/8.0</td>
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Interacting Disease Processes

Acta Paediatrica, 2010
Questions for Industry and Regulators

• How can interactions between disease processes be handled?
  – Randomization at point of second disease process
  – Post hoc analysis?
  – How can animal models help to resolve timing of treatment?
Three Issues

Biomarkers

Timepoints

Simulation
High or Low Oxygen Saturation and Severe Retinopathy of Prematurity: A Meta-analysis

**AUTHORS:** Minghua L. Chen, MD, MPH, a Lei Guo, PhD, b,c
Lois E. H. Smith, MD, PhD, d Christiane E. L. Dammann, MD, a,e and Olaf Dammann, MD, MS a,f,g

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**Early postnatal weeks**

- Reduce Oxygen

**≥32 postconceptual weeks**

- Increase Oxygen

*Chen et al., Pediatrics 2010; 125:e1483-92*
Interventions

A. In Utero: Normal vessel growth

B. Phase I: Vessel growth stops
   - \( \downarrow \text{IGF-1} \)
   - \( \downarrow \text{VEGF} \)
   - \( \downarrow \text{EPO} \)
   - \( \downarrow \omega-3 \text{ PUFA} \)

C. Phase II: Retinal neovascularization
   - \( \uparrow \text{IGF-1} \)
   - \( \uparrow \text{VEGF} \)
   - \( \uparrow \text{EPO} \)
   - \( \downarrow \omega-3 \text{ PUFA} \)

D. Resolution:
   - Supplement to normal levels
     - IGF-1
     - \( \omega-3 \) PUFA
   - Control \( O_2 \) exposure to prevent suppression of VEGF and EPO

Modulation of Inflammation

Anti-VEGF

IGF-1 Replacement

Hellström, Smith & Dammann, Lancet 2013
Questions for Industry and Regulators

• How can multi-phasic effects be accounted for during drug development?
Three Issues

- Biomarkers
- Timepoints
- Simulation
# Infection, Oxygen, and Immaturity: Interacting Risk Factors for Retinopathy of Prematurity

<table>
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<tr>
<th>Group</th>
<th>Gestational age &lt;26 weeks</th>
<th>Oxygen at 28 days</th>
<th>Any sepsis</th>
<th>ROP yes, n</th>
<th>ROP no, n</th>
<th>ROP yes, %</th>
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<td>23</td>
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Tufts Population Model of ROP Occurrence

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<td>Sepsis</td>
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<th>Run 1</th>
<th>Run 2</th>
<th>Run 3</th>
<th>Run 4</th>
<th>Run 5</th>
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Fried, Hescott, & Dammann, unpublished
Clinical Trial Simulation

% create vector of treatment times
initialCycleTimes = ...;
initialTime = cycleTime = (endTime - cycleTime);
doseTimesWithinCycle = ...;
initialTime = hoursInDay/dailyDoses : timeOnDrug;
doseTimes = reshape(...
    repmat(doseTimesWithinCycle', 1, length(initialCycleTimes)) + ...
    repmat(initialCycleTimes, length(doseTimesWithinCycle), 1), ...
    1, length(initialCycleTimes) + length(doseTimesWithinCycle)));
doseTimes = [doseTimes, endTime]; % adding end time of treatment
doseTimes = doseTimes/24;
doseAmount = doseInitial;
end
Questions for Industry and Regulators

- Could clinical trial simulation reduce the uncertainties around the interactions
  - E.g. if reduction in infection using standard approaches, such as Matching Michigan, leads to reduced inflammation, what is the impact on ROP
  - What do industry and stakeholders look for in such a model?
  - Could the Tufts Computational Population model of ROP contribute to clinical trial simulation?
Standardization of Key Elements When Targeting Systemic Inflammation in Order to Prevent ROP

• **Timepoints**
  • Recruitment
  • Intervention
  • Monitoring
  • Outcome assessment

• **Biomarkers of**
  • Exposure to be modified
  • Intervention
  • Disease process
  • Outcome (diagnosis, progression)

• **Simulation**
  • Population models
  • Clinical trial simulation
Thank you!

NIH / NEI
Placenta Microbiology → ? → Retinopathy of Prematurity

European Union

Tufts Collaborates!
Computational Population model of Retinopathy of Prematurity
AntiVEGF in ROP

Melissa S H Liew
Therapeutic Area Head
Novartis Pharmaceuticals
ROP is an aggressive vasoproliferative disorder

- Retinopathy of prematurity is a condition related to abnormal retinal vessel development
  - **Vascular endothelial growth factor is thought to be a mediator**

- Current “standard of care” treatment – laser ablation therapy of the avascular retina
  - Destruction of tissue stimulating abnormal vessel development
  - Intravitreal anti-VEGF agents may be a more targeted therapy

Adapted from Mintz-Hittner et al NEJM 2011
AntiVEGF in ROP

• 50 publications identified reporting on bevacizumab use in ROP
  • >700 ROP patients (>1,200 eyes) exposed to intravitreal bevacizumab
  • 0.25mg – 1.25mg; typically 0.625mg

• 18 publications identified reporting on ranibizumab use in ROP
  • >130 ROP patients (>250 eyes) exposed to intravitreal ranibizumab
  • 0.15mg – 0.30mg; typically 0.25mg

• Following BEAT-ROP and multiple case series, key questions remain:
  • RBZ for treatment of ROP?
  • Further characterize the comparative efficacy of anti-VEGF vs Laser
  • Further characterize the comparative safety of anti-VEGF vs Laser
  • Evaluate which dose of anti-VEGF has best risk:benefit profile
Development of the RAINBOW Study

Health Authorities

PDCO (EU)
FDA
PMDA

Steering Committee

Alistair Fielder, London
Brian Fleck, Edinburgh
Domenico Lepore, Rome
Neil Marlow, London
Andreas Stahl, Freiburg
What went well

- High engagement of the ROP Medical Community
- Strong agreement and support regarding need for a well conducted randomized controlled trial evaluating ranibizumab vs. laser
  - RBZ associated with lower systemic VEGF suppression vs BCZ

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab</th>
<th>Bevacizumab</th>
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<tbody>
<tr>
<td>MOA /class</td>
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<tr>
<td>Molecular weight</td>
<td>48 kDa</td>
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<td>Half-life in the human eye</td>
<td>9 days</td>
<td>6.7 days</td>
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<tr>
<td>Systemic elimination half-life</td>
<td>2 hours</td>
<td>20 days</td>
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What are the Challenges - Dose selection

- Both ocular efficacy and potential on target toxicity are directly related to AntiVEGF exposure
- PK Compartment size: Smaller systemic volume of distribution in infants than in adults leads to a potentially higher systemic exposure and toxicity

- nAMD
- Elderly female
- Vitreous volume 4.0ml
- Systemic circulation 65ml/kg
- 3,575ml for 55kg lady
- ROP
- Neonate
- Vitreous volume 1.69ml
- Systemic circulation 95ml/kg
- 95ml for 1,000g neonate

Howie SR 2011. WHO; 89: 46-53
What are the Challenges - Dose selection

- **Efficacy**
  - High enough to induce a therapeutic effect
  - Drug concentration in vitreous

- **Safety**
  - Low enough to avoid unnecessary toxicity
  - Drug concentration in systemic circulation

Intent to study lower doses lower than 50% adult dose
Minimize systemic exposure whilst ensuring therapeutic response
Dose rationale- Based on pharmacokinetic modeling

- Objective: Characterize benefit-risk of ranibizumab doses in premature infants with retinopathy of prematurity by comparing predicted ocular and systemic exposure in children with reference exposure after an intravitreal injection of 0.5 mg ranibizumab in adults.

- Challenges
  - exposure in vitreous and serum is only a surrogate marker of eventual efficacy and toxicity of ranibizumab.
  - exposure in infants was calculated using allometric scaling of PK parameters and could not be independently verified due to lack of PK data in children at this time.
Overview of the RAINBOW Study

A randomized, controlled study evaluating the efficacy and safety of Ranibizumab compared with laser therapy for the treatment of Infants Born prematurely With retinopathy of prematurity

1:1:1 randomization

- Ranibizumab 0.2 mg
- Ranibizumab 0.1 mg
- Laser Therapy

24 weeks after starting treatment

Core Study H2301

Rainbow

Extension Study H2301E1

5 years of age
Other Challenges

• Reliable administration of low volumes

• ROP grading
  • Inter- and intra-grader agreement

• Recruitment
  • Increasing off label use of AntiVEGF in ROP
    • Some investigators do not wish patients to be treated with laser
  • Concerns about systemic toxicity in infants with AntiVEGF
    • Some investigators do not wish patients to be treated with AntiVEGF
Summary

• **RAINBOW** study will evaluate the following:
  
  • Characterize the efficacy of RBZ vs Laser
    • Investigator grading of ROP – grading guide
    • Central reading center for grading of digital images
  
  • Capture Long term safety outcomes
    • Evaluate serum ranibizumab and plasma VEGF
    • Capture and report ocular and non-ocular AEs
  
  • Evaluate which dose of anti-VEGF has best risk: benefit profile
    • 0.1mg and 0.2mg ranibizumab vs Laser
PREVENT ROP
SHIRE

Adina Tocoian
Medical Director Shire
IGF-1 target range – healthy in-utero serum level

IGF-1 target range – 28-109 µg/L

Intra-uterine IGF-1 levels and the correlation between ROP and serum IGF-1 levels in prematurely born infants
ROP: IGF-1 and VEGF roles in development

A. In utero, normal vessel growth. IGF-1 nl, VEGF nl.
B. Premature birth, vessel growth stops. ↑IGF-1, ↑VEGF.
C. Maturing retina, hypoxia. ↓IGF-1, ↓VEGF, ↓↑VEGF.
D. Retinal neovascularization. ↑IGF-1 to "threshold," ↓↑VEGF.

NI vessel growth in retina, ↓VEGF. Resolution of ROP.
↓VEGF. Proliferative retinopathy, retinal detachment.

↑IGF-1
Simulation of 250 μg/kg/24 h dose over 6 w treatment
Study ROPP 2008-01

Determination of the rhIGF-1/rhIGFBP-3 dose, administered as a continuous infusion, required to establish and maintain longitudinal serum IGF-1 levels within physiological levels in premature infants, to prevent ROP.

Phase 2, Randomized Controlled, Assessor-blind, Dose Confirming, Pharmacokinetic, Safety and Efficacy, Multicenter Study.

4 sections: A, B, C, D.

Primary Outcome Measures:
Severity of ROP, as compared to the severity of ROP in an untreated control population

Sample size: 120 premature neonates
Inclusion Criteria:

- Subject between GA of 26 w + 0 d and 27 w + 6 d (Study Section A) or between GA of 23 w + 0 d and 27 w + 6 d (Study Sections B, C, and D), inclusive.

Exclusion Criteria:

- Detectable gross malformation
- Known or suspected chromosomal abnormality, genetic disorder, or syndrome
- Persistent blood glucose level <2.5 mmol/L or >10 mmol/L at Study Day 0 (day of birth)
- Anticipated need of administration of erythropoietin (rhEPO) during treatment
- Any maternal diabetes requiring insulin during the pregnancy
- Clinically significant neurological disease (Stage 1 IVH allowed)
- Monozygotic twins
- Subject participating or plans to participate in a clinical study of another investigational study drug
Secondary Outcome Measures:

- Time to discharge from neonatal intensive care
- Area under curve for maximum severity of ROP stage
- Development of maximum severity of ROP stage \( \geq 3 \) at any time during the study
- Development of BPD
- Body weight, length, head circumference
- Brain development assessed by changes in brain volume
- Development of IVH
- Adverse Events
  - Clinical laboratory parameters, physical examination, vital signs, concomitant medications/procedures, echocardiogram
  - Anti-IGF-1/IGFBP-3 antibodies
  - Serum concentrations of IGF-1, IGFBP-3 and ALS
Title:
Long-term safety and efficacy outcome study comparing children previously enrolled in study ROP-2008-01 for the prevention of ROP (PEDAL).

Primary Outcome Measures:
• Severity of ROP, as compared to the severity of ROP in an untreated control population.

Time follow-up: until 5.5 years CA
Outcome measures

- Adverse Event- Physical examination, cardiac size (echocardiogram), kidney and spleen size, any other gross abnormalities (abdominal ultrasound) and concomitant medications/procedures
- Visual acuity as assessed by an age-appropriate method
- Corrective lens determination, as assessed by standard guidelines published by the AAO
- Ocular alignment and ocular motor examination in primary gaze and in as many of 9 positions of gaze as possible as assessed by corneal light reflex and by the cover test
- Refraction as assessed by retinoscopy with cycloplegia
- Stereoacuity as assessed with standardized, age-appropriate tools
- Retinal layer and optic nerve development as assessed by optical coherence tomography (OCT)
Coffee Break
30 minutes
Coffee Break
30 minutes
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<td>Melissa Liew (Novartis), Adina Tocoian (Shire)</td>
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<td>Alistair Fielder (City University London)</td>
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<td>Ann Hellstrom (University of Gothenburg)</td>
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<td>Neil Marlow (University College London)</td>
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<td>Wiley Chambers (US Food and Drug Admin.)</td>
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<td>Reiko Shimizu (Pharmaceutical and Medical Devices Agency, Japan)</td>
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<td>Ralph Bax (European Medicines Agency)</td>
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<td>12:15 pm</td>
<td>Voting on Priority Projects for ROP</td>
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<td>12:30 pm</td>
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Alistair Fielder
City University, London, UK
Retinopathy of Prematurity

Alistair Fielder

City University, London, UK
Financial Disclosure

Honoraria from Clarity Medical Systems for presentations at meetings & workshops in Middle East

Commercial interest in RetVas

Novartis Rainbow Study Protocol Steering Committee
Topics

• ROP natural history

• Classification of ROP and problems that may have impact on practice or research
  – Collecting robust data

• Creating robust outcome measures
  – Acute phase
  – Longterm
Estimates ROP-induced mild & severe vision impairment

Blencowe et al Ped Res 2013
Challenge for (large) Clinical (international) Studies

• You cannot tell clinicians what to do, if differs significantly from standard practice
  – Actually you can but they will ignore because you cannot ignore clinical dogma (*overstated*)

• How to conduct robust multinational clinical research?
  – Work within internationally accepted definitions
  – But bypass and/or obtain *additional* information through *subcategories* or *technology*
ROP Natural History
Highly Stylised

• Clearly described natural history
• Timing of onset & progression largely determined by postmenstrual age & is consistent across ethnic groups & settings
• More mature babies have an earlier postnatal age at onset & more protracted course than the more immature babies
Describing ROP

- Retinal vascularisation proceeds centrifugally
  - Zones of ICROP & these
  - Predict outcome

- ROP - 4 descriptors
  - Severity - by stage
  - Location - by zone
  - Extent - by clock hour
  - Activity - plus disease

*ICROP 1984, 1987 & 2005*
ROP Stage 1

- White within retina
- Arcades of vessels leading up to the line

Should 1 & 2 be merged?

& some stage 2 here
ROP Stage 2

- Increase in volume, extends off retina
- White or pink
- Neovascular tufts posterior to ridge

& some stage 1 here
ROP Stage 2
ROP Stage 3
Aggressive Posterior ROP
ROP Stage 4a

Extrafoveal
ROP Stage 4b

Fovea involved
ROP Stage 5
Plus Disease

Spectrum of

- Engorgement of posterior pole BVs
- Iris vessel engorgement
- Pupil rigidity
- Vitreous haze
Pre-Plus

Intermediate stage between normal and plus
An important sign that ROP may progress
Treatment

**ETROP – recommendations 2003**

- **Type 1 ROP** - Requires Rx
  - **Zone I**
    - Any ROP *with plus*
    - Stage 3 *with or without plus*
  - **Zone II**
    - Stage 2 or 3 ROP *with plus*
    - Stage 2 *with plus*
So Far So Good

Excellent classification

Clear treatment indicators

What can go wrong?
Difficulties with Classification

• **Zone**
  – Described well but errors occur & important in studies

• **APROP**
  – Overdiagnosed but will not result in overtreatment

• **Plus**
  – THE major challenge - experts do not agree & leads to variations in treatment
“Measure what is measurable, everything that is not measurable, make measurable”

Galileo Galilei

When you cannot express it in numbers your knowledge is of a meagre & unsatisfactory kind

Lord Kelvin
Issues with changing / improving the classification

- What type of classification is acceptable to regulators?
- What type of classification is acceptable to clinicians?
  - ICROP I & II - self-selected but internationally agreed
- How should a new / improved classification be decided?
  - How long have you got?
  - Work within but use novel stratification
- Is central or consensus reporting the answer?
Collecting Robust data
The gold standard?
Issues with data standards

- Who defines the standards?
- How are standards defined?
- What are the technological implications?
Reverse engineering from human vision

Human visual system sees what a machine cannot measure

subpixel processing

Ng, Wilson, Cocker & Fielder
Wilson et al JAAPOS 2012
Issues with new technologies

- What sort of evidence is needed before new technologies are used in clinical trials?
- Who gathers the evidence?
Outcome Measures – Short Term

• Maximum stage of acute phase ROP
  – ~31 and 40 weeks PMA

• Structural outcome measure of the ROP process
  – But not function

• It reflects ROP activity alone
  – Only outcome measure to achieve this

• Can be recorded & analysed
Outcome Measures - Long Term

• Robust assessment of structure & function
  – 5 years of age, the first age possible
  – Visual functions, refractive state & (almost) full ophthalmic assessment

• But results are not a measure of the ROP process but contaminated by:
  – ROP treatment – if any
  – Effect of preterm birth *per se*
  – Neurological damage - CVI
Outcome Measures - Long Term

- Ocular structure
  - Morphology & refractive state
  - Fine retinal structure
  - Retinal vascular organisation

- Visual functions – Uniocular & binocular
  - Acuity, CS, Colour, Field
  - Electrophysiology

- Visual pathway & eye movements
Ann Hellstrom
University of Gothenburg
Ophthalmologic outcome measures in ROP studies
Ann Hellström, Professor
Queen Silvia Children’s Hospital, Gothenburg
ROP outcome dependent on timing of intervention

Phase 1
Vessel growth stops

Phase 2
Retinal vasoproliferation

Prevention
Late stage treatment
Brain at birth in baby born at 22 weeks

- Chorioamnionitis
- Postnatal sepsis
- Extrauterine growth retardation
- Necrotising enterocolitis

- Hyper-hypoxia
- Hyperglycemia
- Brain lesions
- Suboptimal nutrition

Growth factors for angio- and neurogenesis ↓

Brain at birth in baby born fullterm
Follow-up variables

1. Dependent on tester
2. Acquires cooperability, concentration, endurance

Function
- Visual acuity (VA)
- Stereo-acuity
- Visual fields (VF)
- Contrast sensitivity
- Color vision
- Visual processing
- Electroretinography (ERG)
  - full field
  - multifocal
Follow-up variables

Structure
• Retcam fundus photographs
• Optical Coherence tomography (OCT)
• Fluorescein angiography (FA)

Refraction in cycloplegia

Ocular alignment
Ocular structures

- Retcam -fundus photographs
- OCT

- Fluorescein angiography
  - Choroid
  - Retinal vessels
Fluorescein angiography at 9 months in general anesthesia *Lepore 2014*

*Figure 1.* Fluorescein angiographic images before treatment and 9 months after treatment showing the junction between the vascularized and avascular retina in an infant born at 24 weeks' gestational age (A and B, bevacizumab injected; C and D, laser treated). There is persistent leakage and irregular branching in both eyes at the time of treatment (A and C). In the eye injected with bevacizumab at 9 months' follow-up (B), there is persistent avascular retina (black circles) together with hypofluorescent areas (white circles), capillary tufts (white arrow), and peripheral shunt at the junction between vascularized and avascular retina. D, The chorioretinal scar 9 months after conventional laser treatment is shown.
Do we need to distinguish between trial end points and clinical assessments?

**Trial end points:**
- Reproducible within individuals and between assessors
- Objective markers that need to be consistent between studies
- Need to be context independent

**Clinical Assessments:**
- Interpreted by the clinician using a combination of data from multiple assessments and clinical history
- Do not need to be reproducible or consistent

• When should clinically useful assessments be included or excluded in clinical trials?
  - All data has an “overhead” for collection and archiving
  - Safety is important
Suggested follow-up

• Neonatally
• 30 months
• 6 years
• 11 years
Primary end point for clinical trials?

• How should we choose?
• Which one?
• When?

• NB Trials for FDA / EMA may have different end points to trials for HTA agencies
  • Although it is good to include HTA outcomes in trials
Suggested neonatal examinations

- ROP screening using indirect ophthalmoscopy
- Retcam before and after ROP treatment
- Retcam after 35 weeks in infants without ROP
- Handheld SD-OCT of optic disk, macula and choroid
- FA?
Suggested follow-up at 30 months post term

- **Vision:** LEA 0.4, or fix and follow toy, torch (Holmström 2014)
- **Nystagmus?** Yes/no
- **Ocular alignment:**
  - Corneal light reflexes
  - Cover test at near fixation
- **Refraction in cycloplegia**
- **Prescription of glasses if indicated according to recommendations by AAO**
Visual outcome at 2.5 and 6.5 years

2.5 years
1% blind
3% visually impaired

6.5 years
2% blind
5% visually impaired
9% below criteria for driving license (<20/40)

EXPRESS-team in press Archives of Ophthalmol
Suggested follow up at 6 and 11 years

6 years
- Visual acuity
  - Blind
  - Visual impairment
  - <20/40
- (Stereoacuity)
- (Contrast sensitivity)
- (Color vision)
- (Visual processing)
- Ocular alignment
- Refraction
- ERG full-field and multifocal
- SD-OCT
- FA

11 years
- Visual acuity
- (Stereoacuity)
- (Contrast sensitivity)
- (Color vision)
- (Visual processing)
- Ocular alignment
- Refraction
- (Visual fields)
- ERG if not performed at the age of six years
Primary end point for clinical trials?

• How closely are these multiple assessments correlated?
  – Functional tests largely dependent on executive functions
Biomarkers for ROP

Phase 1
- Hyperglycemia – Phase 1
- Adiponectin – Phase 1
- VEGF – Phase 2
- IGF-I – Phase 1 & 2
- Postnatal growth – Phase 1 & 2
- Sepsis – Phase 1 & 2

Phase 2
- Retinal vasoproliferation

Vessel growth stops
Complex...large variability in many factors
How do we handle this complexity?

• Preterm morbidity is complex

• Ignore it?
  • Increase sample sizes
How do we handle impact of an intervention on multiple morbidities?

• ROP is a neuro-vascular disease anything affecting neuro-vascular outcome will likely have effects on vascular dependent organogenesis

• Take a systems approach
  • What would that look like?
  • Measurements of a healthier baby...
Thank you
Retinopathy

Retinopathy – important to power studies to assess comorbidities?

Direct eye treatment
- Newborn no compartments are ‘watertight’
- All treatments may affect other systems
- Safety outcomes are critical
  - Renal, Hepatic
  - Neonatal morbidities
  - Long term neuropsychological outcomes

Prevention strategies
- May affect whole body
- Often risk-balance unclear
  - Example SaO₂ targets
- May be positive or negative
  - ‘Developmental arrest’
  - Phase changes after 32w
  - Relative importance of other system effects may be greater
Feasibility

The number of babies <1500g at birth

Rate of ROP students in special class of impaired vision
Impact

• Efficacy
  • Is there critical difference between each site?
  • Is there ethnic factors?
  • Is the evaluation standardized?
  • What is the trustworthy endpoint?
  • What is natural history of ROP?

• Safety
  • Long term impact of growth and vision prognosis
  • Developing the methods to collect valuable safety information from limited sample
Ralph Bax
European Medicines Agency
Priority Projects to Discuss

• Project 1 – Define enrichment strategies for inclusion of participants in studies of prevention or treatment to maximize efficacy signals.

• Project 2 – Define standards for capture and management of data relating to key outcomes in studies of ROP.

• Project 3 – Define outcomes related to ROP (e.g. optimal definition of stages, criteria for scoring photographs, measurement of visual function) and select the best primary outcome for trials of efficacy.

• Project 4 – How to handle multiple outcomes when an intervention affects more than one body system.

• Project 5 – Standardization of key elements in trials that target systemic inflammation in order to prevent ROP.
Project 1 - Enrichment Strategies

• Description:
  • Define enrichment strategies for inclusion of participants in studies of prevention or treatment to maximize efficacy signals

• Feasibility:

• Impact:
Project 2 - Data Standards

• Description:
  • Define standards for capture and management of data relating to key outcomes in studies of ROP

• Feasibility:

• Impact:
• Description:
  • Define outcomes related to ROP (e.g. optimal definition of stages, criteria for scoring photographs, measurement of visual function) and select the best primary outcome for trials of efficacy

• Feasibility:

• Impact:
Project 4 - How to Handle Multiple Outcomes

• Description:
  • How to handle multiple outcomes when an intervention affects more than one body system

• Feasibility:

• Impact:
Project 5- Standardizing in trials targeting systemic inflammation

• Description:
  • Standardization of key elements in trials that target systemic inflammation in order to prevent ROP.

• Feasibility:

• Impact:
• Considering both impact and feasibility, which of the following regulatory science projects is your first choice?
  1. Enrichment Strategies
  2. Data Standards
  3. ROP-specific Outcomes
  4. Multiple Outcomes
  5. Standardizing in Trials Targeting Systemic Inflammation
  6. “Walk-in Option A” (offered up by audience)
  7. “Walk-in Option B” (offered up by audience)
  8. None of the above
• Considering both impact and feasibility, which of the following projects is your **second** choice?
  1. Enrichment Strategies
  2. Data Standards
  3. ROP-specific Outcomes
  4. Multiple Outcomes
  5. Standardizing in Trials Targeting Systemic Inflammation
  6. “Walk-in Option A” (offered up by audience)
  7. “Walk-in Option B” (offered up by audience)
  8. None of the above
Lunch

1 Hour
Second Annual Neonatal Scientific Workshop at the FDA

March 7th, Afternoon
Bacterial Infections, including Necrotizing Enterocolitis (NEC): Overview of the Needs and Regulatory Science Strategies for Improving Neonatal Outcomes

Danny Benjamin
Duke University, Chair
Agenda – Bacterial Infection Session

1:30 pm  Challenges in Conducting Clinical Trials to Treat Infections/NEC and Strategies for Overcoming those Challenges
          Danny Benjamin (Duke University)
          Karel Allegaert (University of Leuven)

2:30 pm  COFFEE BREAK

3:00 pm  Raafat Bishai (AstraZeneca)
          Gary Noel (Janssen Research and Development)
          Michael Caplan (University of Chicago)
          Kelly Wade (Children’s Hospital Philadelphia)
          Mark Turner (University of Liverpool)
          Sumathi Nambiar (US Food and Drug Administration)
          Daniel Keene (Health Canada)

4:45 pm  Voting on Priority Projects for Infections and NEC

5:00 pm  SHUTTLE TO Sheraton Silver Spring Hotel
Bacterial Infections – Good News

• Extrapolation is allowed

• Concept of extrapolation: a disease process in one group of patients (adults) is similar to a second group of patients (children)
  • Not ‘small adults’ but not martians
  • Similar organisms
  • Similar consequences with and without treatment
  • Similar exposure will provide similar results

• Indications commonly pursued in adults and extrapolation
  • Complication urinary tract infections, complicated intra-abdominal infections, complicated skin and soft tissue infections

• Examples when not allowed
  • Community acquired pneumonia
  • Invasive candidiasis
Bacterial Infections – More Good News

• Antibiotics Work: by the time the molecule gets to phase 2
• Tuberculosis: survival of pulmonary disease with triple therapy (90%) vs. placebo (40%)—risk difference of 0.5 (number needed to treat =2)
• Meningitis in the pre-antibiotic era: years of life saved per patient ~70
• Pneumococcal bacteremia: in the two year old, NNT=6
• Compared
  • To cardiology: NNT~100, and 41,000 patient study (GUSTO)
  • To oncology: tumor gets smaller or patient lives several months longer
Bacterial Infections – Still More Good News

• Shown that we can do PK and safety studies

• In 2005, 400,000 neonates in North America received ampicillin (similar number in EU), and other antinfectives were ~20 of the most commonly used therapeutics in the neonatal intensive care unit

• ‘Appropriate’ dosing of ampicillin in neonates <28 weeks gestational age was based on 0 extremely premature neonates in the peer-reviewed literature

• Acyclovir, Ampicillin, Anidulafungin (don’t use), Cefipime, Ceftazidime, Clindamycin, Daptomycin, Fluconazole, Metronidazole, Micafungin, Meropenem, Piperacillin-tazobactam, Rifampin, Ticarcillin-clavulaunic acid (Timentin), and Voriconazole (need therapeutic drug monitoring)
  • Most under an IND
  • Most substantially changed or modified dosing
  • Most sponsored by NICHD

• Leveraged that success in 2012
Bacterial Infections – Every silver lining has a cloud
Cloud #1: Safety

• Safety: while the drugs probably work and we can do the dosing studies, safety is a series of much more difficult questions
  • Drug development paradox
  • Financial pressures of a 7-day drug vs. a daily drug taken for decades

• Does meropenem cause more seizures than imipenem (or even more than other beta lactams)

• Sample size to detect 5% absolute difference (~1,600)

• Logistics of 400 infant trial: 60 sites, 24 months

• Electronic health records

• Potential solutions
  • Modeling adult data
  • Master protocols
  • Post-marketing registries and active surveillance
Bacterial Infections
Cloud #2 Central Nervous System

- Cerebrospinal fluid: neonates and the ability to localize infection
- Probability of infection: given one positive blood culture, the probability of meningitis from Serratia is 14%, S. aureus ~5% (think ~10% for Gram negative rods and ~5% for Gram positive cocci)
- Vancomycin: the data upon which the statement ‘does not penetrate the CSF’ is based on 12 healthy adults in 1957
- Penetration: based upon, size of molecule, lipophilicity, concentration gradient, inflammation, and further complicated by changing permeability with development, intraventricular hemorrhage, and shunt physiology
Bacterial Infections
Cloud #2 Central Nervous System

• Once a neonate has culture-proven meningitis, the probability of repeat positive culture is ~25%
• Despite the need to document clearance, not all neonatologists do so
• Samples: very difficult to secure in an FDA-compliant trial
• Meropenem example: 200 infants, 8 samples (estimate a ratio)
• Limited number of sites that get samples
• Animal models: large vs. small animal models

• Potential solutions
  • Balancing the achievable with the impactful
  • Use of large animal models as bridging studies
  • Sparse patient sampling nested within studies obtained per standard of care
Bacterial Infections
Cloud #3 Costs of Development

- Costs of drug development and infrastructure needed to conduct trials
- Very limited number, and well known indications
- Gram positive anti-infective, Gram negative anti-infective
- Safety as primary endpoint

Potential solutions
- Development of the master protocol
- Example #1 of a master protocol in NICHD’s Pediatric Trials Network
  - Pediatric Opportunistic PK Study (POPS), 2010-2016 (ongoing)
  - ~40 molecules; added ~24 since start, dropped ~12
  - Under an IND
  - Consent, case report form, manual of procedures, safety & PD per drug, genomics as needed, special patient populations (obesity, neonates, extracorporeal membrane oxygenation)
- Examples #2 from the Pediatric Trials Network
- Other examples from the EU, oncology, etc.
Bacterial Infections: Use of existing data

- Anti-hypertensive trials
- Access to data
- Office of Pediatric Therapeutics, Cardio-Renal Division, Clinical Pharmacology
- Primary problem was lack of pediatric clinical pharmacology—lack of range in the dose-ranging studies
- Incentives around the exclusivity program
- Series of publications in the peer-reviewed literature—Hypertension
- Trial design vs. ‘the answer is’
- Access to data vs. public access
Challenges in Conducting Clinical Trials to Treat Infections/NEC and Strategies for Overcoming those Challenges

Karel Allegaert
University of Leuven
do not simply trust ‘handbooks’ and ‘common practices’

practices vary extensively
both drug choice and dosing
guidelines are not the only solution

new issues on side effects are emerging
microbiome, and the impact of exact timing
renal toxicity

dosing regimens, feasibility vs PK/PD
amikacin
meropenem

Bacterial resistance: the next challenge?
do we always need vancomycin

What about ‘the rest of the world, route of administration?’
many cultures, (very) few positive
new biomarkers have not solved this issue
(same case can be built for NEC)

Blackburn et al, Arch Dis Child 2012
FIGURE 3. Variation in overall proportions of antibiotic use (J01) by ward type (N = 2172 children treated with at least 1 antibiotic, N = 50 European and 23 non-European hospitals). SPMW indicates specialist pediatric medical ward; BMT-solid, Bone Marrow Transplantation and Solid Organ Transplantation.
California, 40-fold variability in antibiotic use rate (n=217)

surgical volume

NEC

proven infection

level of care

mortality
<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Postnatal age (days)</th>
<th>Current weight (g)</th>
<th>Duration infusion (minutes)</th>
<th>Dose (mg/kg)</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neofax® (2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 or **</td>
<td>0-7</td>
<td>-</td>
<td>30</td>
<td>18</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>8-28</td>
<td>-</td>
<td></td>
<td>15</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>&gt; 28</td>
<td>-</td>
<td></td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>30-34</td>
<td>0-7</td>
<td>-</td>
<td></td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>&gt; 7</td>
<td>-</td>
<td></td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>&gt; 34</td>
<td>-</td>
<td></td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>RedBook® (2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>1-30</td>
<td>&lt; 1200</td>
<td>7.5</td>
<td>18-24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-7</td>
<td>1200-2000</td>
<td>7.5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 7</td>
<td>1200-2000</td>
<td>7.5-10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;7</td>
<td>&gt; 2000</td>
<td>7.5-10</td>
<td>8-12</td>
<td></td>
</tr>
<tr>
<td>BNFc (2009)</td>
<td>all</td>
<td>all</td>
<td>30</td>
<td>15</td>
<td>24</td>
</tr>
</tbody>
</table>

*let's make things better: where is the physiology?*
**Ciprofloxacin** (enterobacter spp),
25 % of units available data, CSF

**Fluconazole** (candida spp)
20 fold 24h dosing range
16 % as recommended (16 mg/kg/24h)
AIMS
Antibiotics are a key resource for the management of infectious diseases in neonatology and their evaluation is particularly challenging. We reviewed medical literature to assess the characteristics and quality of randomized controlled trials on antibiotics in neonatal infections.

METHODS
We performed a systematic search of PubMed, Embase and the Cochrane Library from January 1995 to March 2010. Bibliographies of relevant articles were also hand-searched. We included all randomized controlled trials that involved neonates and evaluated the use of an antibiotic agent in the context of a neonatal infectious disease. Methodological quality was evaluated using the Jadad scale and the Cochrane Risk of Bias Tool. Two reviewers independently assessed studies for inclusion and evaluated methodological quality.

RESULTS
A total of 35 randomized controlled trials were evaluated. The majority were conducted in a single hospital institution, without funding. Median sample size was 63 (34–103) participants. The most frequently evaluated antibiotic was gentamicin. Respectively, 18 (51%) and 17 (49%) trials evaluated the therapeutic or prophylactic use of antibiotics in various neonatal infections. Overall, the methodological quality was poor and did not improve over the years. Risk of bias was high in 66% of the trials.

CONCLUSIONS
Design and reporting of randomized controlled trials of antibacterial agents in neonates should be improved. Nevertheless, the necessity of implementing such trials when antibacterial efficacy has already been established in other age groups may be questioned and different methods of evaluation should be further developed.
Reasonable to assume (pediatric vs adult)
- Similar disease progression?
- Similar response to intervention?

No

Conduct PK studies
Conduct safety/efficacy trials

No

Is there a PD measurement that can be used to predict efficacy?

Yes

Conduct PK/PD studies to get CR for PD measurement
Conduct PK studies to achieve target concentrations based on CR
Conduct safety trials

No

Reasonable to assume similar CR in pediatrics and adults

No

Conduct PK studies to achieve levels similar to adults
Conduct safety trials

Yes
**TOP DOWN**
Clinic to mechanistic (population-based)

<table>
<thead>
<tr>
<th>Data gathering</th>
<th>Modelling</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Data</td>
<td>Population-based PK (Covariates?)</td>
<td>Confirming</td>
</tr>
<tr>
<td>Demography</td>
<td>PBPK/IVIVE</td>
<td>Learning</td>
</tr>
<tr>
<td>Physiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BOTTOM UP**
*In vitro to In vivo (IVIVE)*
Amikacin clearance in neonates: variability in addition to age/weight

A Neonatal Amikacin Covariate Model Can Be Used to Predict Ontogeny of Other Drugs Eliminated Through Glomerular Filtration in Neonates

\[
CL_i = CL_p \times \left(\frac{bBW}{bBW_{\text{Median}}}\right)^{1.34} \times (1 + \left(0.213 \times \frac{\text{PNA}}{\text{PNA}_{\text{Median}}}\right)) \times 0.838_{\text{ibuprofen}}
\]

**Drug specific property**

**Amikacin covariate model**

\[
CL_i = CL_p \times \left(\frac{bBW}{bBW_{\text{Median}}}\right)^{1.34} \times (1 + \left(0.213 \times \frac{\text{PNA}}{\text{PNA}_{\text{Median}}}\right)) \times 0.838_{\text{ibuprofen}}
\]

**Model-based predicted amikacin CL (L/h)**

- PNA = 28
- PNA = 14
- PNA = 1

**Birth weight (g)**

De Cock *et al*. Pharm Res 2014
\[ CL_i = \left\{ CL_{p \text{amikacin}} \times \left( \frac{BWb}{BWb_{\text{median}}} \right)^{1.34} \times (1 + (0.213 \times \frac{PNA}{PNA_{\text{median}}})) \right\} + \left\{ CL_{p \text{cefazolin}} \times \text{Covariates} \right\} \]

Developmental changes in GFR based on amikacin clearance

Developmental changes in tubular processes

**Total clearance of cefazolin**

**Clearance of cefazolin through GFR**

**Clearance of cefazolin through tubular secretion**
**Table 1** Original and simplified model-based dosing regimens of amikacin in neonates with postnatal age ≤30 days and final dosing regimen proposed after the prospective validation

<table>
<thead>
<tr>
<th>Current body weight (g)</th>
<th>Original model-based dosing regimen (4)</th>
<th>Simplified model-based dosing regimen</th>
<th>Final proposed dosing regimen after prospective validation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PNA &lt; 14 days</td>
<td>PNA ≥ 14 days</td>
<td>PNA &lt; 14 days</td>
</tr>
<tr>
<td></td>
<td>PNA ≥ 14 days</td>
<td>PNA ≥ 14 days</td>
<td>PNA ≥ 14 days</td>
</tr>
<tr>
<td>0–800</td>
<td>16 mg/kg, 48 h (gp 1)</td>
<td>20 mg/kg, 42 h (gp 2)</td>
<td>16 mg/kg, 48 h (gp 1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 mg/kg, 42 h (gp 2)</td>
</tr>
<tr>
<td>800–1,200</td>
<td>16 mg/kg, 42 h (gp 3)</td>
<td>20 mg/kg, 36 h (gp 4)</td>
<td>16 mg/kg, 42 h (gp 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 mg/kg, 36 h (gp 4)</td>
</tr>
<tr>
<td>1,200–2,000</td>
<td>15 mg/kg, 36 h (gp 5)</td>
<td>19 mg/kg, 30 h (gp 6)</td>
<td>15 mg/kg, 36 h (gp 5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 mg/kg, 30 h (gp 6)</td>
</tr>
<tr>
<td>2,000–2,800</td>
<td>13 mg/kg, 30 h (gp 7)</td>
<td>18 mg/kg, 24 h (gp 8)</td>
<td>15 mg/kg, 30 h (gp 7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 mg/kg, 24 h (gp 8)</td>
</tr>
<tr>
<td>≥2,800</td>
<td>12 mg/kg, 24 h (gp 9)</td>
<td>17 mg/kg, 20 h (gp 10)</td>
<td>15 mg/kg, 24 h (gp 9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 mg/kg, 20 h (gp 10)</td>
</tr>
</tbody>
</table>

*The original dosing regimen was described previously (4), and the simplified dosing regimen was used in the current study. The differences between the original and simplified regimens are highlighted in boldface and italic, and differences between the simplified and final dosing regimens are in boldface, italic, and shaded. Based on current body weight and postnatal age, 10 different patient groups (gp) were considered. The dosing interval was prolonged 10 h when ibuprofen was coadministered or when asphyxia was diagnosed/considered by the treating physician. The duration of the intravenous infusion was 20 min. PNA, postnatal age.*
Duration of vancomycin treatment for coagulase-negative *Staphylococcus* sepsis in very low birth weight infants

Nehama Linder,¹,²,⁴ Daniel Lubin,¹,⁴ Adriana Hernandez,¹ Limor Amit¹ & Shai Ashkenazi³,⁴

¹Department of Neonatology, Rabin Medical Center, ²Neonatal Intensive Care Unit and ³Pediatric Infectious Disease Unit, Schneider Children’s Medical Center of Israel, Petach Tikva, and ⁴Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
vancomycin

10 mg/kg, 60 minutes

<30 wks GA
q18h, >14 days 12h

30-36 wks GA
q12h, >14 days 8h

>36 wks GA
q12 h, >7 days 8h

Target AUC 400
Staph aureus (MRSA) pneumonia in adults

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Coagulase negative Staphylococcus (CoNS) is the major causative pathogen of late-onset sepsis in very low birth weight (VLBW) infants.
- Nearly all VLBW infants with CoNS sepsis are treated with vancomycin.
- Vancomycin is associated with a risk of toxicity and resistance but there are no guidelines regarding the duration of its use in this setting.

WHAT THIS STUDY ADDS

- Treatment with vancomycin for 5 days after the last positive blood culture is associated with a satisfactory outcome when there is no evidence of endovascular thrombi or infective endocarditis.
- Prolonged treatment with vancomycin is not associated with adverse effects.
- Further well-controlled prospective studies are needed.
Reasonable to assume (pediatric vs adult)
- Similar disease progression?
- Similar response to intervention?

Yes to both

Conduct PK studies
Conduct safety/efficacy trials

No

Reasonable to assume similar CR in pediatrics and adults

No

Conduct PK studies to achieve levels similar to adults
Conduct safety trials

Yes

Is there a PD measurement that can be used to predict efficacy?

Yes

Conduct PK/PD studies to get CR for PD measurement
Conduct PK studies to achieve target concentrations based on CR
Conduct safety trials

No
### Table 6. Effectiveness Results

<table>
<thead>
<tr>
<th>GA &lt;32 Weeks</th>
<th>GA ≥32 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PNA &lt;2 Weeks, No. (%)</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Evaluable for effectiveness, No.</td>
<td>39</td>
</tr>
<tr>
<td>Effectiveness success</td>
<td>29 (74)</td>
</tr>
<tr>
<td>Death&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Presumptive clinical cure score ≥7</td>
<td>35 (90)</td>
</tr>
<tr>
<td>Presumptive clinical cure score &lt;7</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Presumptive clinical cure score missing</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Change in antibiotic therapy</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Cultures negative for bacteria</td>
<td>27 (69)</td>
</tr>
<tr>
<td>Cultures not done</td>
<td>12 (31)</td>
</tr>
</tbody>
</table>

Abbreviations: GA, gestational age; PNA, postnatal age.

<sup>a</sup> Death occurring ≤7 days from end of study meropenem.

<sup>b</sup> Of the 23 participants with change in antibiotic therapy, 1 also died and 1 had a presumptive clinical cure score <7.
Table 4. Frequently Occurring (≥5 Participants) Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>GA &lt;32 Weeks</th>
<th></th>
<th>GA ≥32 Weeks</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PNA &lt;2 Weeks</td>
<td>PNA ≥2 Weeks</td>
<td>PNA &lt;2 Weeks</td>
<td>PNA ≥2 Weeks</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>39</td>
<td>103</td>
<td>31</td>
<td>27</td>
<td>200</td>
</tr>
<tr>
<td>AST increased&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0 (0)</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>2 (7)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>2 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (11)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Conjugated bilirubin increased&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (13)</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Hyperglycemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (5)</td>
<td>2 (2)</td>
<td>1 (3)</td>
<td>0 (0)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Hypoglycemia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (8)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 (5)</td>
<td>6 (6)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Hypotension&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (3)</td>
<td>5 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>4 (10)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>0 (0)</td>
<td>5 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 (13)</td>
<td>5 (5)</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Seizures</td>
<td>4 (10)</td>
<td>3 (3)</td>
<td>1 (3)</td>
<td>2 (7)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>4 (13)</td>
<td>0 (0)</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

Abbreviations: AST, aspartate aminotransferase; GA, gestational age; PNA, postnatal age.
<sup>a</sup> Defined per the local site.

Table 5. Laboratory Evaluations

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Days 1–7</th>
<th>Days 8–14</th>
<th>Days 15–21</th>
<th>Days 22–28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (No.)</td>
<td>181</td>
<td>173</td>
<td>127</td>
<td>85</td>
<td>53</td>
</tr>
<tr>
<td>Median (range), mg/dL</td>
<td>0.5 (0.1–1.9)</td>
<td>0.4 (0.0–3.1)</td>
<td>0.4 (0.0–2.7)</td>
<td>0.3 (0.0–2.9)</td>
<td>0.3 (0.0–2.0)</td>
</tr>
<tr>
<td>AST (No.)</td>
<td>60</td>
<td>78</td>
<td>68</td>
<td>55</td>
<td>32</td>
</tr>
<tr>
<td>Median (range), U/L</td>
<td>37 (12–3358)</td>
<td>33 (9–419)</td>
<td>33 (11–308)</td>
<td>40 (15–567)</td>
<td>50 (19–788)</td>
</tr>
<tr>
<td>ALT (No.)</td>
<td>60</td>
<td>80</td>
<td>69</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td>Median (range), U/L</td>
<td>25 (4–956)</td>
<td>18 (5–140)</td>
<td>16 (4–131)</td>
<td>20 (5–605)</td>
<td>27 (8–168)</td>
</tr>
<tr>
<td>Alkaline phosphatase (No.)</td>
<td>64</td>
<td>86</td>
<td>65</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>Median (range), U/L</td>
<td>265 (72–1368)</td>
<td>244 (35–967)</td>
<td>321 (104–1103)</td>
<td>412 (101–1600)</td>
<td>508 (123–1145)</td>
</tr>
<tr>
<td>Direct bilirubin (No.)</td>
<td>70</td>
<td>71</td>
<td>52</td>
<td>34</td>
<td>14</td>
</tr>
<tr>
<td>Median (range), mg/dL</td>
<td>0.6 (0.0–10.8)</td>
<td>0.8 (0.0–10.3)</td>
<td>1.5 (0.0–10.7)</td>
<td>1.7 (0.1–8.5)</td>
<td>3.7 (0.2–6.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
In a multivariate analysis (adjusted for confounding variables) prolonged therapy with antibiotics (≥ 5 days) in the first few days of life was associated with increased mortality, NEC or the combined outcome of death and NEC. The absolute increase in odds of death or NEC for 5-day antibiotics was approximately 4% (NNH= 25) per day after day 5.

### Table 1

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>OR per day of antibiotic use (95% CI), all babies*</th>
<th>OR per day of antibiotic use (95% CI), intubated &gt;7 days*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>1.07 (1.04 to 1.10)</td>
<td>1.09 (1.05 to 1.13)</td>
</tr>
<tr>
<td>Death</td>
<td>1.16 (1.08 to 1.24)</td>
<td>1.13 (1.05 to 1.23)</td>
</tr>
<tr>
<td>NEC or death</td>
<td>1.04 (1.02 to 1.06)</td>
<td>1.04 (1.01 to 1.07)</td>
</tr>
</tbody>
</table>

*Adjusted for study centre, gestational age, small-for-gestational age status, sex, black race, 5-min Apgar score of >5, rupture of membranes for >24 h, outborn, prenatal steroid treatment, intrapartum antibiotic treatment, maternal hypertension, maternal haemorrhage and multiple birth.

- Retrospective cohort study of 4039 ELBW infants who survived at least 5 d.

Early Empiric Antibiotic Use in Preterm Infants Is Associated with Lower Bacterial Diversity and Higher Relative Abundance of *Enterobacter*

Corryn Greenwood, MD$^{1,2}$, Ardythe L. Morrow, PhD$^{1,3,4}$, Anne J. Lagomarcino, MS$^1$, Mekibib Altaye, PhD$^4$, Diana H. Taft, BA$^{1,3}$, Zhuoteng Yu, PhD$^5$, David S. Newburg, PhD$^5$, Doyle V. Ward, PhD$^6$, and Kurt R. Schibler, MD$^1$

**Objectives** To determine the impact of empiric ampicillin and gentamicin use in the first week of life on microbial colonization and diversity in preterm infants.

**Study design** The 16s ribosomal DNA community profiling was used to compare the microbiota of 74 infants born ≤32 weeks gestational age by degree of antibiotic use in the first week of life. The degree of antibiotic use was classified as 0 days, 1-4 days, and 5-7 days of antibiotic administration. All of the antibiotic use was empiric, defined as treatment based solely on clinical suspicion of infection without a positive culture result.

**Results** Infants who received 5-7 days of empiric antimicrobial agents in the first week had increased relative abundance of *Enterobacter* ($P = .016$) and lower bacterial diversity in the second and third weeks of life. Infants receiving early antibiotics also experienced more cases of necrotizing enterocolitis, sepsis, or death than those not exposed to antibiotics.

**Conclusions** Early empiric antibiotics have sustained effects on the intestinal microbiota of preterm infants. Intestinal dysbiosis in this population has been found to be associated with elevated risk of necrotizing enterocolitis, sepsis, or death. (*J Pediatr* 2014;165:23-9).
Figure 2. Simpson diversity index depicted in relation to antibiotic receipt (No, 0 days; brief, 1-4 days; or intensive antibiotics, 5-7 days) during the first 3 weeks of life.
Figure 1. Timing of Low-Dose Penicillin Treatment and Risk of Obesity.

Cox and colleagues transferred cecal microbiota from 18-week-old controls and penicillin-treated mice to 3-week-old germ-free mice to investigate the effects on body composition and metabolism. Mice that received penicillin-altered microbiota gained total mass and fat mass at a significantly faster rate than did mice that received microbiota from controls. Mice whose mothers were treated with penicillin before the birth of the pups and throughout the weaning process had a markedly altered body composition in adulthood, with increased total and fat mass, increased ectopic fat deposition, increased hepatic expression of genes involved in adipogenesis, decreased bone mineral content, and increased bone area. The body composition of adult male mice who had received penicillin after weaning was similar to that of controls.
WHAT’S KNOWN ON THIS SUBJECT: Subtherapeutic doses of antibiotics have been used as growth promoters in animal farming since the 1950s. Antibiotic exposure during infancy is associated with increased body mass in humans.

WHAT THIS STUDY ADDS: The weight-promoting effect of antibiotics is most pronounced when the exposure occurs at <6 months of age or repeatedly during infancy. Increased body mass is distinctly associated with exposure to cephalosporins and macrolides, especially in boys.
Figure 2
Adjusted differences of means (95% CI) for zBMI and zHFA at the median age of 24 months between exposed and unexposed children (zero line) classified by age at first antibiotic exposure. A and B, boys; C and D, girls. Statistical adjustments: Maternal smoking after first trimester, parental relationships, mode of delivery, birth weight and birth length for boys; Maternal smoking after first trimester, mode of delivery and birth weight for girls.
Table 2
Postnatal characteristics of infants associated with retinopathy of prematurity (ROP).

<table>
<thead>
<tr>
<th></th>
<th>ROP</th>
<th>ROP occurrence</th>
<th>ROP progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>Grade 1/2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>N (%)</td>
<td>29 (100)</td>
<td>31 (100)</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Systemic Inflammatory Response Syndrome</td>
<td>0</td>
<td>3 (10)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Ductus arteriosus (treated)</td>
<td>0</td>
<td>5 (16)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Postnatal glucocorticoid</td>
<td>0</td>
<td>4 (13)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>3 (10)</td>
<td>16 (52)</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Hypocarbia</td>
<td>0</td>
<td>9 (29)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>1 (3)</td>
<td>9 (29)</td>
<td>12 (92)</td>
</tr>
</tbody>
</table>

Odds ratios and 95% confidence intervals are from univariable (left) and adjusted (right) logistic regression models. Adjusted models include gestational age <29 weeks as a second independent variable.

Fig. 2. Venn Diagram of prevalence of risk factors chorioamnionitis (CAM), gestational age <29 weeks, and systemic inflammatory response syndrome (SIRS) among 44 children with ROP (sum not equal to 100% due to rounding).

Damman et al, Early Human Develop 2009
NEC = Pathology
INFECTIONS
Bacteria, toxins, virus, fungi,…
Colonization with abnormal microbiota

CIRCULATORY INSTABILITY
Hypoxic-ischemic event
Polycythemia

MUCOSAL INJURY

INFLAMMATORY MEDIATORS
Inflammatory cells (macrophage)
Platelet activating factor (PAF)
Tumor necrosis factor (TNF)
Leukotriene C4, Interleukin 1; 6

ENTERAL FEEDING
Hypertonic formula, medications,
Malabsorption, gaseous distention
H₂, Endotoxine production
Outcomes at 7 years for babies who developed neonatal necrotising enterocolitis: the ORACLE Children Study

Katie Pike,1 Peter Brocklehurst,2 David Jones,3 Sarah Kenyon,4 Alison Salt,5 David Taylor,6 Neil Marlow2

What is known about this topic

- Necrotising enterocolitis is a devastating condition with high mortality and neonatal morbidity.
- It is associated with an increased prevalence of disability in infancy.
- Longer-term sequelae are rarely described.

What this study adds

- Necrotising enterocolitis (NEC) confers an increased risk of functional impairments in middle childhood which has an impact on family life.
- Necrotising enterocolitis also is associated with continuing bowel dysfunction in middle childhood.
• GBS profylaxis
• iv igg ?
• care bundle
• Equipment/DVC
• Locks with AB

• breastfeeding
• prenatal CS
• link with PDA ?
• MEF
• other strategies
  Rec lipase: failed
  Oral insulin
Effects of Preterm Birth on the Kidney

Mary Jane Black, Megan R. Sutherland and Lina Gubhaju
Department of Anatomy and Developmental Biology, Monash University
Australia

Fig. 1. A timeline of human nephrogenesis during gestation. Nephrogenesis is rapidly ongoing at the time when most preterm neonates are delivered.
Renal function and volume of infants born with a very low birth-weight: a preliminary cross-sectional study

M Zaffanello (marco.zaffanello@univr.it)¹, M Brugnara¹, C Bruno², B Franchi¹, G Talamì³, G Guidi², L Cataldi⁴, P Biban⁵, R Mella¹, V Fano⁵

1. Department of Mother-Child and Biology-Genetics, University of Verona, Verona, Italy
2. Department of Morphological-Biomedical Science, University of Verona, Verona, Italy
3. Gastroenterology and Endoscopy Unit, Department of Internal Medicine, University of Verona, Verona, Italy
4. Division of Neonatology, Catholic University of Sacred Heart, Rome, Italy
5. Neonatal and Paediatric Intensive Care Unit, Division of Paediatrics, Major City Hospital, Verona, Italy
6. Neonatal Intensive Care Unit, University of Cagliari, Cagliari, Italy

Aminoglycosides, NSAIDs
Antibiotics and renal branching morphogenesis: comparison of toxicities

Ruud R.G. Bueters¹, Lisanne J.A. Kusters¹, Annelies Klaassen¹, Lambertus P. van den Heuvel¹ and Michiel F. Schreuder¹

Figure 3. Representative immunohistochemical staining of ureteric bud development in metanephroi cultured for 24 h in media with (b) 2,000 μmol/l ceftazidime or (a) vehicle control.
route of administration: to be challenged?

oral instead of intravenous

suspected neonatal infection, but not confirmed BC+sepsis, CSF neg. admission for 7 days of iv antibiotics or discharge with high oral doses?

small studies, feasibility (Manzoni et al.; Autret et al.)

western setting: softer outcome marker (discharge, bounding, BF)

intramuscular instead of oral

African Neonatal Sepsis Trial (AFRINEST) group
oral amoxi vs intramuscular genta+penicillin different scenarios were evaluated (Lancet, 2015a and 2015b)
Voglio farmaci adatti a me.
Sperimentazione? OK.

Solo gli studi clinici condotti sui bambini garantiscono la sicurezza e l'efficacia dei farmaci per loro.

Partecipo anche io.
Coffee Break
30 minutes
Project 1 - Make the Most of Existing Data

• Description:
  • Make the most of existing data:
    To find a way to share data relevant to the design of studies about antibiotics in neonates, between companies and other Sponsors, in a pre-competitive space, by making a case for sharing through defining:
    - The purpose of sharing
    - The methodologies that will be used to analyze the shared data

• Feasibility:
  • The nature of the needed data?
  • Easier in off-patent compounds

• Impact:
  • Sharing experience and data will improve conducting clinical trials in this fragile population,
  • Avoid failed studies
  • Highlight AEs related to neonates in comparison to older population
Expert Panel on Infections

Ensuring New Antibiotics Address the Needs of NICU Patients

Gary J. Noel, MD, FAAP, FIDSA, FPIDS
C.H.I.L.D., Johnson & Johnson
Ensuring new antibiotics address the needs of NICU patients

- Extrapolating efficacy established in clinical trials involving adults (and rarely infants and older children) to newborns has been used to develop current choices of antibiotics for NICU patients.

- New agents in the later stages of development are focused on addressing the emergence of MDR bacterial pathogens.
  - Most clinical development is aimed at assessing efficacy for specific infections in adults:
    - complicated skin and soft tissue infection
    - complicated urinary tract infection
    - hospital associated pneumonia
    - complicated intra-abdominal infection
Ensuring new antibiotics address the needs of NICU patients (cont.)

- Most antibiotics used in the NICU are given to treat “sepsis”.
  - MDR bacteria have emerged as important causes of neonatal sepsis → new agents will be needed
- Extrapolation of efficacy for treatment of “neonatal sepsis” based on results of current clinical trials involving adults is especially challenging.
  - Efficacy conclusions often based on demonstrating non-inferiority in disease localized to a single organ system (eg skin, lung, urinary tract)
  - Adults with sepsis often excluded from initial registration trials
- On Feb 23rd sepsis (in adults) was re-defined by the 3rd international consensus group as “life threatening organ dysfunction caused by a dysregulated host response to infection” JAMA 2016:315:801-10 → observations in this disease state may be most relevant to newborns with serious bacterial infections.
Ensuring new antibiotics address the needs of NICU patients: Points to Consider

- **What data can we collect in adult clinical trials that would better inform our study and use of new antibiotics in neonates?** (eg dose-response relationships, inclusion of septic patients in trials, subgroup analyses of adults with sepsis)

- **What are the pharmacokinetic and pharmacodynamic assessments needed to optimize study and use of new antibiotics in sick neonates?** (eg drug distribution, modeling of dosing that considers parameters altered by sepsis (esp volume of distribution, renal clearance))

- **How can we improve our understanding of the role of bacterial infection as a cause of “neonatal sepsis”?**
  - Accurate diagnosis of serious bacterial infection in the newborn
  - Focused assessment of efficacy in NICU patients with disease caused by bacterial infection
Expert Panel on Infections

Michael Caplan
University of Chicago
Expert Panel on Infections

Kelly Wade
Children’s Hospital Philadelphia
Importance of evaluating antimicrobial drugs in the CNS - IMPACT

- Meningitis is more common in neonates & causes significant morbidity, mortality
  - Concern for ineffective treatments
  - Concern for toxicity
  - Difficult to recognize CNS toxicities in preterm infants, seizures often subclinical
  - Long term neurodevelopmental impairment

- Neonates have less mature blood brain barrier - variable CNS penetration
  - Variation with prematurity, postmenstrual age
  - Variation with inflammation
  - How are drug concentrations related to efficacy?
  - How are drug concentrations related to toxicity?

- Neonatal brain is immature and vulnerable
  - Inflammation, infection, and drug toxicities

- Paucity of data leaves neonates at risk
Importance of evaluating antimicrobial drugs in the CNS – Feasibility

• Animal models and clinical trial designs are needed to evaluate PK/PD targets designed to provide effective treatment and minimize toxicity
  • PK/PD models to evaluate efficacy of antibiotics in treatment of meningitis?
  • PK/PD models to evaluate potential drug toxicity in the CNS of neonates?
  • Understand variation in CNS penetration with post-menstrual age
  • Understand variation in CNS penetration with inflammation

• Opportunistic design has facilitated CSF collection
  • Lumbar puncture and collection of CSF is relatively common in NICU
  • PTN Meropenem study collected 9 samples from 6 infants
  • Opportunistic design for CSF collection can provide robust sample collection
    • 3 sites, extra tube (0.3-1 ml) collected with every LP, frozen at -20°
    • 684 CSF samples over 4 years
Expert Panel on Infections

Mark Turner
University of Liverpool
• Studies of Antimicrobials are important but are not standardised
  • Inefficient
  • Poor comparability
  • Poor generalisability

• Therefore we need to
  • Develop standardised approaches
  • CTTI / EnprEMA are working on other paediatric age groups
  • INC is the natural forum to work on neonates
    • Truly international
Randomized controlled trials of antibiotics for neonatal infections: a systematic review

Florentia Kaguelidou,¹,² Mark A. Turner,³ Imti Choonara,⁴ John van Anker,⁵,⁶,⁷ Paolo Manzoni,⁸ Corinne Alberti,²,⁹ Jean-Paul Langhendries¹⁰ & Evelyne Jacqz-Aigrain¹,²

¹Department of Paediatric Pharmacology and Pharmacogenetics, INSERM CIC9202, APHP, Hopital Robert Debré, 75019 Paris, ²Sorbonne Paris Cité, Univ Paris Diderot, 75019 Paris, France, ³Department of Women’s and Children’s Health, University of Liverpool, Neonatal Unit, Liverpool Women’s Hospital, Liverpool L8 7SS, ⁴Academic Division of Child Health, University of Nottingham, Derbyshire Children’s Hospital, Derby, UK, ⁵Division of Paediatric Clinical Pharmacology, Children’s National Medical Center, Washington, DC, ⁶Departments of Paediatrics, Pharmacology and Physiology, George Washington University School of Medicine and Health Sciences, Washington, DC, USA, ⁷Intensive Care, Erasmus Medical Center-Sophia Children’s Hospital, Rotterdam, the Netherlands, ⁸Neonatology and NICU, S. Anna Hospital, Torino, Italy, ⁹Department of Clinical Epidemiology, INSERM CIES, APHP, Hopital Robert Debré, 75019 Paris, France and ¹⁰NICU, CHC-Site St Vincent, 4000 Rocourt-Liège, Belgium
35 trials

<table>
<thead>
<tr>
<th>Jadad score [median (Q1–Q3)]</th>
<th>2 (1–2)</th>
<th>1 (3%)</th>
<th>12 (34%)</th>
<th>16 (46%)</th>
<th>4 (11%)</th>
<th>2 (6%)</th>
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<td>= 4</td>
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<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>3 (9%)</th>
<th>9 (25%)</th>
<th>23 (66%)</th>
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<tr>
<td>Low</td>
<td></td>
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</tr>
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<td>Unclear</td>
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<tr>
<td>High</td>
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<th>Primary outcome</th>
<th>23 (66%)</th>
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<tbody>
<tr>
<td>Defined§</td>
<td></td>
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</tr>
<tr>
<td>Not defined</td>
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</table>

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<th>Power calculation</th>
<th>14 (40%)</th>
<th>21 (60%)</th>
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<td>Stated</td>
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<tr>
<td>Not stated</td>
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35 trials

<table>
<thead>
<tr>
<th>Domains</th>
<th>Risk of bias assessments – n (%)</th>
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<tr>
<td></td>
<td>High</td>
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<tr>
<td>Sequence generation</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Blinding</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Incomplete data</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>Other sources of bias</td>
<td>11 (31%)</td>
</tr>
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</table>

This work was supported by the European Commission under the Health Cooperation Work Programme of the 7th Framework Programme (Grant agreement n223614)
Clinical trials in neonatal sepsis

Clarissa Oeser¹*, Irja Lutsar², Tuuli Metsvaht³, Mark A. Turner⁴, Paul T. Heath¹ and Mike Sharland¹

¹Paediatric Infectious Diseases Research Group, St George’s, University of London, London, UK; ²Institute of Microbiology, Tartu University, Tartu, Estonia; ³Paediatric Intensive Care Unit, Clinic of Anaesthesiology and Intensive Care, Tartu University Clinics, Tartu, Estonia; ⁴Institute of Translational Medicine, University of Liverpool, Liverpool, UK
<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Baseline parameters</th>
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</thead>
<tbody>
<tr>
<td>suspected infection</td>
<td>PNA, ethnicity, wt, sex</td>
</tr>
<tr>
<td>not specified</td>
<td>PNA, wt, sex</td>
</tr>
<tr>
<td>‘clinical and/or laboratory evidence of sepsis’: positive blood culture + clinical manifestation (not further defined) infection, severe enough to warrant penicillin/aminoglycoside combination suspected or proven bacterial infection definite sepsis: clinical features + positive blood/urine culture probable sepsis: presence of ≥2: pneumonia on X-ray, WCC &lt;500, immature to total neutros &gt;0.2, CRP above reference range, GBS antigen in blood</td>
<td>PNA, sex</td>
</tr>
<tr>
<td>proven or signs of sepsis, high risk of developing sepsis</td>
<td>wt, sex, GA, type of delivery, previous episodes of sepsis, maternal antenatal history</td>
</tr>
<tr>
<td>suspected sepsis, fulfilling septic score ≥10</td>
<td>GA, PNA, wt, sex, presenting abnormalities</td>
</tr>
<tr>
<td>suspected sepsis or meningitis</td>
<td>GA, PNA, wt, sex</td>
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Clinical outcome criteria

<table>
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<tr>
<th>Respiratory</th>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>respiratory problems</td>
<td>haemodynamic changes</td>
</tr>
<tr>
<td>apnoea, ventilator therapy</td>
<td>bradycardia, unexplained sudden collapse,</td>
</tr>
<tr>
<td></td>
<td>disseminated intravascular coagulation</td>
</tr>
<tr>
<td>apnoea (cessation of breathing &gt;15 s,</td>
<td>poor perfusion (CRFT &gt;5 s)</td>
</tr>
<tr>
<td>resulting in bradycardia and cyanosis)</td>
<td></td>
</tr>
<tr>
<td>apnoea, increased oxygen requirement</td>
<td>bradycardia spells, hypotension</td>
</tr>
<tr>
<td>increasing oxygen demand, new requirement for</td>
<td>not specified</td>
</tr>
<tr>
<td>ventilatory support</td>
<td></td>
</tr>
<tr>
<td>unexplained respiratory distress</td>
<td>poor peripheral circulation</td>
</tr>
</tbody>
</table>
# Laboratory parameters

<table>
<thead>
<tr>
<th>WCC</th>
<th>Neutrophils</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>not specified</td>
<td>immature to total neutros &gt;0.2</td>
<td>CRP &gt;20 mg/L</td>
</tr>
<tr>
<td>‘high’ WCC ± positive culture from other site</td>
<td>not specified</td>
<td>not specified</td>
</tr>
<tr>
<td>WCC &lt;5000/mm³</td>
<td>immature to total neutros &gt;0.2</td>
<td>CRP above reference range</td>
</tr>
<tr>
<td>not specified</td>
<td>immature to total neutros &gt;0.2</td>
<td>not specified</td>
</tr>
<tr>
<td>WCC &lt;5000 or &gt;20000/mm³</td>
<td>immature to total WCC ratio &gt;0.2</td>
<td>CRP &gt;10 mg/L</td>
</tr>
<tr>
<td>not specified</td>
<td>neutrophilia, neutropenia, neutropenia, high band count</td>
<td>‘high’ CRP</td>
</tr>
<tr>
<td>not specified</td>
<td>not specified</td>
<td>not specified</td>
</tr>
<tr>
<td>leucopenia, leucocytosis, left shift</td>
<td>not specified</td>
<td>not specified</td>
</tr>
</tbody>
</table>
Primary endpoints

cure/improvement: clinical recovery with eradication of original pathogen without subsequent superinfection, sufficient clinical improvement that further antibiotic therapy was deemed unnecessary, no recurrence of clinical signs after cessation of treatment

failure: death due to infection, modification of treatment because of resistance, clinical deterioration, non-eradication, superinfection, Staphylococcus aureus or Staphylococcus epidermidis

clinical improvement, death, modification of treatment

satisfactory clinical response (signs and laboratory marker abnormalities disappeared or improved), death

complete clinical recovery, bacterial eradication, change of antibiotics, deaths
LACK OF HARMONISATION IN STUDY DESIGN AND OUTCOMES IN PAEDIATRIC ANTIBIOTIC CLINICAL TRIALS REPORTED FROM 2000-2015: A SYSTEMATIC REVIEW

1Laura Folgori, MD; 1,2Julia Bielicki, MD; 1Beatriz Ruiz, MD; 3Mark A. Turner, MD; 4John S. Bradley, MD; 5Daniel K. Benjamin Jr., MD; 6Theoklis E. Zaoutis, MD; 7Irja Lutsar, MD; 8Carlo Giaquinto, MD; 9Paolo Rossi, MD; 1Mike Sharland, MD

In press, Lancet Infectious Diseases
### Table 7. Suggestions for some core elements of a neonatal sepsis trial design

**Criteria for Neonatal Sepsis Trials of AntiMicrobials**
Core elements are in **bold**
Optional elements are in *italics*

#### Inclusion criteria
EOS ≤72 h or LOS >72 h ≤90 days
- **Confirmed sepsis:**
  - ≥1 positive culture of a pathogen from a normally sterile site + ≥1 clinical or laboratory criterion (in the case of coagulase-negative staphylococci and a birth weight of >1000 g: ≥2 positive cultures, >2 h but ≤24 h apart)
- **Probable sepsis:**
  - Post-menstrual age ≤44 weeks: ≥2 clinical and ≥2 laboratory criteria (EMA)
  - Post-menstrual age ≥44 weeks: ≥1 criterion + abnormal temperature or WBCs (International Pediatric Sepsis Consensus Conference)

#### Exclusion criteria
- Previous antibiotics for 24 h, imminent demise contraindications to study drug, baseline organism resistant to study drug
- Gender, gestational age at birth, chronological age, birth weight, current weight, concomitant conditions and medications

#### Neonatal data to record
- Clinical and laboratory parameters: Day 0, Day 3, end-of-study treatment and test of cure (= ≥3 half-lives of study drug after end of treatment), to be captured as absent or present or numerical value

#### Assessments
- Primary endpoints
  - Resolution or significant improvement at test-of-cure visit of clinical signs and laboratory markers that defined sepsis at enrolment
  - No change or modifications of antibiotics within the study treatment (for >24 h)
  - Bacteriological resolution assessed by culture or molecular methods
- **Secondary endpoints:**
  - Population PK analysis, f%M >MIC as target, EUCAST breakpoints as MIC reference
  - Safety to be described by capturing all adverse events until follow-up visit
  - Recurrences, reinfections and new infections within 30 days after end of treatment

---

*J Antimicrob Chemother 2013; 68: 2733–2745*
Neonatal Sepsis – A Regulatory View

• Relatively rare disorder
  • Small patient numbers at high risk
  • Occurrence: cluster versus isolated cases

• Data extrapolation
  • Reduce risk
  • Used important information gathered from animal models, laboratory models and older children

• Study design
  • Non-conventional study design versus RCT
  • Non-conventional/non parametric statistical methodologies
  • Justification

• Clear, precise clinically-relevant case definition
  • Single or multi-organ involvement

• Clearly defined end points
  • Surrogate endpoints/biomarkers

• Long term follow up data
Priority Projects to Discuss

• Project 1 – Make the most of existing data
  • Define theoretical proposal for best way to conduct clinical trials of antibiotics in neonates
  • Develop methodology to validate theoretical proposal using available data and methods (methodology will be used to persuade companies, and other trial sponsors, to share data)

• Project 2 – Standard protocol for new studies
  • Nature of diagnosis (inclusion/exclusion criteria)
  • Nature of endpoints
  • Study design (emphasizing the importance of “new” study designs, adapted to the information gaps and practicalities of trials about antibiotics in neonates)
  • Sample size
  • Assessments during study; blood sampling, use of opportunistic samples etc.

• Project 3 – Specify how to assess the efficacy of new antibiotics in the Central Nervous System (CNS)
  • Define the characteristics of animal models that assess the effects of new antibiotics in the CNS
  • Define acceptable ways to bridge from animals to neonates in this context
  • Define acceptable ways to validate the predictions made by the bridging process
Project 1 - Make the Most of Existing Data

• Description:
  • Make the most of existing data:
    To find a way to share data relevant to the design of studies about antibiotics in neonates, between companies and other Sponsors, in a pre-competitive space, by making a case for sharing through defining:
    • The purpose of sharing
    • The methodologies that will be used to analyze the shared data

• Feasibility:
  • The nature of the needed data?
  • Easier in off-patent compounds

• Impact:
  • Sharing experience and data will improve conducting clinical trials in this fragile population,
  • Avoid failed studies
  • Highlight AEs related to neonates in comparison to older population
Project 2 - Standard Protocol for New Studies

• Description:
  • Standard protocol for new studies
    • Nature of diagnosis (inclusion/exclusion criteria)
    • Nature of endpoints
    • Study design (emphasizing the importance of “new” study designs, adapted to the information gaps and practicalities of trials about antibiotics in neonates)
    • Sample size
    • Assessments during study; blood sampling, use of opportunistic samples etc.

• Feasibility:
• Impact:
Project 3 - Assessing Efficacy of New Antibiotics in the Central Nervous System

• Description:
  • Specify how to assess the efficacy of new antibiotics in the Central Nervous System
    • Define the characteristics of animal models that assess the effects of new antibiotics in the CNS
    • Define acceptable ways to bridge from animals to neonates in this context
    • Define acceptable ways to validate the predictions made by the bridging process

• Feasibility:

• Impact:
Considering both impact and feasibility, which of the following regulatory science projects is your first choice?

1. Make the most of existing data
2. Standard protocol for new studies
3. Specify how to assess the efficacy of new antibiotics in the CNS
4. “Walk-in Option A” (offered up by audience)
5. “Walk-in Option B” (offered up by audience)
6. None of the above
Considering both impact and feasibility, which of the following projects is your second choice?

1. Make the most of existing data
2. Standard protocol for new studies
3. Specify how to assess the efficacy of new antibiotics in the CNS
4. “Walk-in Option A” (offered up by audience)
5. “Walk-in Option B” (offered up by audience)
6. None of the above
Thank You
Second Annual Neonatal Scientific Workshop

Welcome

March 8th, Morning
9:00 am  Welcome to Day 2 and Brief Highlights of Day 1
Susan McCune (US Food and Drug Administration)

9:10 am  Regulatory Science for Neonates
Janet Woodcock (US Food and Drug Administration)

9:30 am – 12:30 pm  
Hemodynamic Adaptation: Overview of the Needs and Regulatory Science Strategies for Improving Neonatal Outcomes
Mark Turner (University of Liverpool), Chair
Second Annual Neonatal Scientific Workshop

Susan McCune, M.D.
Deputy Director
Office of Translational Sciences
CDER/FDA

Introduction
March 8, 2016
March 8, 2016

9:00 am  Welcome to Day 2 and Brief Highlights of Day 1
SUSAN MCCUNE (US Food and Drug Administration)

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SHARI TARGUM (US Food and Drug Administration)
RALPH BAX (European Medicines Agency)
“Nothing in the world is worth having or worth doing unless it means effort, pain, difficulty” – Theodore Roosevelt
INC AND THE NICU

The International Neonatal Consortium will concentrate its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of pre-term birth.
Drug Development Disconnect

Majority of drugs used are off-label

Very few new therapies are being developed specifically for neonates

28 drugs studied in neonates
- 46% not used in NICUs
- 29% used in fewer than 60 neonates

Research and Development Process

- **Drug Discovery**: 3-6 years
- **Pre-Clinical**: 6-7 years
- **Clinical Trials**
  - **Phase 1**: 20-100 volunteers, 5 years
  - **Phase 2**: 100-500 volunteers, 6-7 years
  - **Phase 3**: 1000-5000 volunteers, 6-7 years
- **IND Submitted to FDA**
- **NDA Submitted to FDA**: 0.5-2 years
- **LARGE SCALE MFG**
- **FDA Review**
- **Post Marketing Surveillance**: 5-10,000 volunteers

**Number of Compounds:**
- 5,000-10,000 compounds

**One FDA-Approved Drug**

**SOURCE:** PhRMA 2008, Stages of Drug Development Process and attrition rate of compounds as they travel through the drug development process over time.
**Likelihood of Approval by Drug Development Phase**

Table 3: Comparison of our study with previous drug development success rate studies

<table>
<thead>
<tr>
<th>Phase to NDA/BLA</th>
<th>This study (2013) all indications</th>
<th>This study (2013) lead indications</th>
<th>DiMasi et al.(^6) lead indications</th>
<th>Kola et al.(^8) lead indications</th>
<th>Abrantes-Metz et al.(^9) lead indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase success</td>
<td>60.1%</td>
<td>67.6%</td>
<td>64%</td>
<td>55%</td>
<td>55.7%</td>
</tr>
<tr>
<td>Phase LOA</td>
<td>50.0%</td>
<td>58.4%</td>
<td>60%</td>
<td>42%</td>
<td>NA</td>
</tr>
<tr>
<td>NDA/BLA to approval</td>
<td>83.2%</td>
<td>86.4%</td>
<td>93%</td>
<td>77%</td>
<td>NA</td>
</tr>
<tr>
<td>LOA from phase 1(^a)</td>
<td>10.4%</td>
<td>15.3%</td>
<td>19%</td>
<td>11%</td>
<td>26.4%(^b)</td>
</tr>
</tbody>
</table>

Number of drugs in sample advanced or suspended\(^b\):
- 5,820
- 4,736
- 1,316
- NA
- 2,328

Dates of source data (duration):
- 2003–2011 (9 years)
- 1993–2009 (17 years)
- 1991–2000 (10 years)
- 1989–2002 (14 years)

Number of companies:
- 835
- 50
- 10
- NA

\(^a\) Probability of FDA approval for drugs in phase 1 development.
\(^b\) Total number of transitions used to calculate the success rate (the \(n\) value noted in the text).
\(^c\) Abrantes-Metz, et al.\(^9\) reported 26.4% from phase 1 to phase 3.

If we were to conservatively apply the 83.2% NDA/BLA success rate found in this study, Abrantes-Metz would yield the highest LOA from phase 1 (21%). NA, data not available.

http://www.nature.com/nbt/journal/v32/n1/pdf/nbt.2786.pdf
Product Failures in Drug Development

Most of the product failures in phase II and III trials are because researchers are unable to demonstrate efficacy or sufficient safety.

**Efficacy**

**Safety**

**Strategic**

**Pharmacokinetics/bioavailability**

**Commercial/financial**

**Not disclosed**

How Can the Scientific Community Help?
Consortia Deliverables

http://consortiapedia.fastercures.org/
Efforts Toward Developing Evidentiary Criteria

- PhRMA-FDA workshop, 2007
- Institute of Medicine “Workshop on Biomarker Qualification”, 2009
- FDA-cosponsored biomarkers workshop with HHMI, 2013
- FDA-cosponsored Brookings meeting, “Advancing the Use of Biomarkers and Pharmacogenomics”, 2014
- FDA-cosponsored workshop with M-CERSI and Critical Path Institute, “Evidentiary Considerations for Integration of Biomarkers in Drug Development” held August 2015
- Brookings Biomarker Meeting, October 2015
- FDA-FNIH Biomarker Consortium Workshop planned for 2016
Focus on Evidentiary Criteria

• **BEST** Resource
  - Biomarkers, **Endpoints**, and other **Tools**
  - Product of the Biomarker Working Group charged by the FDA-NIH Joint Leadership Council to develop a glossary of harmonized terminology for biomarkers and endpoints

BEST Biomarker Categories

- Susceptibility/risk biomarker
- Diagnostic biomarker
- Prognostic biomarker
- Predictive biomarker
- Monitoring biomarker
- Pharmacodynamic/response biomarker
- Safety biomarker
Validation of a Biomarker Test

- **Analytical validation** - Establishing that the performance characteristics of the test are acceptable in terms of its sensitivity, specificity, accuracy, precision, as applicable.
  - Technical performance
  - Says nothing about clinical correlations
  - Poor analytical validation may impede clinical validation

- **Clinical validation** - Establishing that the test, acceptably identifies, measures, or predicts the concept of interest (i.e., aspect of an individual’s clinical, biological, physical, or functional state, or experience).
  - Establish clinical associations
  - Many statistically significant p-values in published literature
  - Not guaranteed to be useful

- **Fit-for purpose validation**
  - Qualification (regulatory mechanism to establish suitable for use in medical product development)
  - Clinical utility determination (favorable benefit-to-risk for clinical use)

Dr. Lisa McShane, NICHD Sumner J Yaffe Lecture Series in Pediatric Clinical Pharmacology, 2/23/16
Then

Communication with FDA

Now

Concept: S.McCune
Graphic: T.Benthin
Summary of ROP and Infection Polling
Results of ROP Discussion

N=73

<table>
<thead>
<tr>
<th></th>
<th>First</th>
<th>Second</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Enrichment Strategies</td>
<td>5%</td>
<td>14%</td>
</tr>
<tr>
<td>B. Data Standards</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>C. ROP-specific Outcomes</td>
<td>25%</td>
<td>26%</td>
</tr>
<tr>
<td>D. Multiple Outcomes</td>
<td>14%</td>
<td>19%</td>
</tr>
<tr>
<td>E. Standardizing in Trials Targeting Systemic Inflammation</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>F. Combination B and C</td>
<td>48%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Online – 9 votes
First  A=1; C=4; D=4
Second A=1; B=3; C=3; E=2
# Results of Infection Discussion

N=64

<table>
<thead>
<tr>
<th></th>
<th>First</th>
<th>Second</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Make the most of existing data</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>B. Standard protocol for new studies</td>
<td>44%</td>
<td>29%</td>
</tr>
<tr>
<td>C. How to assess efficacy in the CNS</td>
<td>36%</td>
<td>48%</td>
</tr>
</tbody>
</table>

**Online – 5 votes**

First  A=3; B=1; C=1
Second A=1; B=2; C=2
March 8, 2016

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Hemodynamic Adaptation: Overview of the Needs and Regulatory Science Strategies for Improving Neonatal Outcomes

Mark Turner
INC Co-Director, U-Liverpool, Chair
Agenda – Hemodynamic Adaptation

9:30 am  An Overview of Hemodynamic Issues that Pose Regulatory Challenges; Keith Barrington (Canada) Heike Rabe (Brighton and Sussex Medical School)

10:15 am  COFFEE BREAK

10:45 am  PANEL DISCUSSION
Gene Dempsey (University College Cork, Ireland)
Jeffrey Jacobs (Johns Hopkins Hospital)
Janis Dionne (BC Children’s Hospital, Vancouver)
Neil Marlow (University College London)
Tonse Raju (NICHD/NIH)
Shari Targum (US Food and Drug Administration)
Ralph Bax (European Medicines Agency)

12:15 pm  Voting on Priority Projects for ROP

12:30 pm  LUNCH
Generalisable ways to facilitate

The rational use of data to support claims that a drug has a useful effect when used to treat a specific indication

When is data / biomarker “regulatory ready”

Specific to a particular application

- Drug / indication
- Biomarker Qualification
Generalisable ways to facilitate

The **rational use of data** to support claims that a drug has a useful effect when used to treat a specific indication

When is data / biomarker “regulatory ready”

*Specific to a particular application*

- *Drug / indication*
- *Biomarker Qualification*
The rational use....

Rational use:
• Assumptions
• Model
• Predictions
• Data
• Test model and validate predictions
• Conclusions
Rigour
Data:
• Reliable measurements
• Reliable collection

Stringency
Regulatory Readiness

Data

Rational Use

Data
Regulatory Readiness: Case 1

Rational Use

Data
Regulatory Readiness: Case 1

Good understanding of how to use data and sufficient data
Regulatory Readiness: Case 1

Rational Use

- Good understanding of how to use data and sufficient data

Data

Regulatory Engineering
Regulatory Readiness: Case 2

Rational Use vs. Data

[Graph showing a point in the 'Rational Use' quadrant]
Regulatory Readiness: Case 2

- Good understanding of how to use data
  - Extrapolation
  - Well-justified protocol
Regulatory Readiness: Case 2

Rational Use

Data

Gather data

Good understanding of how to use data
- Extrapolation
- Well-justified protocol
Regulatory Readiness: Case 3

Rational Use

Data
Regulatory Readiness: Case 3

Sufficient high quality data about the drug and the condition
Regulatory Readiness: Case 3

Develop the case to move from data to indication

Sufficient high quality data about the drug and the condition

(this may involve collecting some more data)
Regulatory Readiness: Case 4

Rational Use

Data
Neither data nor understanding
Rational Use

Develop understanding

Neither data nor understanding

Data
Regulatory Readiness: Case 4

Rational Use

- Develop understanding
- Gather data (in a way that develops understanding)
- Neither data nor understanding
Regulatory Readiness and INC

Diagnose the current situation
Make a plan to improve the current situation
Execute the plan
Cardiovascular adaptation to birth in the very preterm infant

Keith J Barrington
CHU Sainte Justine
Hemodynamic Adaptation

- I have no conflicts of interest to declare
Why focus on the very preterm?

- Very frequent interventions for cardiovascular support
- Extreme variability between centers
- Frequent long term adverse outcomes
- Observational data showing associations between intervention and adverse outcomes
Laughon et al: the ELGAN study

<table>
<thead>
<tr>
<th>Gestational age, wk</th>
<th>Total n</th>
<th>No Treatment n=249</th>
<th>Any Treatment n = 1138</th>
<th>Vasopressor Treatment n = 470</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Proportion of Infants, %</td>
<td>P = .001</td>
<td>P = .0005</td>
</tr>
<tr>
<td>23</td>
<td>85</td>
<td>7</td>
<td>93</td>
<td>52</td>
</tr>
<tr>
<td>24</td>
<td>246</td>
<td>10</td>
<td>90</td>
<td>47</td>
</tr>
<tr>
<td>25</td>
<td>289</td>
<td>16</td>
<td>84</td>
<td>34</td>
</tr>
<tr>
<td>26</td>
<td>338</td>
<td>18</td>
<td>82</td>
<td>32</td>
</tr>
<tr>
<td>27</td>
<td>429</td>
<td>27</td>
<td>73</td>
<td>25</td>
</tr>
<tr>
<td>Center</td>
<td>% Treated</td>
<td>Lowest MAP d1</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>---------------</td>
<td>----</td>
<td>--------</td>
</tr>
<tr>
<td>A</td>
<td>29</td>
<td>28</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>46</td>
<td>27</td>
<td>2</td>
<td>(1–4)</td>
</tr>
<tr>
<td>C</td>
<td>61</td>
<td>20</td>
<td>4</td>
<td>(2–7)</td>
</tr>
<tr>
<td>D</td>
<td>69</td>
<td>24</td>
<td>5</td>
<td>(3–9)</td>
</tr>
<tr>
<td>E</td>
<td>80</td>
<td>25</td>
<td>9</td>
<td>(5–20)</td>
</tr>
<tr>
<td>F</td>
<td>85</td>
<td>24</td>
<td>13</td>
<td>(6–27)</td>
</tr>
<tr>
<td>G</td>
<td>91</td>
<td>23</td>
<td>24</td>
<td>(11–50)</td>
</tr>
<tr>
<td>H</td>
<td>92</td>
<td>23</td>
<td>26</td>
<td>(13–52)</td>
</tr>
<tr>
<td>I</td>
<td>93</td>
<td>23</td>
<td>32</td>
<td>(7–145)</td>
</tr>
<tr>
<td>J</td>
<td>93</td>
<td>25</td>
<td>34</td>
<td>(15–78)</td>
</tr>
</tbody>
</table>
## Variability in inotrope Rx

<table>
<thead>
<tr>
<th>Center</th>
<th>% Treated</th>
<th>Lowest MAP d1</th>
<th>OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>6</td>
<td>19</td>
<td>1 (1–6)</td>
<td>3 (1–9)</td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>20</td>
<td>2</td>
<td>3 (1–10)</td>
</tr>
<tr>
<td>F</td>
<td>15</td>
<td>21</td>
<td>3 (1–7)</td>
<td>3 (1–10)</td>
</tr>
<tr>
<td>M</td>
<td>18</td>
<td>25</td>
<td>3 (1–9)</td>
<td>4 (2–12)</td>
</tr>
<tr>
<td>D</td>
<td>20</td>
<td>22</td>
<td>4 (1–10)</td>
<td>5 (2–14)</td>
</tr>
<tr>
<td>B</td>
<td>27</td>
<td>37</td>
<td>6 (2–15)</td>
<td>8 (3–22)</td>
</tr>
<tr>
<td>H</td>
<td>32</td>
<td>21</td>
<td>7 (3–17)</td>
<td>12 (5–30)</td>
</tr>
<tr>
<td>K</td>
<td>38</td>
<td>21</td>
<td>9 (4–22)</td>
<td>11 (4–27)</td>
</tr>
<tr>
<td>C</td>
<td>44</td>
<td>19</td>
<td>12 (4–30)</td>
<td>19 (7–52)</td>
</tr>
<tr>
<td>J</td>
<td>46</td>
<td>23</td>
<td>13 (5–31)</td>
<td>25 (10–65)</td>
</tr>
<tr>
<td>I</td>
<td>48</td>
<td>25</td>
<td>14 (5–42)</td>
<td>34 (11–107)</td>
</tr>
<tr>
<td>E</td>
<td>52</td>
<td>24</td>
<td>16 (6–42)</td>
<td>48 (17–132)</td>
</tr>
</tbody>
</table>
What normally happens?

• Numerically low blood pressures are frequent in the first 3 days of life
• No clear correlation between “hypotension” and systemic perfusion
• Most “hypotension” due to low vascular resistance
• Spontaneous elevation of BP
Both body weight and gestational age are important in determining BP after birth.

Defining hypotension

• Statistically (<10%le)
• Outcomes (Threshold for worse outcome)
• Treatment thresholds proven to improve outcomes

• Currently, most common are MAP < GA, and MAP <30
  • Neither statistically valid, nor associated with outcomes, nor proven treatment threshold

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Dependent variable</th>
<th>IVH</th>
<th>BPD</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td>0.76 (0.72 to 0.80)</td>
<td>0.71 (0.67 to 0.75)</td>
<td>0.69 (0.62 to 0.77)</td>
</tr>
<tr>
<td>Female gender</td>
<td></td>
<td>0.86 (0.72 to 1.03)</td>
<td>0.61 (0.51 to 0.75)</td>
<td>0.64 (0.44 to 0.94)</td>
</tr>
<tr>
<td>Multiple birth</td>
<td></td>
<td>1.28 (1.05 to 1.55)</td>
<td>0.75 (0.60 to 0.93)</td>
<td>1.32 (0.88 to 1.97)</td>
</tr>
<tr>
<td>Small for gestational age (&lt;10th percentile)</td>
<td></td>
<td>0.65 (0.47 to 0.88)</td>
<td>2.59 (2.00 to 3.37)</td>
<td>2.86 (1.80 to 4.55)</td>
</tr>
<tr>
<td>Maternal steroid treatment</td>
<td></td>
<td>0.64 (0.47 to 0.87)</td>
<td>1.13 (0.80 to 1.60)</td>
<td>0.68 (0.38 to 1.24)</td>
</tr>
<tr>
<td>Maternal treatment with antibiotics</td>
<td></td>
<td>0.86 (0.69 to 1.06)</td>
<td>0.88 (0.70 to 1.11)</td>
<td>1.07 (0.68 to 1.69)</td>
</tr>
<tr>
<td>Maternal treatment with tocolytics</td>
<td></td>
<td>1.14 (0.93 to 1.40)</td>
<td>0.93 (0.75 to 1.15)</td>
<td>1.13 (0.73 to 1.75)</td>
</tr>
<tr>
<td>Birth due to amniotic infection</td>
<td></td>
<td>0.90 (0.72 to 1.13)</td>
<td>0.71 (0.55 to 0.91)</td>
<td>0.70 (0.43 to 1.13)</td>
</tr>
<tr>
<td>Birth due to placental abruption</td>
<td></td>
<td>1.40 (1.02 to 1.90)</td>
<td>1.00 (0.70 to 1.42)</td>
<td>0.78 (0.38 to 1.59)</td>
</tr>
<tr>
<td>Inborn</td>
<td></td>
<td>1.01 (0.55 to 1.85)</td>
<td>1.14 (0.56 to 2.31)</td>
<td>1.03 (0.32 to 3.35)</td>
</tr>
<tr>
<td>Apgar &lt;7 at 5 min of age</td>
<td></td>
<td>1.54 (1.24 to 1.91)</td>
<td>1.08 (0.85 to 1.37)</td>
<td>1.63 (1.08 to 2.44)</td>
</tr>
<tr>
<td>Umbilical artery pH &lt;7.1</td>
<td>1.45 (0.89 to 2.31)</td>
<td>0.76 (0.43 to 1.32)</td>
<td>1.12 (1.09 to 5.60)</td>
<td></td>
</tr>
<tr>
<td>Early-onset sepsis</td>
<td></td>
<td>2.06 (1.16 to 3.67)</td>
<td>1.32 (0.71 to 2.45)</td>
<td>2.47 (1.09 to 5.60)</td>
</tr>
<tr>
<td>Treatment with inotropes during the first 24 h of life</td>
<td>1.86 (1.43 to 2.42)</td>
<td>2.40 (1.82 to 3.16)</td>
<td>1.48 (0.92 to 2.38)</td>
<td></td>
</tr>
<tr>
<td>Lowest mean arterial blood pressure during the first 24 h of life (mm Hg)</td>
<td>0.97 (0.96 to 0.99)</td>
<td>0.96 (0.94 to 0.98)</td>
<td>0.94 (0.90 to 0.98)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Frequencies of indicators of hypotension and developmental delay (row percents).

<table>
<thead>
<tr>
<th>Exposures and BSID outcomes</th>
<th>Lowest ¼ile MAP§</th>
<th>Vaso-pressor¶</th>
<th>Labile MAP†</th>
<th>BSID &lt; 70</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MDI</td>
</tr>
<tr>
<td>Lowest ¼ile MAP§</td>
<td>Yes</td>
<td>45</td>
<td>42</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>20</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Vasopressor¶</td>
<td>Yes</td>
<td>38</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>16</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Labile MAP†</td>
<td>Yes</td>
<td>39</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>17</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>BSID MDI &lt; 70</td>
<td>Yes</td>
<td>25</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>21</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>BSID PDI &lt; 70</td>
<td>Yes</td>
<td>24</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>21</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Maximum number of infants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Row percent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

§ Lowest ¼ile MAP: lowest MAP recorded in the first 24 hours, in the lowest quartile for gestational age
¶ Vasopressor: treatment for hypotension in the first 24 hours, using any vasopressor (dopamine, dobutamine, epinephrine)
† Labile MAP: labile blood pressure, defined as the upper quartile of the difference in the lowest and highest MAP
BSID: Bayley Scales of Infant Development; MDI: Mental Developmental Index; PDI: Psychomotor Developmental Index
Does hypotension need treating?

• Why do so many extremely preterm babies receive treatment?
• Concerns about “pressure-passive” cerebral circulation, and that hypotension leads to decreased brain perfusion
• Many centers treat infants when Mean BP <30 mmHg
• Many others treat when Mean BP < GA in weeks
A systematic review: criteria for selection


• Prospective cohort studies of unselected groups of VLBW infants, entered at the time of birth.

• Regular reliable measurement of BP with standardized cranial ultrasound assessment, preferably performed masked.

• Preferably the infants should not have received therapy for hypotension.
Systematic review

• None of the publications satisfied *a priori* criteria.

• 3 studies had good data on the incidence of IVH and frequent evaluation of BP, all limited.

• Miall-Allen had very few infants.

• Bada presented all results for <1 kg together (n=16). (Extrapolation to the smallest infants is probably not reliable).

• Watkins, retrospective, but appear useful for current neonatology.
<table>
<thead>
<tr>
<th>First Author</th>
<th>Number of infants</th>
<th>BP measurement Method</th>
<th>IVH ascertainment</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bada HS\textsuperscript{114}</td>
<td>VLBW infants, 72 without and 28 with greater than grade 1 IVH.</td>
<td>BPs from UACs recorded every minute (then averaged over 15 minutes),</td>
<td>Head U/S at 6, 12 and 24 hours, then daily for 7 days. Tapes were read blindly.</td>
<td>Norms for groups &gt;1000g and &lt;1000g without IVH produced. BPs in infants with IVH were below postnatal age curves, but infants also less mature. Then matched a group with the same gest. as the IVH infants; the IVH infants still had lower BP, as well as lower Apgars, and lower worst pH.</td>
</tr>
<tr>
<td>Miall-Allen VM 1987\textsuperscript{119}</td>
<td>33 infants, 26 to 30 wk gestation; birth wt ranged 700-1700g.</td>
<td>Continuous BP measurement from arterial line</td>
<td>Ultrasounds “at least daily” by examiner unaware of BPs.</td>
<td>Albumin given to an unknown number of infants, 7 received dobutamine or dopamine or both. Sustained mean BP &lt;30mmHg significantly associated with major IVH or PVL, (n= 9).</td>
</tr>
<tr>
<td>Watkins AMC\textsuperscript{40}</td>
<td>131 VLBW infants for 4 days. 58 infants with IVH, 22 with ischaemic lesions.</td>
<td>BP from art. lines for first 4 d of life. Data taken retrospectively from charts.</td>
<td>Daily cranial ultrasounds for 4 days, then weekly. Not blinded.</td>
<td>Developed 10\textsuperscript{th} percentiles for 100 gram birth weight groups at each 12 hours of life Hypotension &lt;10\textsuperscript{th} percentile for more than 2 hours was associated with decreased survival and increased IVH. Some infants received blood products or dopamine, data not given.</td>
</tr>
</tbody>
</table>
Treatments for hypotension

• Recommendations (NANN 2010)

• Based on NO data
Cardiac output in babies is complicated

• In adults it is simple

• Right Ventricular Output, (not left)
  • As long as there is no significant foraminal shunt

• SVC flow
LVO & RVO

Ductus Arteriosus

LV Output

RV Output
Figure 3 Scatter plot of mean blood pressure (BP) against superior vena cava (SVC) flow for all observations. Reference lines represent SVC flow of 41 ml/kg/min and mean BP of 30 mm Hg.

Functional Echocardiography

• Threshold of 40 mL/kg/min well-supported but a bit simplistic
  • Ignores HgB, SpO2, VO2
• Not simple to measure SVC flow
• Inter-observer variability
• Intermittent
NIRS

• Gold Standard?
• Tissue oxygenation is what we are really concerned about
• Some analyses suggest +/- 17% accuracy
• Are low results correlated with long term outcomes?
• How low is too low?
NIRS and Echo,
Moran, Miletin, Pichova and Dempsey 2009
Figure 1. The course of rcSO2 (A), FTOE (B), and tcSaO2 (C) in preterm infants with GMH-IVH or PVHI versus a preterm control group.

Verhagen E A et al. Stroke 2010;41:2901-2907
The course of the values for rsco2 (A), FTOE (B), and tcSao2 (C) during the first 2 weeks after birth in infants with and without TPE. Differences between the 2 groups (P < .05, TPE versus no TPE).

Can we affect the cerebral NIRS signal?


• 166 babies <28 weeks gestation randomized

• NIRS either masked or open

• Protocol to respond when NIRS outside target range (55 to 85%)
Fig 3 Burden of hypoxia and hyperoxia by treatment group.
Moving forward 1.

• Practicality: most current treatments for “circulatory compromise” in the preterm infant are based on measurements of blood pressure, and trying to raise blood pressure, when it is considered too low
  • How much does dopamine, compared to placebo, actually increase blood pressure?
  • Does increasing blood pressure improve clinical outcomes, are there intermediate (biomarker) measurements that correlate well enough with clinical benefit?
The HIP trial

• Successful FP7 application, PI Gene Dempsey,
• RCT of 800 infants less than 28 weeks
  • Arterial catheter in place
  • Mean BP <GA-1 mmHg
• Masked trial, dopamine or placebo
• If max study drug dose reached (20 mcg/kg/min) further treatment only if signs of poor perfusion
• If signs of poor perfusion during treatment, rescue
• Primary outcome survival without serious brain injury
• Co-primary outcome: survival without neurodevelopmental impairment to 2 years CA.
Moving Forward

• Define signs of cardiovascular compromise that are reliable indicators of poor outcome ("biomarkers")

• Decide on interventions that are worth investigating to improve those signs and those outcomes
Moving Forward

• Most promising biomarker: cerebral NIRS
  • SafeBOOSC
  • RCTs of methods to improve cerebral NIRS saturations, do they also improve long term outcomes?
Hemodynamic Adaptation: Challenges in Neonatal Drug Studies

Heike Rabe
Brighton & Sussex Medical School
University of Sussex
University of Brighton
Postnatal Changes in Circulation

- Placental circulation stops
- Fetal shunts close
- PDA: Change to left-right shunt
- Capillary bed: dilated, resistance decreases
Challenges in Neonatal Circulatory Failure

- No internationally agreed definition of circulatory compromise/shock
- Treatment with unlicensed drugs
- Traditional criteria:
  - Blood pressure: normal mean defined as equal to gestational age*
  - Capillary refilling time
  - Urine output
  - Requirement for ventilation
- *Linderkamp 1981

Outcome measure: **Survival without brain damage**
- 8 countries
- 18 partners

- 11 clinical trial sites
- 3 clinical trials
  - NeoCirc-001 (&001A - PK) start 2014
  - NeoCirc-001 (&001B – PK/PD)
  - NeoCirc-002
  - NeoCirc-003
Aims:

• Provide an age appropriate formulation of Dobutamine
• A new definition of neonatal circulatory failure
Hemodynamic Adaptation

• **Pathophysiology**
  - Hypovolaemia
  - Peripheral dilatation
  - Reduced cardiac output/ venous return
  - Increased pulmonary resistance
  - Infection
  - Toxic metabolites
  - Congenital malformations (heart, endocrine etc)

• -> concentrate on *first 72 h* after birth
• -> define suitable *short term outcome measures*

**Outcome measure:** *Survival without brain damage*
Implications for future studies

• Circulatory failure definition depends on
  • Age group: preterm, term,
  • Age of life e.g. transition after birth, first 4 weeks of life
  • Underlying other conditions
  • Antenatal risk factors

• Consider whether short term biomarkers change?
Non-invasive Assessments of Neonatal Haemodynamics

- Clinical examination:
  - capillary refilling time
  - skin colour
  - blood pressure
  - urine output
  - regional oxygenation

- NIRS:

- Echocardiography and Doppler:

- Laser Doppler and White light Spectroscopy:

- Pulse Oxymetry:

- Biochemical:
  - Cardiac output
  - Superior vena cava flow
  - peripheral vasomotion
  - oxygenation and perfusion index
  - Lactate
Capillary Refilling Time

- Press skin for 5 seconds
- Release and observe time to reperfuse
- Observer dependant
- Skin areas:
  - Foot
  - Hand
  - Toes and fingers
  - Sternum
### Table 3: Diagnostic accuracy of central-peripheral temperature difference (CPTd) and capillary refill time (CRT) for prediction of low superior vena cava flow in preterm infants < 30 weeks gestation

<table>
<thead>
<tr>
<th></th>
<th>Sn</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR−</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPTd ≥ 2°C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 hours</td>
<td>29 (15 to 42)</td>
<td>78 (65 to 90)</td>
<td>20 (8 to 32)</td>
<td>85 (74 to 96)</td>
<td>1.29</td>
<td>0.92</td>
</tr>
<tr>
<td>10 hours</td>
<td>41 (27 to 55)</td>
<td>66 (52 to 79)</td>
<td>41 (27 to 55)</td>
<td>66 (52 to 79)</td>
<td>1.19</td>
<td>0.90</td>
</tr>
<tr>
<td>All observations</td>
<td>40 (32 to 48)</td>
<td>69 (61 to 77)</td>
<td>23 (16 to 30)</td>
<td>83 (77 to 90)</td>
<td>1.30</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>CRT ≥ 3 seconds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 hours</td>
<td>54 (45 to 63)</td>
<td>79 (72 to 86)</td>
<td>23 (16 to 31)</td>
<td>93 (89 to 98)</td>
<td>2.55</td>
<td>0.58</td>
</tr>
<tr>
<td>10 hours</td>
<td>59 (50 to 68)</td>
<td>75 (67 to 82)</td>
<td>51 (42 to 60)</td>
<td>80 (73 to 87)</td>
<td>2.33</td>
<td>0.55</td>
</tr>
<tr>
<td>All observations</td>
<td>55 (50 to 60)</td>
<td>80 (76 to 84)</td>
<td>33 (29 to 38)</td>
<td>91 (88 to 94)</td>
<td>2.78</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>CRT ≥ 4 seconds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 hours</td>
<td>38 (30 to 47)</td>
<td>93 (88 to 97)</td>
<td>38 (30 to 47)</td>
<td>93 (88 to 97)</td>
<td>5.24</td>
<td>0.66</td>
</tr>
<tr>
<td>10 hours</td>
<td>26 (18 to 33)</td>
<td>97 (93 to 100)</td>
<td>77 (70 to 84)</td>
<td>74 (67 to 82)</td>
<td>7.44</td>
<td>0.77</td>
</tr>
<tr>
<td>All observations</td>
<td>29 (24 to 33)</td>
<td>96 (94 to 98)</td>
<td>55 (50 to 60)</td>
<td>88 (85 to 91)</td>
<td>6.84</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals.

**LR+**, Positive likelihood ratio; **LR−**, negative likelihood ratio; **NPV**, negative predictive value; **PPV**, positive predictive value; **Sn**, sensitivity; **Sp**, specificity.
Blood pressure in the Transition Period

Figure 1. Currently suggested lower and upper limits for normal blood pressure in neonates [2].

Farrugia Future Cardiol 2013
Implications for future studies

• Several methods for assessment of circulatory failure available
• Some surrogate methods

• Critical appraisal required
• Neonatal studies: non-invasive preferred
• Global application
Hemodynamic Adaptation

- Bravo 2015
  - RCT Dobutamine vs Placebo preterm infants
  - Stepwise dose-response: 10-15-20 µg/kg/min

- Short term Biomarkers identified:
  - Lactate
  - Negative Base Excess
  - Low blood pressure
  - Low SVCF
Hemodynamic Adaptation

• Implications for future studies:
• Choose entry criteria wisely
• Simple and widely available
• Well defined age group
• Well defined condition needing treatment
• Well prescribed treatment algorithm derived from available studies and decades of experience
• Need academia, industry and regulatory entities working together
Hemodynamic Adaptation: NEO-CIRC Lessons

• Age appropriate formulation of Dobutamine:
  • Reduce excipients: Sodium Metabisulphate

  • -> reduced toxicity in vulnerable neonatal metabolism
  • -> reduced shelf life of new drug
  • -> trial halted
  • -> adjustments to manufacturing process
  • -> trial completed
Delay at start/end of infusion

**NEOCIRC-001 END OF INFUSION CALCULATIONS [VYGON Ready-set “Unite” 836.205]**

1. List the rates of all infusions flowing through the same catheter as the 0.9% saline flush for NEOCIRC port (Q1 in example above):

<table>
<thead>
<tr>
<th>Port</th>
<th>Drug</th>
<th>Infusion rate (ml/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>NEOCIRC saline flush</td>
<td>Q1=</td>
</tr>
<tr>
<td>Q2</td>
<td>PN + other drugs</td>
<td>Q2=</td>
</tr>
<tr>
<td>Q3</td>
<td>Lipid</td>
<td>Q3=</td>
</tr>
</tbody>
</table>

2. Calculate time to clear dead space (Delay at end of infusion): ___________ min

\[
\text{Time to clear dead space [ml]} = \left( \frac{V_A}{Q_1} + \frac{V_B}{Q_1 + Q_2} + \frac{V_{\text{Catheter}}}{Q_1 + Q_2 + Q_3} \right) \times 60
\]

Where: \(V_A = 0.22 \text{ ml}, V_B = 0.76 \text{ ml}\)

** The above formula is only valid for the set-up shown in the diagram, with a dedicated NEOCIRC dobutamine port before the filter (Q1).

** The EXACT set-up and volume values need to be verified by the NEOCIRC RESEARCH TEAM in advance of any calculation and the formula adapted if needed.

3. Date and ACTUAL time NEOCIRC infusion pump stopped:

4. Date and time of EFFECTIVE END of NEOCIRC infusion (S+2):

Time to baby: 30 min
End clearance: 74 min
Understanding the changes in inotrope stability using a clinical model of infusion

C Thompson PAS 2016
Understanding the changes in inotrope stability using a clinical model of infusion

C Thompson PAS 2016
Hemodynamic Adaptation

NeoCirc001- PK/PD studies

Multicentre pilot trial to *observe* the effects of Dobutamine on SVC flow and other biomarkers in preterm neonates < 33 weeks in the first 72 hours including PK/PD data.
NeoCirc001A: Data

- 6 hourly intervals:
  - Blood gas
  - Lactate
  - Hb, Blood sugar
  - Capillary refill
  - SVCF 6-12 h
  - Use of inotropes

- Additional information:
  - Ventilatory requirements
  - Urine output
  - Other medication
  - aEEG; NIRS; MRI at term, SvO2 (selected centres)
  - *PK sampling after end of Dobutamine infusion*
## Dobutamine Half Life

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>2-3 min</td>
</tr>
<tr>
<td>NEO-CIRC: Neonatal Piglet (Mielgo unpublished data)</td>
<td>5.6 min  (wash out: 28-40 min)</td>
</tr>
<tr>
<td>NEO-CIRC 001A: (unpublished data)</td>
<td>Mean 24 min (wash out up to 180 min)</td>
</tr>
</tbody>
</table>
Hemodynamic Adaptation

• Implications for future studies:
  • NEO-CIRC001A provided much needed information of PK half life time and time to drug stability
  • Study delay to entry into baby’s blood circulation
  • Future new drug development: stability as infused and in nursery like environment
  • Test different preparations
  • Discuss standard infusions
Coffee Break
30 minutes
Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Gene Dempsey
University College Cork, Ireland
Practical Challenges: Administration
Who are the PDCO?

E. M. Dempsey · K. Connolly
Neonatal Specific Formulations

• Adult preparations
  • Dilution: Errors
  • Infection
  • Time

• Neonatal Formulations
  • Vial size
  • Wastage
  • Excipients
Administration

- Preterm presents many challenges
  - Size (Weight)
  - Fluid volume
  - Limited access
  - Low flow rates
  - Multiple infusions
Administration- Drug Delivery Times

- Factors Influencing Delivery
  - Height between catheter tip and pump
  - Syringe size and design
  - Infusion tubing size and design
  - Vascular access devices
  - Inline filters
  - Connecting multiple infusions to a single line by add on devices
Practical Challenges: Recent Trials
Recent Trials

- NIH: ELGAN BP
- HIPHOP
- TOHOP
- AHIP
- HIP
- Neocirc
Early Blood Pressure Management in Extremely Premature Infants (ELGAN BP)

- Preterm Infants 23-26/+6
- First 24 hrs with invasive line in situ
- 4 groups:
  1. dopamine/placebo
  2. dopamine/hydrocortisone
  3. placebo/placebo
  4. placebo/hydrocortisone.
Early Blood Pressure Management in Extremely Premature Infants (ELGAN BP)

**Figure.** Flow diagram of infants.
23-30 weeks gestation

- **eligible**
  - BP < threshold?
    - yes
      - Randomize
        - Treatment 1
        - observation
          - hypoperfusion?
            - Yes
              - Treatment 2
            - No
              - observation
    - no

- **Treatment 1**
- **observation**
TOHOP

- Treatment of Hypotension of Prematurity: a Randomized, Non-blinded Cohort Clinical Trial

- Preterm Infants 23-30 weeks

Inclusion Criteria:
- Idiopathic arterial hypotension as defined by a mean BP in mmHg less than the GA in weeks at birth.
- Written parental consent

Exclusion Criteria:
- Prior inclusion indirect clinical or direct laboratory evidence of poor organ/tissue perfusion (plasma lactate >6 mmol/L on two consecutive measurements and/or urine production <0.6 mL/kg/h for a 6-hour period
- Intrauterine exposure to excessive maternal vasoactive medication (i.v. use of labetolol)
- Clinically and/or microbiologically proven sepsis
- Major congenital abnormalities
- Postnatal age at the time of the development of systemic hypotension >72 hours
- No arterial line for continuously monitoring of blood pressure
Mean BP < Gestational Age

- Standard treatment protocol
- Compromised tissue perfusion (NIRS, lactate urine output)

Neurodevelopmental outcome assessment at 24 months
Bayley Scales of Infant Development III
The HIP Trial

HIP stands for: Management of Hypotension In the Preterm Extremely Low Gestational Age Newborn

The HIP Trial is an EU FP7 funded project that will be the largest multicentered European study in Extremely Low Gestational Age Newborns (ELGANs).

Please click here for a summary, for background, for objectives and for impact of the HIP Trial research project.
The aim of the NEO-CIRC project is to produce safety and efficacy data on the use of Dobutamine in the treatment of hypotension in pre and full term babies.

- Neonates 24 to 32+6 weeks
- Postnatal age < 72 hours
- Parental informed consent
- Clinical signs indicating infants at risk of poor perfusion (i.e. evidence of haemodynamic insufficiency) defined as:

  - Either two or more of:
    1. Mean blood pressure (MBP) < gestational age (GA) - 1 mmHg (invasive/non-invasive, two readings 15 min apart);
    2. SVC flow < 51 ml/kg/min;
    3. CRT > 4 sec;
    4. Lactate > 4 mmol/l
    5. Base excess < -9 mmol/l
Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Jeffrey Jacobs
John Hopkins Hospital
Hemodynamic Adaptation: Measurement of Blood Pressure
Blood Pressure Trends in Neonates
Hypertension in the NICU

Janis Dionne, MD, FRCPC
Clinical Assistant Professor, Department of Pediatrics, Division of Nephrology, University of British Columbia, Canada

Medical Director, Pediatric Kidney Services, BC Provincial Renal Agency
Method of BP Measurement

**Direct**
- Intra-arterial (Umbilical, Radial, Others)

**Indirect**
- Sphygmomanometer (Mercury or Aneroid)
  - Palpation
  - Auscultation
- Ultrasonic Doppler

**Oscillometric Device**
- Measures MAP, calculates SBP & DBP
- Each manufacturer uses different algorithms to determine BP values
Several studies show statistically good correlation between oscillometric BP and intra-arterial measures.

**Clinical issues:**
- Different devices over- or under-estimate BP by varying amounts.
- Correlation studies use cut-off values of (+/−) 5 to 10 mmHg for statistical similarity but this difference is large in neonates and can change the clinical impression.
- Most over-estimate BP in the lowest range (MAP <30 mmHg) with risk of under-recognition of hypotension.
Determination of Optimal Cuff Width/Arm Circumference in Infants

Optimal cuff width to arm circumference ratio is 0.45 to 0.70


Luma G et al. *Am Fam Physician* 2006;73:1158
A Standard Protocol for Blood Pressure Measurement in the Newborn


• BP measured by oscillometric method
• Infant lying prone or supine
• Appropriate sized cuff (cuff width/arm circumference ratio 0.45-0.70)
• Right upper arm
• After cuff placement, left undisturbed for 15 min
• Infant asleep or in quiet awake state
• 3 successive BP readings at 2 minute intervals
• (1.5 hours after a feed or medical intervention)
BP patterns in neonates seem complex and have not been extensively studied

- Most studies are based on a small number of infants (150-300) from various countries

- BUT this could be easily studied through the international consortium

Project 2 – Blood Pressure

• Description:
  • Blood pressure: standards for measurement and identification of normal values throughout the neonatal period (high and low blood pressure)

• Feasibility:
  • Use standardized BP measurement methods in NICUs
  • Record BP values on thousands of stable infants
  • With data analysts and statisticians create better normative data for full range of BP

• Impact:
  • This group could easily develop strong normative data that would form the basis for clinical standards and establish core metrics for future research studies
  • We could evaluate BP trends in premature infants and develop standardized tables or graphs to use based on gestational age at birth and postmenstrual age
Neonatal Hypertension

• Definition of hypertension in neonates:
  • 95th percentile BP, no hard outcome studies

• Healthy newborns: incidence ~ 0.2%

• In NICU: incidence 1-2%
  • Often presents within first 1-2 weeks of life
  • Most commonly in premature infants
  • May present later in infants with chronic lung disease
  • Incidence has not been increasing over time
Key Points

• The most common causes are renovascular and renal parenchymal (~50%)

• Some causes are iatrogenic: medications, excess saline, TPN

• New technologies often come with complications (ECMO 40-50% infants develop hypertension)

• Clinical presentation may be asymptomatic, non-specific feeding intolerance, irritability, tachypnea, apnea OR
  
  • Congestive heart failure, cardiogenic shock, or seizures

• Chronic hypertension in children leads to left ventricular hypertrophy, hypertensive retinopathy, albuminuria and renal damage, and possibly neurocognitive deficits
## Medication Usage

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasodilators</strong></td>
<td>53%</td>
<td>64%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Calcium Channel Blockers</strong></td>
<td>62%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td><strong>ACE Inhibitors</strong></td>
<td>36%</td>
<td>51%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Alpha &amp; Beta Blockers</strong></td>
<td>15%</td>
<td>18%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td></td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td><strong>None</strong></td>
<td></td>
<td>26%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Multiple agents</strong></td>
<td>51%</td>
<td>45%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Sahu R et al. 2013 J Pediatr 163:84-88  
Seliem W et al. 2007 Pediatr Nephrol 22:2081-2087
Key Points

• All antihypertensive drug classes are potentially available and have been used but few have been systematically studied in this population

• Concerns exist over use of blockers of the renin-angiotensin-aldosterone system in prems due to the importance of this hormone system in renal development

• Hypertensive crises are a life-threatening emergency that need prompt management with IV antihypertensives

• Chronic hypertension management in infants requires available, tolerable, and practical drug suspension formulations
Follow-up of NICU Hypertension

• Most cases (80%) of hypertension from NICU course resolve by 6-12 months of age

• Hypertension related to chronic lung disease may take longer to resolve or even present during NICU follow-up

• Specific diagnoses are associated with increased risk of hypertension over time e.g. polycystic kidney disease, coarctation of aorta, renal vein thrombosis
Neonatal Risk Factors for Later Renal and Cardiovascular Disease

• Prematurity $\rightarrow$ hypertension and chronic kidney disease
• IUGR $\rightarrow$ hypertension, altered vascular regulation

• Cause is likely multi-factorial
  • Incomplete nephrogenesis and hyperfiltration
  • Acute kidney injury
  • Genetic predisposition
  • Postnatal weight gain (controversial)
Implications for Regulatory Science

- Need to establish dosage regimens
  - Surrogate outcomes, e.g. control of BP
- Need to examine clinically important outcomes

- Practical problems with trials
  - Case finding
  - Recruitment
  - Tailor assessments to the neonatal context
    - Don’t use protocols for adults or older children that have been “cut and paste”
- Likely to need better understanding of natural history before trials can be defined optimally
Questions?
Hypotension – research and safety outcomes – use of 2 year outcomes

Direct causal pathway

- Other neonatal pathway
- Intervention
- Rearing at home
- 2 year outcome

Indirect causal pathway

- Other neonatal pathway
- Intervention
- Neonatal effect
- 2 year outcome
- Rearing at home
- Other effect

Examples:
- MgSO₄
- Melatonin
- Developmental intervention
- Indometacin – via PDA, IVH, other?
- Caffeine – via reduced BPD, diuretic effect
- Respiratory intervention – reduced BPD
Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Tonse Raju

National Institute of Child Health and Human Development
Second Annual Neonatal Scientific Workshop
at the FDA: March 7-9, 2016
Hemodynamics Subgroup

Tonne N. K. Raju, MD, DCH
Chief, Pregnancy and Perinatology Branch
Eunice Kennedy Shriver National Institute of Child Health and
Human Development, National Institutes of Health
Outline

- Summary of an NRN study--feasibility
- Issues and obstacles in conducting RCTs
- Understanding these may help guide discussion
- Normal BP dynamics during the first 24 hours in the 23⁰/₇–26⁶/⁷ weeks of GA infants from this study—secondary analyses paper
Study Purpose

- To assess whether enrollment into an RCT could be achieved with traditional consent mechanisms within a reasonable time and without increased risk of morbidity or mortality.

- Infants 23-0/7 to 26-6/7 weeks gestation, who had protocol-defined low BP in the first 24 postnatal hours were enrolled.

- Excluded: if they received a fluid bolus, indomethacin, or ibuprofen; had major birth defects; or lacked UAC access

- 2X2 factorial design: The study infants were administered
  - 6 mcg/kg/min dopamine (increased as needed q 20 min up to 15 mcg/kg/min or equivalent volume placebo
  - 1 mg/kg hydrocortisone or placebo
Four Intervention Groups

- Dopamine/placebo
- Dopamine/hydrocortisone
- Placebo/hydrocortisone
- Placebo/placebo
BP Threshold for low BP

<table>
<thead>
<tr>
<th>Postnatal hour</th>
<th>1-6</th>
<th>7-12</th>
<th>13-18</th>
<th>19-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mm Hg</td>
<td>24</td>
<td>25</td>
<td>26</td>
<td>27</td>
</tr>
</tbody>
</table>

MAP, mean arterial blood pressure.
• December 3, 2009
• December 3, 2010
• Study endpoint:
• Successful enrollment of 60 infants in one year, with a protocol deviation ≤20%
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• December 3, 2010
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• Successful enrollment of 60 infants in one year, with a protocol deviation ≤20%
• December 3, 2009
• December 3, 2010
• Study endpoint:
• Successful enrollment of 60 infants in one year, with a protocol deviation ≤20%
Outcomes for the 10 infants enrolled in the pilot study

<table>
<thead>
<tr>
<th>Patient</th>
<th>NRN center</th>
<th>BW, g</th>
<th>GA, weeks</th>
<th>Sex</th>
<th>Study infusion medication</th>
<th>Study syringe medication</th>
<th>Survived to hospital discharge</th>
<th>Grade III/IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>780</td>
<td>25</td>
<td>Male</td>
<td>Placebo</td>
<td>Hydrocortisone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>790</td>
<td>25</td>
<td>Male</td>
<td>Dopamine</td>
<td>Placebo</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>700</td>
<td>26</td>
<td>Female</td>
<td>Dopamine</td>
<td>Hydrocortisone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>840</td>
<td>26</td>
<td>Female</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>530</td>
<td>24</td>
<td>Male</td>
<td>Placebo</td>
<td>Hydrocortisone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>868</td>
<td>25</td>
<td>Female</td>
<td>Placebo</td>
<td>Placebo</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>630</td>
<td>23</td>
<td>Male</td>
<td>Placebo</td>
<td>Placebo</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>D</td>
<td>580</td>
<td>25</td>
<td>Female</td>
<td>Dopamine</td>
<td>Placebo</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>D</td>
<td>885</td>
<td>25</td>
<td>Female</td>
<td>Dopamine</td>
<td>Hydrocortisone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>D</td>
<td>750</td>
<td>24</td>
<td>Female</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

- Placebo – Placebo 4 infants
- Hydrocortisone alone 2 infants
- Dopamine alone 2 infants
- Dopamine and hydrocortisone 2 infants
Infant Outcomes

- 8 of the 10 infants survived.
- 2 deaths in placebo/placebo group
  One on day 20 and the other, day 60
- Two protocol deviations—study syringe medication was stopped without exit criteria, because of presumed risk of intestinal perforation with the simultaneous indomethacin treatment
Issues

- Antenatal consent obtained in 39, postnatal in 17
  - None of these met the eligibility criteria
- Parents of 20/58 eligible infants (34%) not approached
  - In 13 of these, the attending physician decided not to
- In 7 of 58, either the mother or the father was unavailable; or the mother was under medications
- Only 10 of the remaining 38 eligible infants’ parents gave a consent; 23 declined, 5 had other reasons (too late, or use of open label therapy for low BP)
Summary of Major Issues

- Low percentage met all eligibility criteria
  - Only 1/3 had protocol-defined low BP; perhaps because 93% women received antenatal glucocorticoids

- Earlier administration of indomethacin (44% of screened infants); often “prophylactic” for IVH

- Difficulty in consenting process: Only 17% success; nearly 5 women need to be approached to successfully obtain one consent

- “Waiver of consent”—Emergency research model?

- Physician equipoise? 22% not approached by the MDs

- Also because wide variation in management practice
BP Changes during the first 24 h

GA Specific BP changes during the first 24 h

Secondary analyses
367 infants, 18,709 measurements
Thank you....
Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Shari Targum

US Food and Drug Administration
Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Ralph Bax

European Medicines Agency
Priority Projects to Discuss

• Project 1 – Definition of neonatal shock: how to measure it and when to apply the diagnosis

• Project 2 – Blood pressure: standards for measurement and identification of normal values throughout the neonatal period (high and low blood pressure)

• Project 3 – Practicalities of clinical trials: administration and formulation issues
Project 1 – Definition of neonatal shock

• Description:
  • Definition of neonatal shock: how to measure it and when to apply the diagnosis

• Feasibility:

• Impact:
Project 2 – Blood Pressure

• Description:
  • Blood pressure: standards for measurement and identification of normal values throughout the neonatal period (high and low blood pressure)

• Feasibility:

• Impact:
Project 3 – Trial Practicalities

• Description:
  • Practicalities of clinical trials: administration and formulation issues

• Feasibility:

• Impact:
Considering both impact and feasibility, which of the following regulatory science projects is your **first** choice?

1. Definition of neonatal shock: how to measure it and when to apply the diagnosis
2. Blood pressure: standards for measurement and identification of normal values throughout the neonatal period (high and low blood pressure)
3. Practicalities of clinical trials: administration and formulation issues
4. “Walk-in Option A” (offered up by audience)
5. “Walk-in Option B” (offered up by audience)
6. None of the above
Considering both impact and feasibility, which of the following projects is your second choice?

1. Definition of neonatal shock: how to measure it and when to apply the diagnosis
2. Blood pressure: standards for measurement and identification of normal values throughout the neonatal period (high and low blood pressure)
3. Practicalities of clinical trials: administration and formulation issues
4. “Walk-in Option A” (offered up by audience)
5. “Walk-in Option B” (offered up by audience)
6. None of the above
Lunch
1 Hour
Second Annual Neonatal Scientific Workshop
March 8th, Afternoon
“Progress of the International Neonatal Consortium – Workgroup Updates”

Ron Portman, INC Co-Director
Novartis, Chair
## Agenda – Workgroup Updates

<table>
<thead>
<tr>
<th>Time</th>
<th>Workgroup</th>
<th>Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:30 pm</td>
<td><strong>Clinical Pharmacology Workgroup</strong></td>
<td>Bob Ward (University of Utah)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Karel Allagaert (University of Leuven)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jeff Barrett (Sanofi)</td>
</tr>
<tr>
<td>2:00 pm</td>
<td><strong>Seizures Workgroup</strong></td>
<td>Janet Soul (Harvard University)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ronit Pressler (Great Ormond Street Hospital)</td>
</tr>
<tr>
<td>2:30 pm</td>
<td><strong>COFFEE BREAK</strong></td>
<td></td>
</tr>
<tr>
<td>3:00 pm</td>
<td><strong>Bronchopulmonary Dysplasia (BPD) Workgroup</strong></td>
<td>Robin Steinhorn (Children’s National Hospital)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wolfgang Göpel (University Lübeck/VOC)</td>
</tr>
<tr>
<td>3:45 pm</td>
<td><strong>Data Workgroup</strong></td>
<td>Tom Diacovo (Columbia University)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kate Costeloe (Queen Mary University of London)</td>
</tr>
<tr>
<td>4:30 pm</td>
<td><strong>Concluding Remarks</strong></td>
<td>Jon Davis, INC Co-director (Tufts Medical Center)</td>
</tr>
</tbody>
</table>
INC’s First Year: From Mission Statement to the First Four Workstreams

**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.
What are the Goals of Neonatal Drug Development Programs?

- Determine safety and efficacy of the product for the claimed indications in neonates (same or different than adults or older children): based on need
- Provide information to support dosing and administration for each neonatal subpopulation for which the product is safe and effective
- Propose labeling
- Use age appropriate and acceptable formulation(s)
- Ensure involvement of parent and nurses in design and study feedback
Year 1: Building the Consortium Community

101 Members, 23 Countries, 6 Stakeholder Communities, 4 Workstreams, 2 Major Meetings (EMA and FDA)

- Davis, J. “Global Efforts to Accelerate the Development of Safe and Efficacious Therapies for Newborns.” AAP’s *Section on Advances in Therapeutics and Technology* (SOATT) Newsletter, Fall 2015.
Year 1: Developing Priorities

**INC AND THE NICU**

The International Neonatal Consortium will concentrate its efforts on those conditions most commonly encountered in Neonatal Intensive Care Units (NICUs), and on the prevention of pre-term birth.
The First Four INC Workgroups:
Keeping a Regulatory Focus

Potential Deliverables that address Regulatory Science, Regulatory Engineering, Regulatory Logic, and Regulatory Reality

• Standardized methods and consensus-derived standards-of-care.
• Draft master protocols and innovative trials designs.
• Draft decision criteria for conducting clinical trials of new therapies.
• Drug Development Tools endorsed or qualified by the regulatory agencies for a specific context of use:
  • Safety and Efficacy Biomarkers
  • Clinical Outcome Assessments (COA)
  • Modeling approaches such as physiologically based pharmacokinetic and disease progression models, as well as clinical trial simulation tools.
• Considerations for use of excipients and safer formulations.
Year 1 Consortium Accomplishments

- INC’s Clinical Pharmacology Workgroup finalized a white paper to assist regulators in preparing guidance on the clinical pharmacology considerations for the design and execution of clinical trials with neonatal participants.

- INC developed comments on the notice of proposed rulemaking (NPRM) “Federal Policy for the Protection of Human Subjects” to the Office for Human Research Protections.

- FDA and NIH completed an **Overview of Products Studied in Neonates**

**In-process**

- The Seizure Workgroup is developing a **master protocol** for treating seizures.

- The BPD Workgroup is developing a **condition definition** for BPD.

- The Data Workgroup is developing a document with normal lab values and ranges and supporting the efforts of other workgroups.
White Paper

• INC’s Clinical Pharmacology Workgroup finalized a white paper to assist regulators in preparing guidance on the clinical pharmacology considerations for the design and execution of clinical trials with neonatal participants.
Bob Ward, Karel Allegaert, Jeff Barrett

• Clinical pharmacology encompasses a broad range of knowledge of medications as well as pathophysiology of diseases that can inform clinical trials and their results
  • Study design
  • Regulatory requirements
  • Pharmacometrics
  • Pharmacogenetics
  • Pharmacodynamic measures/surrogate markers

• The CP WG has interest in several different areas of the INC initiative, but they share a common link of clin pharmacol
  • Every clinically focused group should have clin pharmacol expertise represented within the skills of the group
The output from the clinically focused groups can provide important data that informs future neonatal studies as well as developmental biology/pharmacology/pathophysiology.

Recommend that the Clinical Pharmacology group provide expertise to: BPD, Seizures, NAS, and Data WG’s insuring that pharmacometrics is represented on each group:

- Clinical trial designs developed by these groups should receive thorough review by regulators, sponsors, clinical trialists, NICU nurses and parents; they can become prototypes for future studies in these therapeutic areas & related areas.

- Pharmacometrics results should be reported both within and outside the study for collation into a package that helps to describe pathways of developmental pK in premies.

Recommend continued scheduled discussion of these areas within the clin pharm WG to obtain input from the broad range of expertise represented.
1. Focusing on Neonatal Abstinence Syndrome, including study design, excipients/formulations, outcome measures
2. Developing risk assessments for excipients/formulations
3. Supplying expertise to both the Seizure and BPD Workgroups on study design, excipients/formulations (e/fs), outcome measures (OMs)
4. Developing study designs for selected therapeutic areas
5. Supplying expertise to the Seizure Workgroup on study design, e/fs, OMs
6. Supplying expertise to the BPD Workgroup on study design, e/fs, OMs
Clin Pharm Workgroup Members

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

Janet Soul, Harvard University
Ronit Pressler, Great Ormond Street Hospital
Why treat neonatal seizures?

• Associated with poor outcome and increasing evidence that seizures contribute to poor outcome
• No new AED developed/tested in newborns (1st line PB)
• No evidence base for current management of neonatal seizures
• Risk due to frequent off-label use of antiepileptic drugs
• Diagnosis often made clinically or aEEG, not adequate for drug development
Challenges of drug development

• Unique age-specific seizure & drug mechanisms
• Ethical predicament
  • Vulnerable age group
  • Acute seizures, critically ill, many co-morbidities
• Logistical difficulties
  • Diagnosis and monitoring
  • Challenges of AE & AR Reporting
  • Recruitment
  • Regulatory requirements (EMA/FDA, GCP)
• Expensive, but low return
How to overcome the challenges

- Target-specific AED design
- Study design
  - Randomised controlled trials
  - Pure placebo group not justifiable
  - Gold standard for seizure diagnosis (cEEG)
  - Innovative methods (EEG analysis, statistics, PK)
- High ethical standards (e.g. continuous consenting)
- Multicenter, collaborative trials
- Central funding necessary
Seizures Workgroup Members

- Janet Soul - Harvard University, Co-chair
- Ronit Pressler - GOSH, Co-chair
- Albert Allen – Lilly
- Angela Men – OTS/CDER/FDA
- Brian Tseng – Novartis
- Fernando Gonzalez - UCSF
- Geraldine Boylan - University College Cork
- Heike Rabe - Brighton & Sussex Medical School
- Jennifer Mayberry – Graham’s Foundation
- John Lantos – Children’s Mercy Hospital, KCMO
- Jon Davis – TuGs Medical Center
- Karen New – COINN
- Luc Masson – INJENO (parents of children with epilepsy)

- Marilee C. Allen – Johns Hopkins
- Neil Marlow – University College London Hospital
- Norm Hershkowitz – CDER/FDA
- Pam Simpkins – Janssen
- Phil Sheridan – CDER/FDA
- Pierre Gressens - Diderot University Paris
- Ron Portman – Novartis & INC Co-director
- Scott Denne – Indiana University, Riley Children’s
- Skip Nelson – Office of Pediatrics, US FDA
- Stephane Auvin – Robert Debré Hospital, Paris
- Susan McCune – CDER/FDA
- Sylvie Benchetrit – ANSM, France and PDCO
- Wakako Eklund - NANN
Seizure Workgroup deliverables

Master Protocol for clinical trials to evaluate the safety and efficacy of therapies to treat seizures in neonates

• Elements of a Master Protocol defined and subgroups formed to draft those sections of the protocol

• Ensuring a global perspective of the master protocol (inviting participation from Japan, Korea, Canada, Australia)

• Identifying relevant data that could be collected by the INC Data Workgroup
Subgroups Update

• **Protocol Design**
  • Inclusion/exclusion, treatment arms, choice of competitor, trial design, statistics

• **Drug-related issues**
  • Manufacturing, formulation, excipients, PK/PD, and drug specific safety issues.

• **Primary Outcome Measures**
  • Definition of seizure outcome measure, EEG monitoring protocol, minimum standard of EEG monitoring.

• **Secondary Outcome Measures**
  • Including short-term (safety, neurological status) and long-term outcomes (e.g. development, disability, epilepsy and long-term safety)

• **Ethics and Parent Involvement**
  • Ethical challenges of neonatal AED trials, ethical consideration of study design, methods of consent, consent form, parent involvement in trials
Protocol Design

- Janet Soul - Harvard University
- Ronit Pressler – GOSH
- Karen Walker - COINN
- Pam Simpkins – Janssen
- Jon Davis – Tufts
- Pollyanna Hardy - Oxford University
- Mark Turner – University of Liverpool
- Stephane Auvin – Robert Debré Hospital, Paris
- Brian Tseng – Novartis
- Philip H. Sheridan – CDER/FDA
- Norm Hershkowitz – CDER/FDA
- Susan McCune – CDER/FDA
Protocol Design Group

• Inclusion / Exclusion Criteria
  • 35-43 weeks term babies
  • Advantages of a homogeneous etiology (i.e., HIE) for a Phase 3 trial, acknowledging limitations
  • Consider broader inclusion criteria for early phase trials of PK, safety, pharmacodynamics
  • Exclusion for metabolic disorders, safety criteria regarding renal/hepatic failures, drug-specific issues
Protocol Design Group

• Treatment Arm, Choice of Competitor, Trial design

• Phenobarbital (PB) as comparator, since:
  • Most common and standard drug used to treat neonatal seizures
  • Acknowledge limitations of data regarding PB efficacy although some efficacy data available
  • Fewer drug-interactions for PB compared with other drugs (such as phenytoin, lidocaine or newer drugs)
  • Ethically problematic to use placebo given evidence suggesting harm of neonatal seizures
  • No comparator needed if early phase PK study only
  • Comparator, i.e., control, to assess safety, even for early phase trials
Protocol Design Group

- **Treatment Arm, Choice of Competitor, Trial design**
  - **Phase 3 Trial Design:**
    - Randomization, masking (blinding) should be used
    - 1st line drugs to compare with phenobarbital rather than placebo
    - Add-on (2nd line) drugs could potentially be compared with placebo, if well-defined time limit used?
      - Depends in part on primary outcome variable definition, e.g., time to seizure cessation vs. other measure of seizure control
      - Needs input from Ethics/Parent group
  - **Superior efficacy needed for FDA approval**
    - Not sufficient to demonstrate similar efficacy (i.e., non-inferiority) with fewer adverse effects
    - Superiority does NOT require establishing that PB is efficacious drug, if PB is considered the ethically accepted ‘standard’ therapy
    - Non-inferiority design requires more patients and phenobarbital would need to be shown to be effective
Protocol Design Group

- Treatment Arm, Trial design, Statistical approach
  - Stratification:
    - Ideally stratify by seizure etiology or seizure severity but logistically impossible early in seizure course
    - Other variables to consider for stratification: center, hypothermia
  - Sample size:
    - Depends on defining detectable difference that is clinically meaningful to determine power, sample size
    - Large variability in seizure burden between subjects affects sample size
  - Adaptive design could be used for treatment arms
    - Advantage of minimizing sample size,
  - Crossover design? (e.g., such as LEV vs. PB trial)
    - Effect on sample size?
  - Statistical methods for analyzing primary and secondary outcomes
  - Definition of analysis population (intention to treat) relating to protocol non-adherence (eg, as randomized analysis)
  - Subgroup post-hoc analysis
    - Later analysis by subgroup, such as etiology, seizure burden
    - Include biomarkers of inflammation/ infection collected soon after birth, genetic factors
Protocol Design Group

- Phase 1/2 or Early Phase Trial Design:
  - Objectives:
    - Test use in newborns, particularly for new drugs
    - Test metabolism/elimination, dosing
  - Stratification:
    - May stratify by hypothermia (other variables?), expected to affect drug metabolism, safety or other factors being tested
    - Difficult to stratify by other variables that are not usually determined by time of randomization
  - Avoid adaptive design?
    - Concerns regarding assessment of drug safety
    - May not be best for determining appropriate dose given large variability in seizure burden
Drug Related Issues

• Heike Rabe - Brighton & Sussex Medical School
• Marielee Allen - John Hopkins
• Sylvie Benchetrit - French National Agency for medicines and Health Products Safety/EMA PDCO
• Angela Men - FDA
• Ronald Portman - Novartis Pharmaceuticals
• Roy Turner - Novartis Pharmaceuticals
• Alexander Vinks - Cincinnati Children’s Hospital Medical Center
Drug Related Issues - aims

1. Always required: Investigator’s Brochure
2. Manufacturing & excipients (Ron Portman)
3. Age appropriate formulations
4. Dose of administration
5. Measures of drug levels for adequate analysis of PK/PD (Alexander Vinks)
6. PK/PD analysis approach
7. Drug specific safety measures, incl biomarkers
8. Drug specific concomitant care & interventions (permitted/prohibited)
Drug Related Issues: discussion points

• Drug specific safety measures
  • Toxicity/side effects; drug specific:
    • What would be typical side effects to look out for?
    • What would be good biomarkers for safety/toxicity?

• Drug specific concomitant care & interventions (permitted / prohibited)
  • Which concomitant medication should be prohibited?
Primary Outcome Measures

• Geraldine Boylan – University College Cork
• Fernando Gonzalez – University of California, San Francisco
• Sylvie Benchetrit – ANSM, France and PDCO
• Marilee C. Allen – Johns Hopkins
• Jon Davis – Tufts Medical Center
• Janet Soul – Harvard University
• Philip H. Sheridan – CDER/FDA
• Norm Hershkowitz – CDER/FDA
• Susan McCune – CDER/FDA
• Primary Outcome Measures Section of the Master Protocol
  • Definition of seizure outcome measure, EEG monitoring protocol, minimum standard of EEG monitoring.
  • Identify any additional topics that should be included in this subgroup’s draft of the master protocol.
Primary Outcome Measures

• **Decisions made**
  - Continuous video EEG monitoring required to screen trial participants and to measure efficacy of AED
  - Simultaneous ECG and respiration (artefacts)
  - 24 hour EEG interpretation required
  - Remote access essential if no local expert available
  - Central EEG reading technically possible

• **Decisions to be made**
  - Baseline seizure burden required to enter trial
    - 2-3 minutes of seizures (single or cumulative) on EEG
    - 30 sec
    - Any EEG defined seizure of >10 seconds sufficient
  - Primary Endpoint –
    - Abolition of all EEG seizures or %reduction e.g. 80%?
  - How long do you monitor to ensure seizure freedom after treatment? 8 hours, 12 hours, 24 hours or 48 hours
Secondary Outcome Measures Subgroup Members

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

• Short-term outcomes
  • Neonatal neuroimaging studies: MRI
    • Timing and protocol
    • Single central reader vs inter-rater reliability training
    • Standardized scoring system for abnormalities
  • Neonatal neurological assessment
    • Timing; difficulties (i.e. not critically ill or sedated, awake)
    • Assessment method used (e.g. Amiel-Tison, Hammersmith)

• Long-term outcomes
  • Followup age: 2 yrs for major NDD, 3-5 yrs is the earliest for a more complete assessment of cognition, executive fcn, & behavior
  • Neuroimaging studies: Followup MRI during infancy/childhood?
  • Neurodevelopmental disability: dx CP
  • Neurocognitive outcomes: Looking beyond Intellectual Disability
    • Bayley 3rd ed is most widely used but very problematic
    • Need a larger group of experts to choose best tests to use
  • Neurobehavioral outcomes
  • Functional outcomes
Members of the Ethics and Parent Involvement Subgroup

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

• Outline ethical challenges of AED Trials in neonates
• Literature review on ethical considerations of AED trials
• Ethical issues of study design
  • Use of placebo
  • Delayed treatment (with appropriate stopping rules)
  • Use of prophylactic medication
• Consent
  • Methods of consent (continuous consenting, deferred consent)
  • What to include in patient information sheet
• Parent involvement in trials
Outline ethical challenges of AED Trials in neonates - done

Literature review on ethical considerations of AED trials - done

Ethical issues of study design
  • Use of placebo, not acceptable for drug development
  • Delayed treatment (with appropriate stopping rules), on-going, probably also not acceptable
  • Use of prophylactic medication, on-going

Consent
  • Methods of consent. On-going
    • deferred consent (waiver) controversial
    • discussion on complexity of initial information (verbal vs written)
    • continuous consenting works well
  • What to include in patient information sheet: On-going

Parent involvement in trials. On-going
  • Active involvements essential for study design, consent form, and in trial steering committee
Data Collection for Seizures

- Conceptional age at birth / at seizure onset
- Gender and other demographics
- APGAR and cord pH
- Diagnosis confirmed by
- Seizure types
- Aetiology of seizures (e.g. HIE, stroke)
- Other diagnosis / comorbidity
- Head US results
- MRI results
- EEG findings if available
- First line drug (and response)
- Second line drug (and response)
## Seizure Workgroup Timelines and Deliverables

<table>
<thead>
<tr>
<th>MAY</th>
<th>JUN</th>
<th>JUL</th>
<th>AUG</th>
<th>SEP</th>
<th>OCT</th>
<th>NOV</th>
<th>DEC</th>
<th>JAN</th>
<th>FEB</th>
<th>MAR</th>
<th>APR</th>
<th>MAY</th>
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<tr>
<td>Prioritizing workgroups</td>
<td></td>
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<tr>
<td>Selecting Co-Chairs and sending invitations</td>
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</tr>
<tr>
<td>Initial discussions to set timelines and deliverables</td>
<td>Face to Face Workshop</td>
<td></td>
<td>INC Workshop at the FDA</td>
<td>Incorporating Workgroup Input</td>
<td>Regulatory Submission</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Seizures: Drafting Master Protocol</td>
<td></td>
<td></td>
<td></td>
<td>Incorporating Broader INC Input</td>
<td>Internal Review</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- **Sept 1 - October 23, 2015**: Initial workgroup discussions on potential deliverables and timelines (Seizures, BPD, Data)
- **October 1 - March 12**: Seizures Workgroup: Drafting Master Protocol
- **October 23**: Face-to-face Clin Pharm Workshop and INC working
- **March 7 - 8, 2016**: Second Annual Neonatal Scientific Workshop at the FDA
- **March 8 - 9, 2016**: Seizures Workgroup Face to Face Workshop at a DC area hotel
- **March - May**: Incorporating input from Seizure Workgroup, the INC Coordinating Committee, and other INC Members.
- **May 15**: Internal C-Path review of Master Protocol
- **May 30**: INC submits Master Protocol to FDA, EMA, PMDA
Thank You

http://c-path.org/programs/inc
Coffee Break
30 minutes
BPD Workgroup

Robin Steinhorn, Children’s National Hospital
Wolfgang Göpel, University of Lübeck
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
- Eduardo Bancalari - Jackson Medical Center, Miami
- Dirk Bassler – University of Zurich
- Carol Blaisdell – NHLBI/NIH
- Giuseppe Buonocore – University of Siena, Italy
- Jon Davis – Tufts University
- Danièle De Luca - South Paris University Hospitals
- Anne Greenough – King’s College, London
- Ninna Gullberg - Karolinska University Hospital & PDCO
- Helmut Hummler – University of Ulm, Germany
- Alan Jobe - Cincinnati Children’s Hospital
- Matt Laughon - UNC
- Susan McCune –FDA/CDER
- Marek Migdal - Children's Memorial Health Institute, Warsaw, Poland
- Christian Speer - University of Wurzburg, Germany
- Linda Storari - Chiesi
- Anthony Durmowicz – FDA/CDER/DPARP
- Ron Portman - Novartis, & INC co-director
- Mark Turner – U. of Liverpool
BPD in Preterm Infants

• Most common complication of preterm birth
  • 30-60% of infants born <29 weeks PMA and weighing ≤1250 g
  • The incidence of BPD has increased with increasing survival of LBW infants (<1000 g)

• Effects can last into adolescence and adulthood
• Few effective, evidence-based therapies
• Preventing BPD would solve many other morbidities of prematurity, including long term neurodevelopmental impairment
Challenges to BPD Prevention Research

• BPD – complex phenotypes (BPD in a 25 week infant is probably a different disease than that in a 29 week infant)
• Multi-institutional collaborations essential, but introduce tremendous variability in practice and outcomes
• Current challenges in balancing risks and benefits of preventive strategies
  • Some premature infants not destined to develop disease will be exposed to experimental therapies with potential adverse effects
  • Adverse effects of drugs may not be evident for months or years
Abnormal pulmonary development associated with BPD

-volutrauma
-infection & inflammation
-hyperoxia and oxidant injury
-poor nutrition
-structurally & biochemically immature lung
-poor respiratory drive and apnea

Responses of individual patients modulated by genetic, epigenetic and antenatal factors
Regulatory Readiness: Case 3

Rational Use

Develop the case to move from data to indication

Sufficient high quality data about the drug and the condition

(this may involve collecting some more data)
Why BPD-definition as the first step?

• Several BPD definitions are used in large trials and epidemiology.
• BPD viewed as an important surrogate parameter for long term outcome... but different definitions and considerable differences in BPD prevalence between centers and countries prevent identification of useful therapies.
• A diagnosis of BPD has low predictive value for long term outcome of an individual preterm infant.
# Commonly Used BPD Definitions

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Definition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northway</td>
<td>1979</td>
<td>Oxygen use at 28 days of life</td>
<td></td>
</tr>
<tr>
<td>Shennan</td>
<td>1988</td>
<td>Oxygen use at 36 weeks PMA</td>
<td>A child on 4 LPM HFNC support and 21% O₂ at 36 weeks would not have BPD</td>
</tr>
<tr>
<td>Modified Shennan</td>
<td></td>
<td>Assigns infants discharged in room air before 36 weeks PMA as no BPD</td>
<td></td>
</tr>
<tr>
<td>NIH Consensus</td>
<td>2001</td>
<td>• None (≤ 28 days of oxygen support)</td>
<td>A child placed on HFNC support for 2-3 days for worsening apnea would have BPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mild (oxygen or respiratory support at &gt; 28 days but on room air at 36 weeks PMA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Moderate (≤ 30% oxygen at 36 weeks)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe (≥ 30% oxygen or positive pressure at 36 weeks PMA)</td>
<td></td>
</tr>
<tr>
<td>Walsh “Physiologic”</td>
<td>2003</td>
<td>SpO₂ &lt; 88% after 60 minute room air challenge at 36 weeks PMA</td>
<td></td>
</tr>
</tbody>
</table>
Six questions concerning BPD Definition

- Q1: Transient respiratory insufficiency of prematurity (TRIP)
- Q3: Predictive models, biomarkers
- Q4: Subtypes
- Q2: BPD-Definition
- Q5: Ongoing morbidity
- Q6: Important outcomes for families

Time

Hospital  Home
Are there sufficient predictive models for BPD? Recent RCTs with BPD/death as endpoint

<table>
<thead>
<tr>
<th>Study/Country</th>
<th>Intervention</th>
<th>Gestational age</th>
<th>N</th>
<th>BPD or death</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREMILOC / France</td>
<td>Hydrocortisone</td>
<td>26.5 ± 0.7</td>
<td>521</td>
<td>40 vs. 49%</td>
<td>Lancet 2016; Epub ahead of print</td>
</tr>
<tr>
<td>Yeh et al. / Taiwan + US</td>
<td>Budesonide + Surfactant</td>
<td>26.6 ± 2</td>
<td>265</td>
<td>42 vs. 66%</td>
<td>Am J Resp Crit Care Med 2016;193:86-95</td>
</tr>
<tr>
<td>NEUROSIS / Europe</td>
<td>Inhaled Budesonide</td>
<td>26.1 ± 1</td>
<td>863</td>
<td>40 vs. 46%</td>
<td>N Engl J Med 2015; 373:1497-506</td>
</tr>
<tr>
<td>NINSAPP / Germany</td>
<td>Less invasive Surfactant (LISA)</td>
<td>25.3 ± 1</td>
<td>211</td>
<td>33 vs. 41%</td>
<td>JAMA Pediatr 2015; 169:723-30</td>
</tr>
<tr>
<td>PHELBI / Germany</td>
<td>Permissive hypercapnia</td>
<td>25.6 ± 1</td>
<td>359</td>
<td>36 vs. 30%</td>
<td>Lancet Respir Med 2015; 3:534-43</td>
</tr>
</tbody>
</table>
What is the optimal timing and definition for the BPD endpoint?

- Oxygenation is the most secure and pragmatic indicator of lung function.
- Pulse oximetry is the only practical way to measure systemic oxygen levels. The threshold should be 90%.
- The optimal time point for BPD assessment is under discussion (graph).
Six questions concerning BPD Definition

- Q1: Transient respiratory insufficiency of prematurity (TRIP)
- Q2: BPD-Definition
- Q3: Predictive models, biomarkers

Q4: BPD-Subtypes

- Q5: Ongoing morbidity
- Q6: Important outcomes for families

Time

Hospital

Home
BPD: gestational age and other risk factors, GNN 2009-2014
BPD: treatment with dexamethasone, surviving infants, GNN 2009-2014

Number of infants
- Total: 4946
- 22 weeks: 36
- 23 weeks: 246
- 24 weeks: 572
- 25 weeks: 709
- 26 weeks: 913
- 27 weeks: 1164
- 28 weeks: 1306

No Dexamethasone %  |  Dexamethasone n

- 22 weeks: 36
- 23 weeks: 246
- 24 weeks: 572
- 25 weeks: 709
- 26 weeks: 913
- 27 weeks: 1164
- 28 weeks: 1306
Inhaled Nitric Oxide in Preterm Infants: An Individual-Patient Data Meta-analysis of Randomized Trials
Pediatrics 2011;128,729, originally published online September 19, 2011, DOI: 10.1542/peds.2010-2725

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Trials</th>
<th>iNO</th>
<th>Control</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or CLD</td>
<td>10</td>
<td>956/1629 (59%)</td>
<td>993/1627 (61%)</td>
<td>0.96 (0.92–1.01)</td>
<td>.108</td>
</tr>
<tr>
<td>Death</td>
<td>11</td>
<td>386/1649 (23%)</td>
<td>374/1649 (23%)</td>
<td>1.05 (0.93–1.18)</td>
<td>.441</td>
</tr>
<tr>
<td>CLD in survivors</td>
<td>9</td>
<td>616/1261 (49%)</td>
<td>660/1273 (52%)</td>
<td>0.93 (0.87–1.00)</td>
<td>.060</td>
</tr>
<tr>
<td>Severe neurologic event after randomization</td>
<td>10</td>
<td>337/1355 (25%)</td>
<td>312/1361 (23%)</td>
<td>1.12 (0.98–1.28)</td>
<td>.092</td>
</tr>
</tbody>
</table>
Prolonged Rupture of Membranes and Pulmonary Hypoplasia in Very Preterm Infants: Pathophysiology and Guided Treatment

Koert de Waal, PhD\(^1\), and Martin Kluckow, PhD\(^2\)

<table>
<thead>
<tr>
<th>Design</th>
<th>Treated with iNO</th>
<th>GA, wk</th>
<th>Ultrasound diagnosis of PH</th>
<th>Pre-iNO MAP, cmH(_2)O</th>
<th>Pre-iNO oxygenation index</th>
<th>Age at start iNO, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>use series</td>
<td>8</td>
<td>24-31</td>
<td>5/8</td>
<td>12-22</td>
<td>25-76</td>
<td>2-11</td>
</tr>
<tr>
<td>use series</td>
<td>5</td>
<td>24-34</td>
<td>Some</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>use report</td>
<td>2</td>
<td>29-31</td>
<td>1/2</td>
<td>n/a</td>
<td>n/a</td>
<td>10-24</td>
</tr>
<tr>
<td>use series</td>
<td>8</td>
<td>24-30</td>
<td>7/8</td>
<td>12.6 +/- 2.8</td>
<td>28.8 +/- 18.3</td>
<td>11.5 +/- 11.6</td>
</tr>
<tr>
<td>XT</td>
<td>6</td>
<td>24-31</td>
<td>2/6</td>
<td>n/a</td>
<td>11-64</td>
<td>12 +/- 8</td>
</tr>
<tr>
<td>use series</td>
<td>9</td>
<td>25-31</td>
<td>4/9</td>
<td>15-19</td>
<td>25-80</td>
<td>0.5-12</td>
</tr>
<tr>
<td>use series</td>
<td>6</td>
<td>26-31</td>
<td>6/6</td>
<td>13-18</td>
<td>23-35</td>
<td>6-24</td>
</tr>
<tr>
<td>use series</td>
<td>7</td>
<td>28-33</td>
<td>Some</td>
<td>n/a</td>
<td>n/a</td>
<td>0.2-15</td>
</tr>
<tr>
<td>short</td>
<td>17</td>
<td>27 +/- 2</td>
<td>17/17</td>
<td>n/a</td>
<td>20-70</td>
<td>1.5-16.5</td>
</tr>
</tbody>
</table>

*airway pressure; n/a, not available; PH, pulmonary hypertension; RCT, randomized controlled trial. t +/- SD.*
Six questions concerning BPD Definition

- Q1: Transient respiratory insufficiency of prematurity (TRIP)
- Q2: BPD-Definition
- Q3: Predictive models, biomarkers
- Q4: BPD-Subtypes
- Q5: Ongoing morbidity
- Q6: Important outcomes for families

Time

Hospital

Home
### Table II. Relationships between combinations of neonatal morbidities and poor outcome at 5 years

<table>
<thead>
<tr>
<th>Neonatal morbidities</th>
<th>No./total no.</th>
<th>% (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>85/759</td>
<td>11.2 (9.0-13.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Any single morbidity</td>
<td>135/590</td>
<td>22.9 (19.6-26.5)</td>
<td>2.4 (1.7-3.2)</td>
</tr>
<tr>
<td>BPD</td>
<td>112/494</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>Brain injury</td>
<td>20/84</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>Severe ROP</td>
<td>3/12</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td>Any 2 morbidities</td>
<td>61/139</td>
<td>43.9 (35.5-52.6)</td>
<td>6.2 (4.1-9.3)</td>
</tr>
<tr>
<td>BPD + brain injury</td>
<td>37/84</td>
<td>44.0</td>
<td></td>
</tr>
<tr>
<td>BPD + Severe ROP</td>
<td>22/53</td>
<td>41.5</td>
<td></td>
</tr>
<tr>
<td>Brain injury + severe ROP</td>
<td>2/2</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>All 3 Morbidities</td>
<td>16/26</td>
<td>61.5 (40.6-79.8)</td>
<td>12.7 (5.6-28.9)</td>
</tr>
</tbody>
</table>
Developing a definition for BPD – Six questions to answer

1. How should we define the early respiratory failure associated with prematurity, particularly after the first few days of life?

2. What is the optimal timing and definition for the BPD endpoint?

3. Are there sufficient predictive models for BPD? Do early comorbidities assist in identifying infants at risk for BPD? Are other surrogate markers available or emerging that will aid in early identification of BPD?

4. Are there subtypes of BPD?

5. How do we factor in the ongoing morbidity associated with BPD through the first years of life?

6. What other outcomes are measurable and of importance to clinicians and families?
“Progress of the International Neonatal Consortium – Workgroup Updates”

The Data Workgroup

Tom Diacovo and Kate Costeloe
First Call: Sept 2015:
Potential Deliverables for the Data Workgroup

• Carrying out an environmental scan of existing neonatal databases that may provide useful information on the natural history of neonatal disease, biomarkers, clinical endpoints (most appropriate definitions and outcomes), standards-of-care, long-term follow-up, medication use patterns, potential drug-drug interactions.

• Establishing normal laboratory ranges for preterm infants (example of request received by Jon Davis for a clinical study with a new monoclonal antibody to prevent RSV).

• Examining background rates of AEs and SAEs from large databases and existing studies in order to facilitate reporting and DSMB/IRB oversight.

• Providing data/analysis to facilitate the projects of the Seizures and Bronchopulmonary Dysplasia (BPD) Workgroups.

• Others?
Data Workgroup Members

Kate Costeloe - Queen Mary U - London, Co-chair

Tom Diacovo - Columbia U, Co-chair

Simin Baygani – Lilly
Laura Brass – TriNetX
Jon Davis – Tufts U
Dominique Haumont - St-Pierre University Hospital
Rose Higgins – NICHD/NIH
Steve Hirschfeld – NICHD/NIH
Roger Soll - Vermont Oxford Network
Satoshi Kusuda – Tokyo Women’s Medical University
Thierry Lacaze – CHEO Research Institute, Ottawa
Susan McCune – CDER/FDA
Ron Portman – Novartis, & INC co-director
Neena Modi - Imperial College London
Prakesh Shah – University of Toronto

Hide Nakamura – National Research Institute for Child Health and Development, Japan
Michael Padula - Children’s Hospital of Philadelphia; PEDSnet
Martin Offringa – University of Toronto
Yun Sil Chang – Samsung Medical Center, South Korea
Kei Lui – Australian and New Zealand Neonatal Network (ANZNN)
Mary Short – Lilly
Brian Smith - Duke University (DCRI)
Charlie Thompson – Pfizer
Catherine Sherwin – University of Utah
Lauren Kelly – Hospital for Sick Children, Toronto
Mark Turner – U. of Liverpool
Making our task Manageable

• Establishing normal laboratory ranges for infants: providing guidance about abnormality.... TOM

• Existing Clinical Databases: Scanning existing large databases: clarifying how they may best support trials & how much has already been done to ‘harmonise’ ..... KATE

• Others?
Data Workgroup – First Project

Developing a document with normal lab values and ranges
(AKA: what is normal?)

Overall goal:
To provide guidance to sponsors, monitors, and investigators of trials with recommendations on assessing the severity of clinical and laboratory abnormalities

Issues to address by stakeholders

1. What are the sources and accessibility of sources for lab values?
2. What criteria do we use to define an abnormality and should it be scalable (mild, moderate, and severe)
3. What are the ideal properties for a criterion for an abnormality?
4. How do we operationalize defining an abnormality
Is there a “NORMAL” lab value?

• “Normal” can mean:
  – A) Normal (Gaussian) distribution
  – B) “Common”, “frequent”, “typical”
  – C) “Healthy”, as in absence of disease

Normal values = mean ± 2SD of normal population
Normal: 95% of normal, asymptomatic patients have numbers in this range on a “bell shaped curve”
Abnormal: By definition, 2.5% of normal patients have lab values either above or below the “normal” range

"I have your lab results. Some of your readings are too high and some are too low. No, they don't balance out."
Moving target
Moving target

“As you go through life, Billy, remember—a moving target is hard to hit.”
Can one establish reference ranges from databases with large collections of clinical laboratory data?


- Pool analyte data from selected reference population
- Plot data frequency against range of values
- Transform data if significantly skewed
- Calculate linear regression
- Determine reference interval from linear portion of curve

Method is in complete agreement with IFCC recommendations
ADVERSE EVENT

Death

Life–threatening
Patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.

Hospitalization (prolonged)
Prolongation of hospitalization was a result of the adverse event.

Disability or Permanent Damage
Significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
FDA Guidance for Industry
Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases such as cancer and HIV/AIDS.

Provides guidance to sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials.

Grading system can be useful in defining a particular study’s stopping rules.

Uniform criteria for categorizing toxicities can improve comparisons of safety data among groups within the same study and also between different studies.
<table>
<thead>
<tr>
<th>Time</th>
<th>Session Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>0800 - 0820</td>
<td>Introduction: what the stakeholders expect from the data group</td>
<td>Mark Turner</td>
</tr>
<tr>
<td>0820 - 0830</td>
<td>Plan for the day</td>
<td>TD / KC</td>
</tr>
<tr>
<td>0830 - 0915</td>
<td>Multi-institutional databases – The How</td>
<td>Jeff Jacobs</td>
</tr>
<tr>
<td>0930 - 0945</td>
<td>Surveying the literature: biomarker outcomes in neonatal trials”</td>
<td>Lauren Kelly</td>
</tr>
<tr>
<td>1000 - 1145</td>
<td>Topic: Defining an abnormal lab event</td>
<td>TD to lead &amp; KC to make notes</td>
</tr>
</tbody>
</table>

1. What are the sources and accessibility of sources for lab values?
2. What criteria do we use to define an abnormality and should it be scalable (mild, moderate, and severe)?
3. What are the ideal properties for a criterion for an abnormality? (clinical versus analytical outcome criteria; generalizable to a large population; precision medicine based?).
4. How do we operationalize defining an abnormality? *(Tom D)*

*The targeted output is a position paper about how to define and provide guidance on safety lab values. *(Tom)*

Stakeholders:
- Industry, regulatory agencies, and academia

Speakers to comment on points 1-3:
- Pharma
  - Mary Short
  - Charlie Thompson
- Regulatory
  - Gerri Baer
  - Ralph Bax (EMA)?
- Academia / NIH
  - Brian Smith
Data Workgroup: Second Project
‘Clinical’ data
Data Workgroup: Second Project
‘Clinical’ data

• Scanning the databases......
Potential utility of data from large datasets

- Reliable estimates of variables across geographic, gestational and post-natal age range

- Understanding differences and potential generalisability of trial results

- Post-marketing: changes over time
Data Workgroup: Second Project

‘Clinical’ data

• Scanning the databases......
• Focus on large vs small specialised databases
• Essential characteristics of databases:
  – Transparent denominators characterised by GA, BWt, sex (at least....)
  – Data dictionary available
• e.g. VON, CNN, UK NNKD, NRND (Japan), ANZNN
• Agreed the key items we are interested to map
• Checking how much has already been done by other groups
• ‘Drugs should only be used to positively influence important clinical outcomes, which need to be defined and used consistently’. Davis & Turner 2015

• Need to define methodologies for sharing and combining data
Definitions 2

• How similar must definitions be to be used for estimating disease rates in different populations and for surveillance?

• Outside RCTs how much of an adverse outcome is too much?

• Some definitions used for surveillance, QI etc are ‘pragmatic’ and might not satisfy regulators, industry (or some clinicians) when assessing effects of interventions......

• Might it be feasible to standardise definitions across EPR, stand-alone clinical databases and clinical trials?
Emerging themes from this meeting

• Rob Califf: ...... ‘continuous qualitative data’

• Reiko Shimuzu: talking about ROP in Japan...global trials to understand differences... and monitor long term safety of (ROP) treatments
Data sources

• The majority of the big datasets depend upon dedicated stand alone data collection.

• When we have agreed a common dataset with standardised definitions.... might it be feasible to ‘mandate’ its inclusion in the electronic patient record...... this could include capture of all interventions and of physiological data
<table>
<thead>
<tr>
<th>Time</th>
<th>Topic: Standardising datasets and definitions of trial outcomes</th>
<th>KD to lead &amp; TD to make notes</th>
</tr>
</thead>
</table>
| Harmonising big data sets 1230 – 1445h | 1. What would be the advantages of agreeing common definitions? (Kate C)  
2. What are the characteristics of definitions that are ‘regulatory ready’ to describe populations, interventions and outcomes? A ‘regulator’  
3. How much commonality is there among definitions used for current large databases in the USA and internationally?  
4. How do we arrive at consensus to harmonise definitions?  
5. How are clinicians encouraged to amend current definitions to facilitate data collection using standard definitions? | 1230-1245  
Gerri Baer 1245 – 1315  
1315 – 1415  
Mike Padula Prakesh Shah |
| Using Electronic Health Records to support clinical trials 1445 - 1520 | What experience is there of the use of EPR data to support clinical trials?  
What standards would be required of electronic patient records to use them as platforms for participant identification, randomisation and data collection for clinical trials? | Neena Modi to lead and group to discuss |
| 1520 - 1600 | Pulling it together and agreeing the work programme | TD / KC |
The targeted output is a position paper describing the advantages for accelerating approval for medicines (and for non-medicinal interventions) of achieving standardisation of definitions across datasets and the practical challenges of achieving this:

KC with a lot of help from friends
We Have a Dream

- Every newborn admitted to the NICU will enroll in a study protocol to optimize outcomes (similar to cancer).
- The definitions for our most important outcomes will be the same worldwide.
- We will collect standardized data on all infants, and the databases will be shared, harmonized, and readily searchable.
- We will be able to easily examine survival and outcome based on region of the world and adopt best practices.
- We will have established normal laboratory values based on birth weight, gestational age and postnatal age.
Concluding Remarks

Jon Davis, INC Co-Director
Tufts Medical Center
## Workgroup Timelines and Deliverables

<table>
<thead>
<tr>
<th>JUN</th>
<th>JUL</th>
<th>AUG</th>
<th>SEP</th>
<th>OCT</th>
<th>NOV</th>
<th>DEC</th>
<th>JAN</th>
<th>FEB</th>
<th>MAR</th>
<th>APR</th>
<th>MAY</th>
<th>JUN</th>
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<tr>
<td>Selecting Co-Chairs and sending invitations</td>
<td>Initial discussions to set timelines and deliverables</td>
<td>Face to Face Workshop</td>
<td>March Face to Face Workshop</td>
<td>Finalize</td>
<td>Dissemination</td>
<td>Finalize</td>
<td>Review</td>
<td>Disseminate</td>
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</table>

- Sept 1-October 23: Initial workgroup discussions on potential deliverables and timelines (Seizures, BPD, Data)
- Sept 1-October 23: Drafting white paper for neonatal clin pharm (Clin Pharm Workgroup)
- October 1 – March 12: Seizures Workgroup: Defining Master Protocol Elements and Content
- October 1 – March 12: BPD Workgroup: Defining BPD
- October 23: Face-to-face Workshop for Clin Pharm Workgroup to finalize white paper
- October 23: Workgroup report out on proposed deliverables and timelines (Seizures, BPD, Data) at INC Working Dinner
- December 18: Clin Pharm Workgroup submits white paper to Coordinating Committee for review
- February 1: INC submits final clin pharm white paper to FDA, EMA, PMDA
- March 9: Face to Face Workshop, Workgroup meetings for path to finalizing on deliverables
- April: Seizures and BPD finalize deliverables
- May: Seizures and BPD Workgroups submit work to Coordinating Committee for review
- June: INC submits final Master Protocol to FDA, EMA, PMDA
- June: INC submits final BPD Definition for publication
Concluding Remarks - ROP

• Need to standardize/harmonize assessments
• Technology may help – minimize stress
• Although retinal pathology important, longer term follow-up to assess visual function is important
• Safety assessments essential due to systemic effects of many of the agents
• Multiple dosing levels must be evaluated
• Industry/investigators need the input of Regulators to design protocols and they need our input in order to provide scientific rationale
## Results of ROP Discussion

**N=73**

<table>
<thead>
<tr>
<th></th>
<th>First</th>
<th>Second</th>
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</thead>
<tbody>
<tr>
<td>A.</td>
<td>Enrichment Strategies</td>
<td>5%</td>
</tr>
<tr>
<td>B.</td>
<td>Data Standards</td>
<td>4%</td>
</tr>
<tr>
<td>C.</td>
<td>ROP-specific Outcomes</td>
<td>25%</td>
</tr>
<tr>
<td>D.</td>
<td>Multiple Outcomes</td>
<td>14%</td>
</tr>
<tr>
<td>E.</td>
<td>Standardizing in Trials Targeting Systemic Inflammation</td>
<td>4%</td>
</tr>
<tr>
<td>F.</td>
<td>Combination B and C</td>
<td>48%</td>
</tr>
</tbody>
</table>

**Online – 9 votes**

First  A=1; C=4; D=4  
Second A=1; B=3; C=3; E=2
Concluding Remarks - Infections

• Common pathways for many complications (Increased risk for PVL, BPD, etc)
• Need to standardize/harmonize assessments
• Obtaining adequate biologic samples before, during and after treatment (bugs gone? SIRS?)
• Safety assessments essential due to systemic effects of many of the agents (infection vs drug)
• PK/PD studies must be conducted (enteral, IM, IV). CSF/other biologic fluid penetration adequate?
• Extrapolation may be possible
• Biomarkers weak – how to select highest risk infants
## Results of Infection Discussion

<table>
<thead>
<tr>
<th>Option</th>
<th>First</th>
<th>Second</th>
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</thead>
<tbody>
<tr>
<td>A. Make the most of existing data</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>B. Standard protocol for new studies</td>
<td>44%</td>
<td>29%</td>
</tr>
<tr>
<td>C. How to assess efficacy in the CNS</td>
<td>36%</td>
<td>48%</td>
</tr>
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</table>

**Online – 5 votes**

First: A=3; B=1; C=1
Second: A=1; B=2; C=2
Concluding Remarks - Hemodynamics

• Extreme variability – BP changes over first few days
• Need to standardize/harmonize assessments
• Unclear if lower BP values and resulting treatment impact tissue oxygenation and organ function
• Little correlation of short term outcomes with longer term neurodevelopmental outcomes
• Real concerns about the stability, volumes, and formulations of the drugs used to treat hypotension
• Is high blood pressure (systolic BP>100 mm Hg) problematic and in need of treatment
Hemodynamic Voting Results

- Standards for Blood Pressure Measurement
  - 1st Choice: 49.2%
  - 2nd Choice: 20.0%

- Define Neonatal Shock
  - 1st Choice: 38.5%
  - 2nd Choice: 23.8%

- Walk-in Option A
  - 1st Choice: 29.2%
  - 2nd Choice: 20.6%

- Practicalities of Clinical Trials
  - 1st Choice: 4.8%
  - 2nd Choice: 10.8%

- None of the above
  - 1st Choice: 1.6%
  - 2nd Choice: 1.5%
Thank You