International Neonatal Consortium

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

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Second Annual Neonatal Scientific Workshop at the FDA

Jon Davis, INC Co-director
Tufts Medical Center

CRITICAL PATH INSTITUTE

INC: We Have a Dream

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

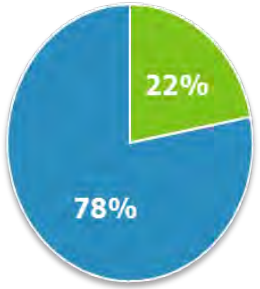
- 6% of the 4,000,000 births each year in the US require NICU admission.
- Prematurity rates worst of any developed country.
- Total cost of prematurity >$29 billion each year.
- Only small improvements in survival and outcome in the last 20 years.
- >90% of drugs used in the NICU are not FDA approved;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

History of Pediatric Initiatives

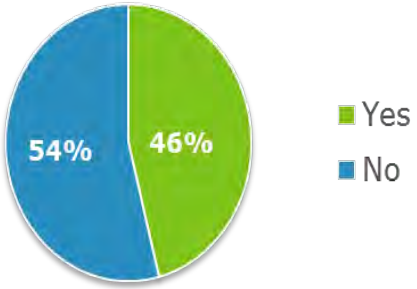
...but 55% of Medicines Still Do Not Have Data in Labels to Guide Appropriate Use in Children

Key initiatives

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



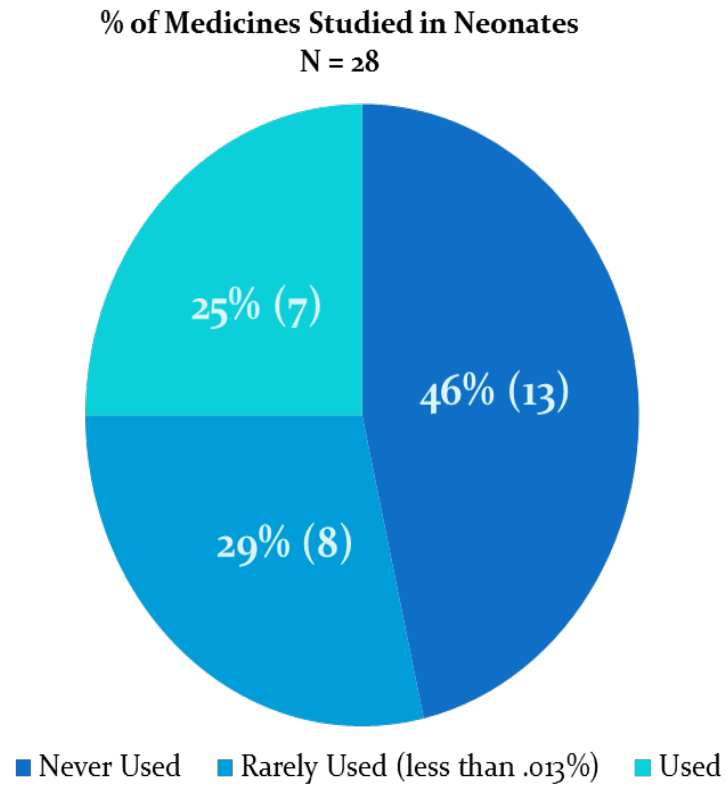
Proportion of medicines in PDR with information on children



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.



Stiers JL & Ward RM. Newborns, One of the Last Therapeutic Orphans to Be Adopted. JAMA Pediatrics. 168:106-8 (2014).

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.

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.

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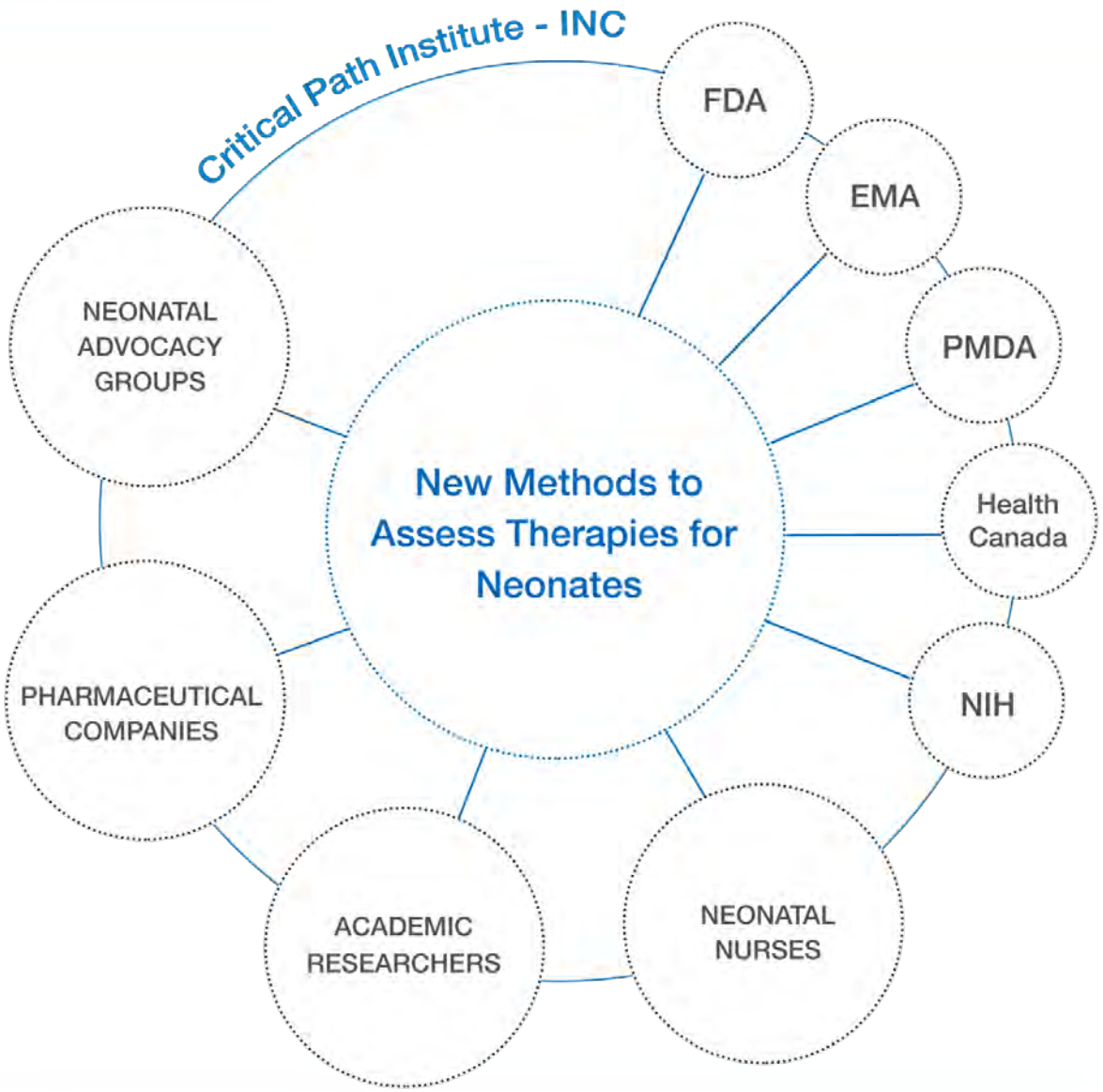
International Neonatal Consortium

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

Members Spanning the Globe



Neonatal Nurses
- NANN
- COINN

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

Families/Advocacy
- Graham's Foundation
- March of Dimes

INC Member Countries

- USA
- France
- Belgium
- Latvia
- Canada
- Switzerland
- EU
- England
- Ireland
- Italy
- S. Korea
- Norway
- Portugal
- Spain
- Australia
- Netherlands
- Germany
- Sweden
- Hungary
- Japan
- New Zealand
- Estonia
- Poland

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

Pediatric Trials Consortium

Deliverables

2015-2016

1

Advisory Report

PTC Advice & Guidance:

- Strategic plan & options
- Optimal leadership
- Operating plan & options
- Financial projections
- Legal Assessment

Critical Path Obtains:

- EIN #
- Tax-exempt status

Funding Decisions

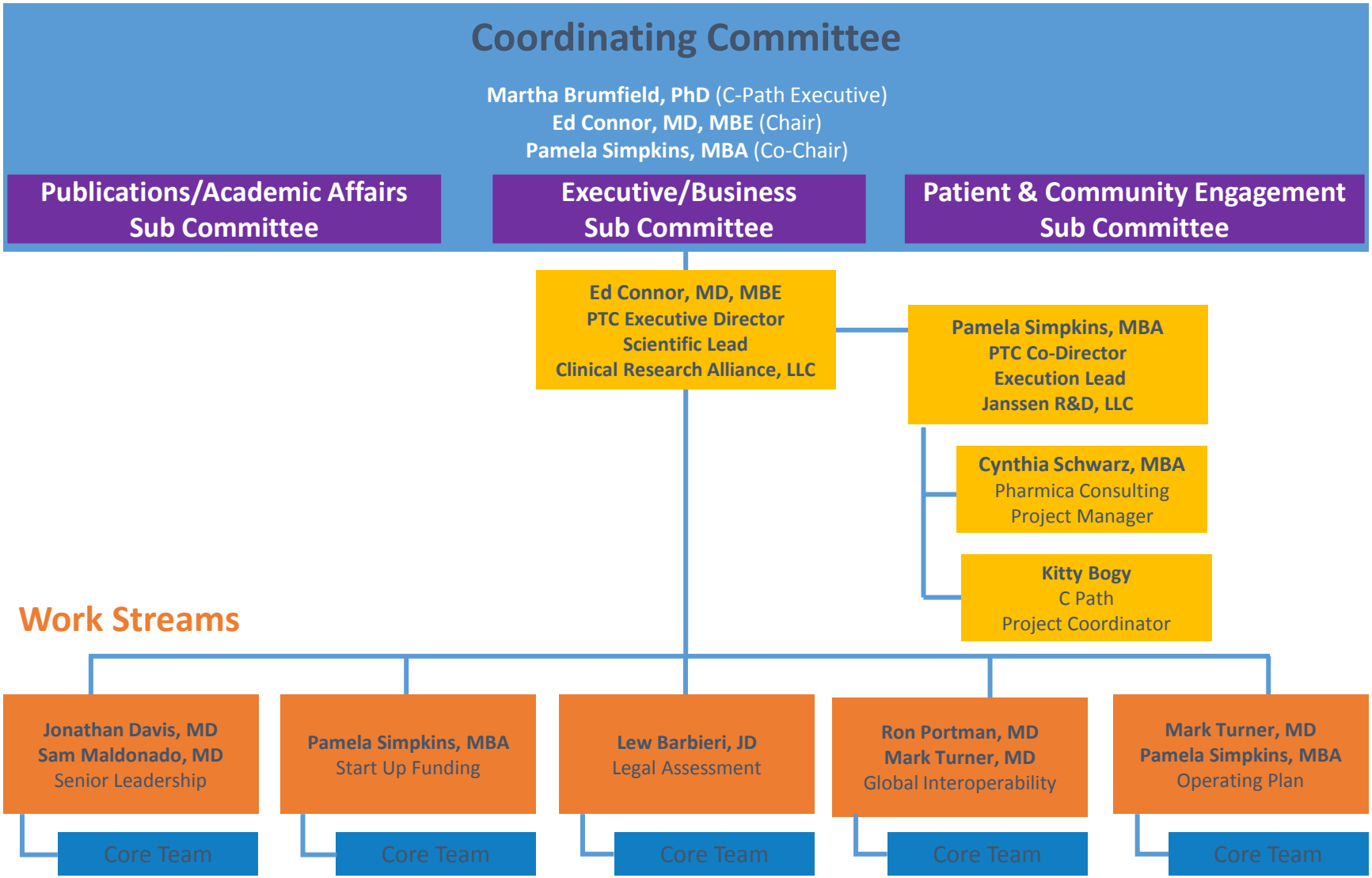
2016-2018

2

Non-Profit:

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

PTC Governance and Roles




INC: Advancing
Maternal - Child Health
Sustainable
Infrastructure
Cooperative
Groups
Knowledgeable
Investigators
Efficient
Regulatory Processes

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Regulatory Science for Neonates

Rob Califf
US Food and Drug Administration

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

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

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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

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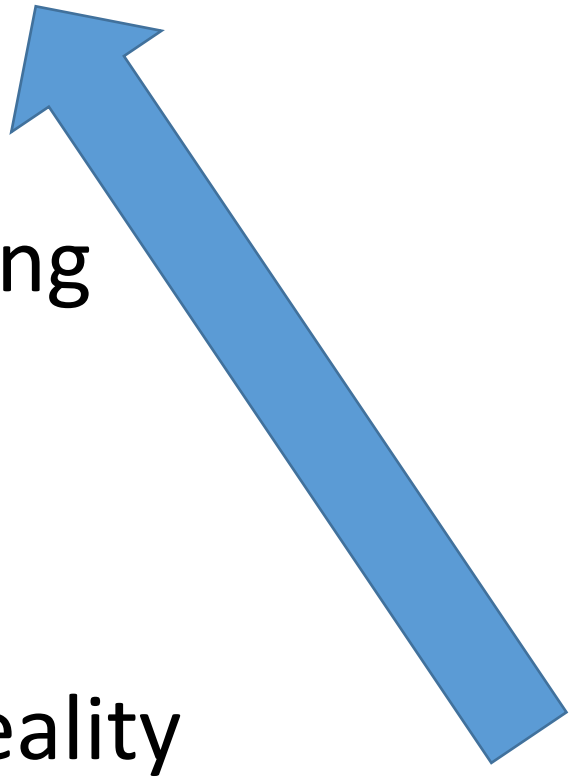


Regulatory Science

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

Regulatory Logic

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

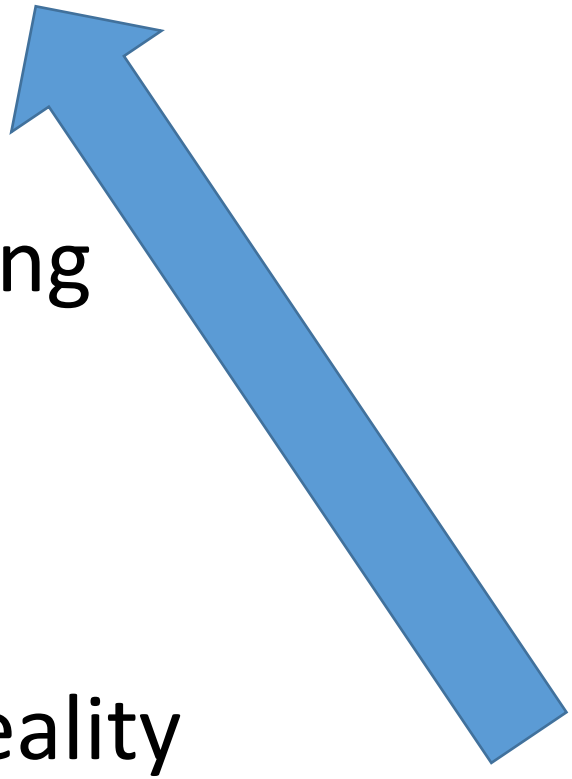
- Each mode of thinking has a place but is separate from regulatory logic

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

Another Community

A Mixed Community

Agenda – ROP Session

9:30 am	Challenges in Conducting Clinical Trials to Treat ROP & Strategies for Overcoming those Challenges Olaf Dammann (Tufts Medical Center)
10:00 am	ROP Panel Melissa Liew (Novartis), Adina Tocoian (Shire)
10:20 am	COFFEE BREAK
10:50 am	ROP Panel (continued) Alistair Fielder (City University London) Ann Hellstrom (University of Gothenburg) Neil Marlow (University College London) Wiley Chambers (US Food and Drug Admin.) Reiko Shimizu (Pharmaceutical and Medical Devices Agency, Japan) Ralph Bax (European Medicines Agency)
12:15 pm	Voting on Priority Projects for ROP
12:30 pm	LUNCH

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.

Pediatric RESEARCH

Open

Beyond Newborn Survival Paper 3

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

Blencowe, Lawn, Vasquez, Fielder, Gilbert, Pediatr Res 74: 35-49

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

Late Bacteremia		ROP			
		Stage 3-5	Zone 1	Prethresh/ Threshold	Plus Disease
Presumed	Univariable	**2.7 (1.8, 3.9)**	**1.9 (1.03, 3.7)**	**2.8 (1.8, 4.5)**	**2.7 (1.6, 4.5)**
	Multivariable*	1.5 (0.9, 2.4)	1.4 (0.7, 2.8)	**1.8 (1.02, 3.2)**	1.6 (0.8, 2.9)
Definite	Univariable	**1.9 (1.4, 2.6)**	**1.8 (1.1, 3.2)**	**2.5 (1.6, 3.7)**	**2.5 (1.6, 4.0)**
	Multivariable*	1.1 (0.7, 1.6)	1.2 (0.7, 2.3)	**1.8 (1.1, 2.9)**	**1.8 (1.05, 2.9)**

Washburn et al, Arch Ophthalmology 2011

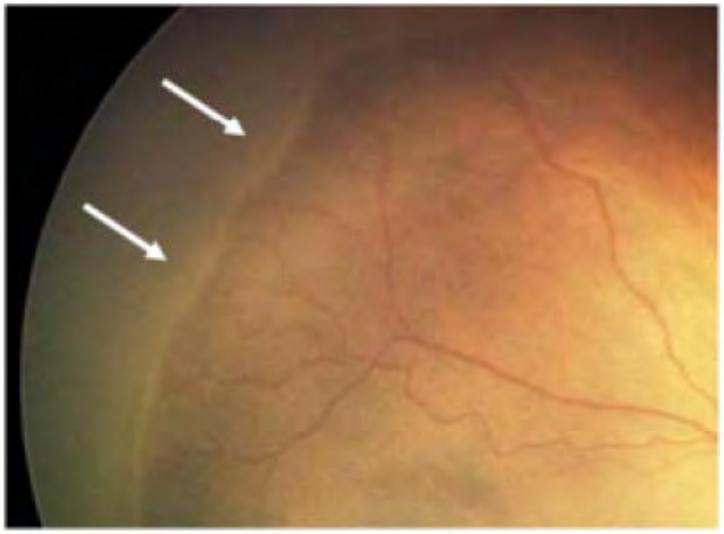
Hong *et al. Journal of Neuroinflammation* 2014, **11**:87
http://www.jneuroinflammation.com/content/11/1/87

JNI JOURNAL OF NEUROINFLAMMATION

RESEARCH Open Access

Neonatal systemic inflammation in rats alters retinal vessel development and simulates pathologic features of retinopathy of prematurity

Hye Kyoung Hong[1†], Hyun Ju Lee[2†], Jung Hwa Ko[2], Ji Hyun Park[1], Ji Yeon Park[1], Chang Won Choi[3], Chang-Hwan Yoon[4], Seong Joon Ahn[1], Kyu Hyung Park[1], Se Joon Woo[1,6*] and Joo Youn Oh[2,5,6*]



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

Top quartile →	twice d 1,7,14	both d 21 & 28	Late in light of early§
CRP	0.9 (0.5, 1.4)	**1.7 (1.01, 3.0)**	**1.8 (1.1, 3.2)**
SAA	1.0 (0.6, 1.6)	**2.2 (1.3, 3.9)**	**2.2 (1.3, 4.0)**
MPO	1.5 (0.9, 2.5)	1.5 (0.9, 2.6)	1.5 (0.9, 2.5)
IL-1β	0.9 (0.5, 1.5)	0.7 (0.4 , 1.3)	0.7 (0.4, 1.4)
IL-6	0.9 (0.6, 1.6)	**1.8 (1.05, 3.0)**	**1.9 (1.1, 3.2)**
IL-6R	1.4 (0.9, 2.2)	1.5 (0.9, 2.6)	1.4 (0.8, 2.5)
TNF-α	0.8 (0.5, 1.4)	1.2 (0.7, 1.9)	1.2 (0.8, 2.1)
TNF-R2	1.1 (0.7, 1.8)	**1.7 (1.03, 2.9)**	**1.7 (1.02, 3.0)**
IL-8	1.4 (0.9, 2.3)	1.6 (0.96, 2.6)	1.5 (0.9, 2.5)

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?

ACTA PÆDIATRICA
NURTURING THE CHILD

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*

	Retina	Lung	(Bacteremia)	
	ROP†	BPD‡	Early§	Late§
Bowel	**3.1 (1.7, 5.8)**	**3.7 (1.9, 7.1)**	0.8 (0.2, 2.7)	1.4 (0.7, 2.5)
Brain	1.1 (0.8, 1.6)	1.0 (0.6, 1.7)	1.2 (0.7, 2.3)	1.2 (0.9, 1.7)
Retina		2.6 (1.7, 3.9)	1.7 (1.1, 2.8)	1.4 (1.1, 1.9)
Lung	62/34		0.5 (0.2, 1.3)	1.4 (0.96, 2.1)
Blood early	35/23.3	5/8.0		**2.1 (1.3, 3.3)**
Blood late	118/92.6	42/31.6	33/20.3	

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

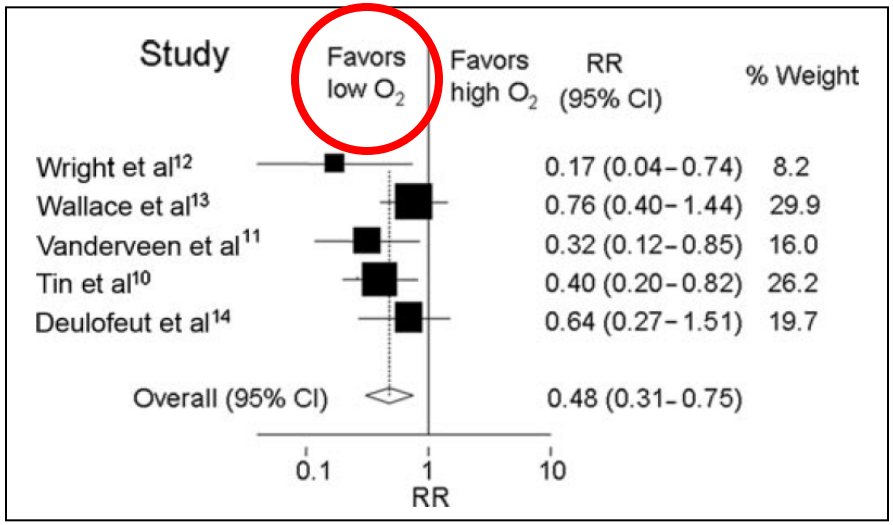
Biomarkers

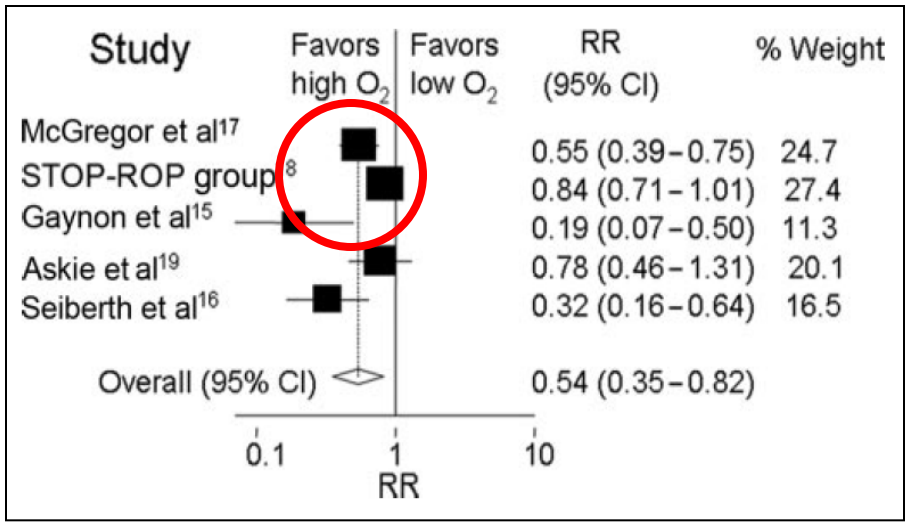
Timepoints

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]





Early postnatal weeks

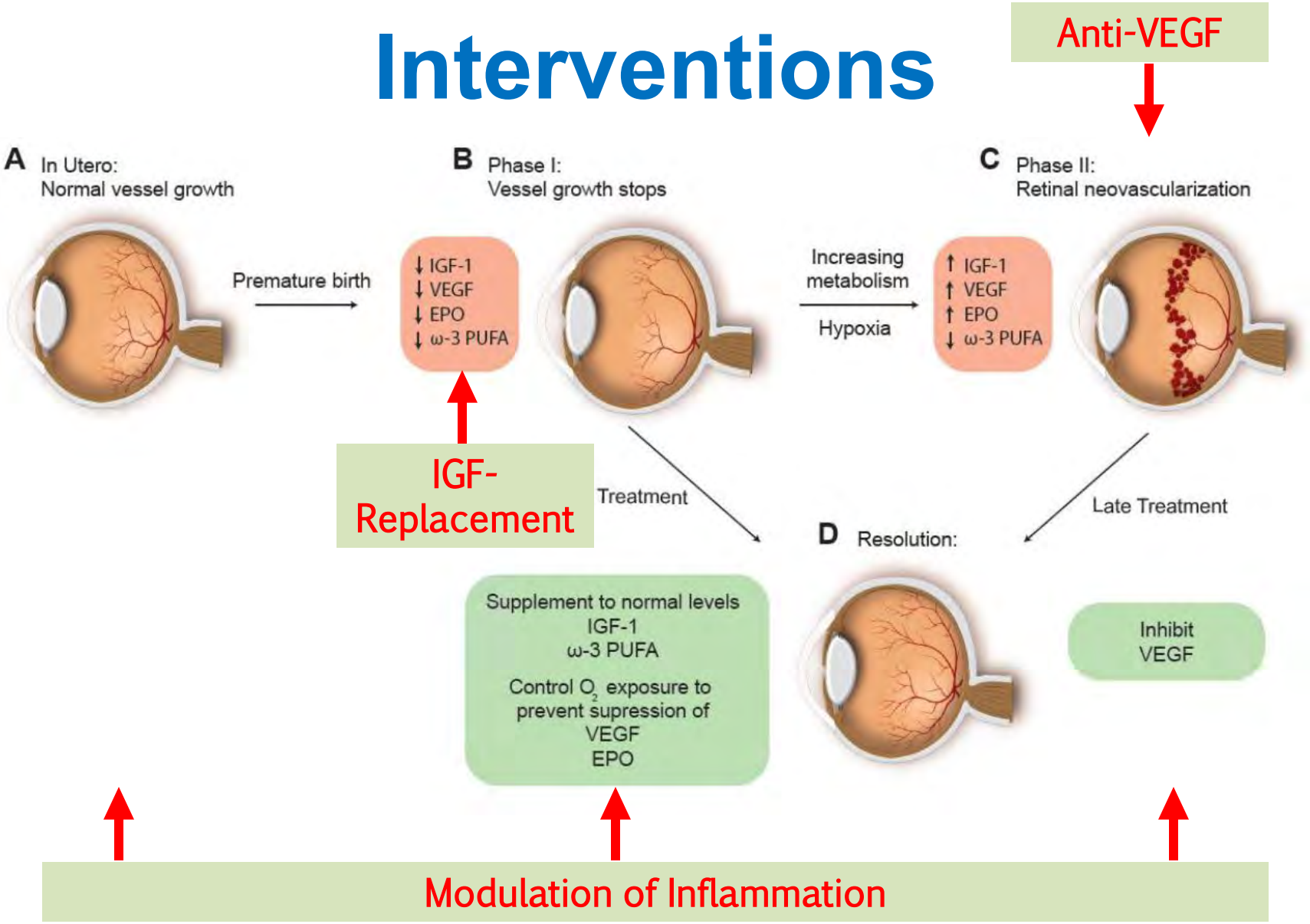
Reduce Oxygen

≥32 postconceptual weeks

Increase Oxygen

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

Interventions



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

Group	Gestational age <26 weeks	Oxygen at 28 days	Any sepsis	ROP		
				yes, n	no, n	yes, %
1	+	+	+	60	11	85
2	+	+	–	61	16	79
3	+	–	+	2	1	67
4	+	–	–	1	3	25
5	–	+	+	53	46	54
6	–	+	–	79	137	37
7	–	–	+	13	12	52
8	–	–	–	23	99	19

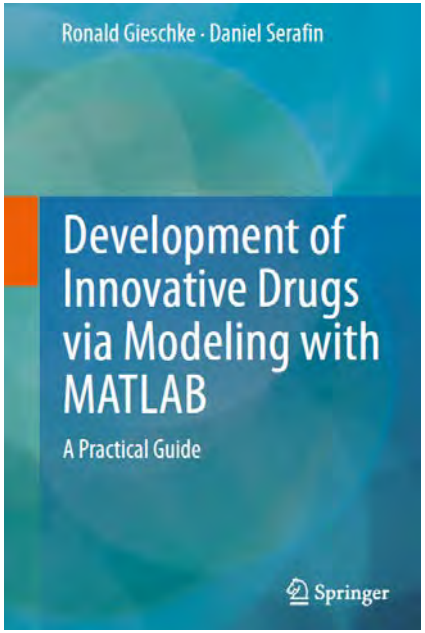
Neonatology, 2011

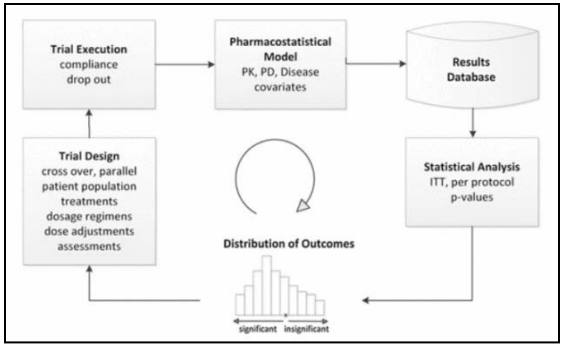
Tufts Population Model of ROP Occurrence

Chen Table 3	Group	1	2	3	4	5	6	7	8
	GA	+	+	+	+	-	-	-	-
	Oxygen	+	+	-	-	+	+	-	-
	Sepsis	+	-	+	-	+	-	+	-
	ROP (% yes)	85	79	67	25	54	37	52	19
Simulation	10 Run Avg.	84	80	65	24	56	38	53	18
	Run 1	85	83	56	29	62	34	55	16
	Run 2	81	79	77	21	59	44	52	11
	Run 3	83	81	66	23	53	42	44	11
	Run 4	89	81	71	27	54	42	49	16
	Run 5	83	77	64	27	41	44	50	16
	Run 6	82	76	70	21	61	35	51	17
	Run 7	85	87	72	30	60	42	53	20
	Run 8	85	77	65	21	64	30	62	27
	Run 9	83	76	58	25	61	29	52	19
	Run 10	87	82	54	15	49	39	67	21

Fried, Hescott, & Dammann, unpublished

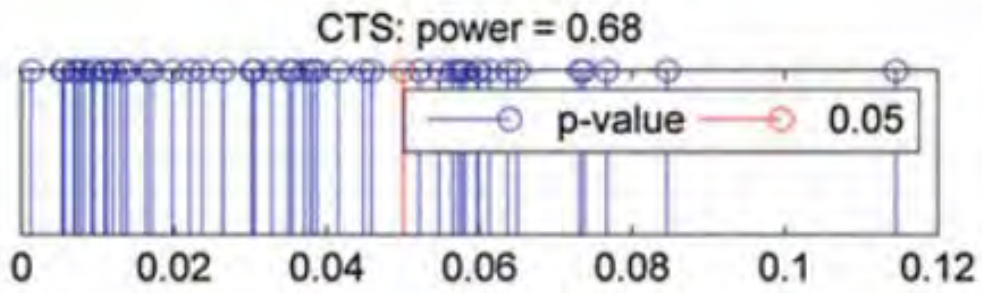
Clinical Trial Simulation

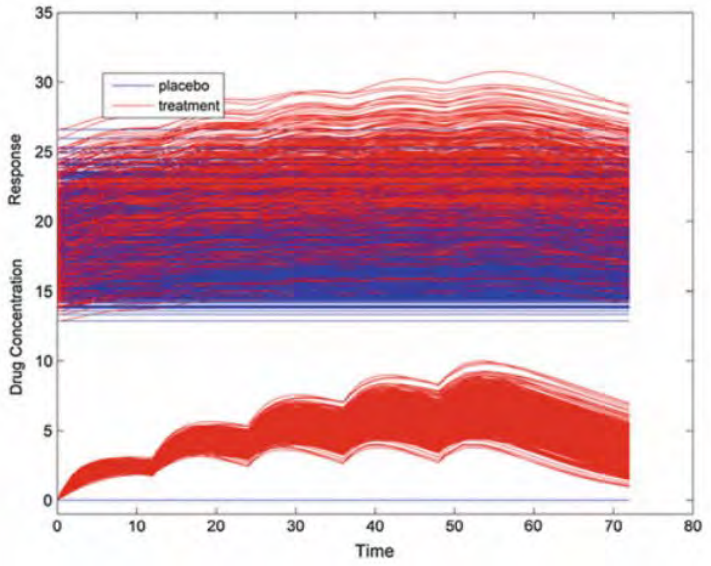





```
% create vector of treatment times
initialCycleTimes = ...
    initialTime : cycleTime : (endTime - cycleTime);
doseTimesWithinCycle = ...
    initialTime : hoursInDay/dailyDoses : timeOnDrug;
doseTimes = reshape(...
    repmat(doseTimesWithinCycle', 1, length(initialCycleTimes))+ ...
    repmat(initialCycleTimes, 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

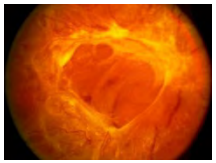
- **Timepoints**
  - Recruitment
  - Intervention
  - Monitoring
  - Outcome assessment
- **Biomarkers** of
  - Exposure to be modified
  - Intervention
  - Disease process
  - Outcome (diagnosis, progression)
- **Simulation**
  - Population models
  - Clinical trial simulation

Thank you!

NIH / NEI

Placenta
Microbiology

?



Retinopathy of
Prematurity

European Union

neobrain

neurobid

neocirculation

Tufts Collaborates!

Tufts UNIVERSITY | Office of the Provost and Senior Vice President

Computational Population model
of Retinopathy of Prematurity

International Neonatal Consortium

AntiVEGF in ROP

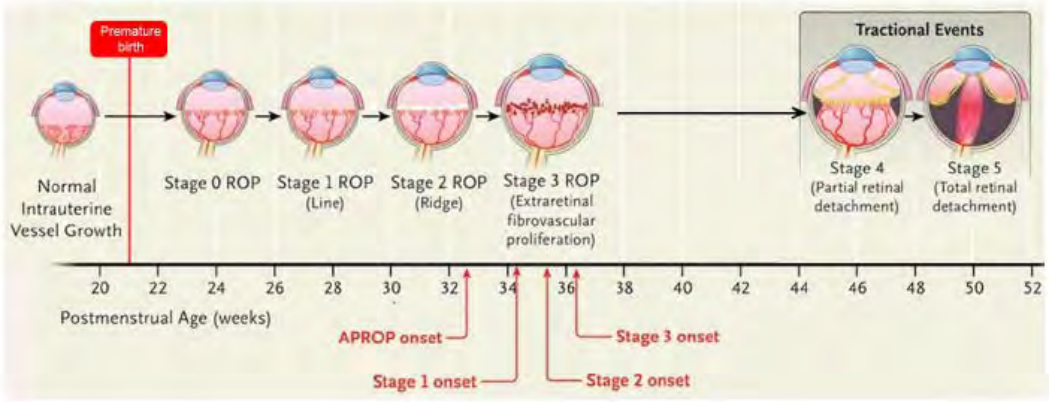
Melissa S H Liew

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**



Adapted from
Mintz-Hittner et al NEJM 2011

- 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

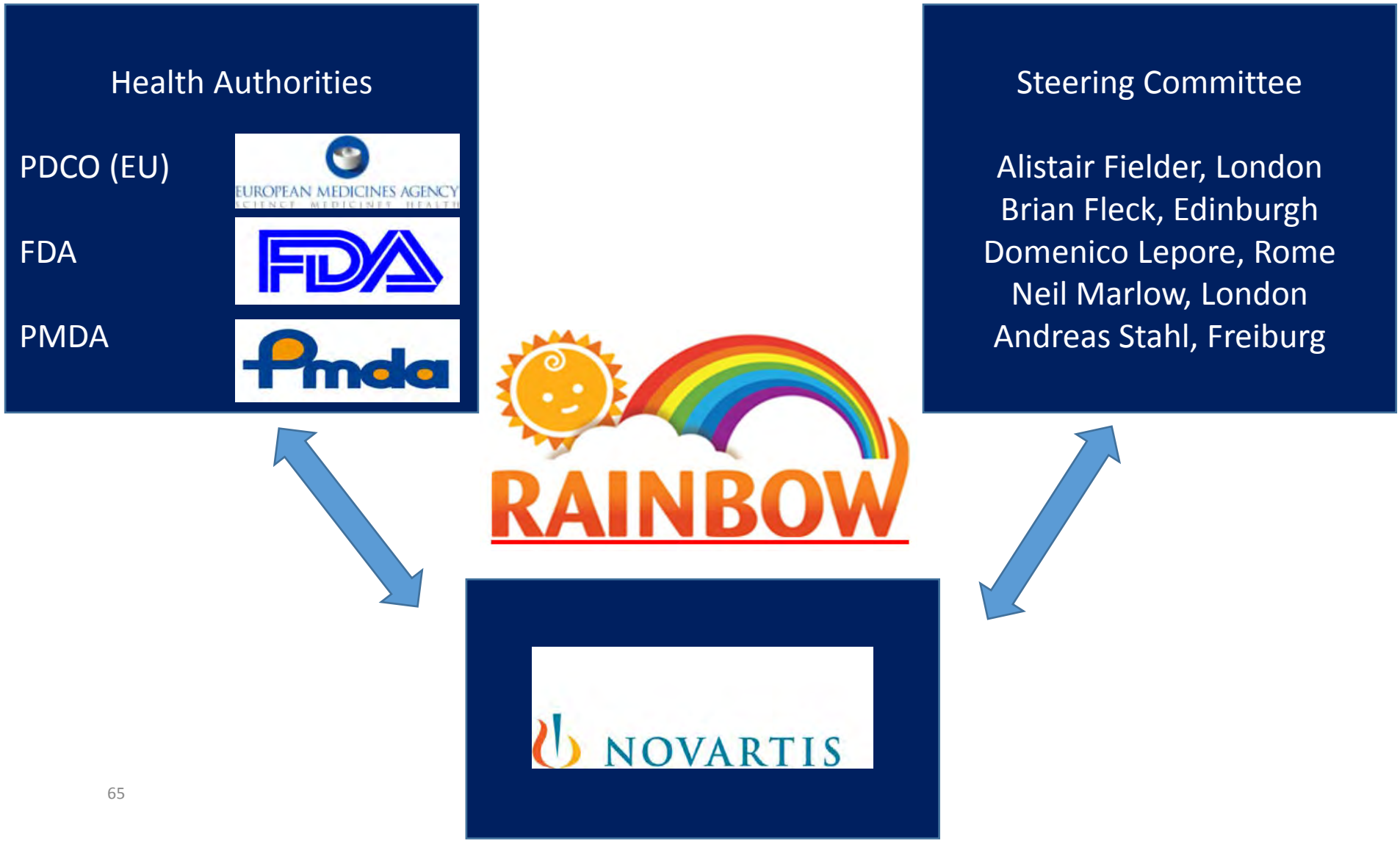
AntiVEGF in ROP

- 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



Development of the RAINBOW Study

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

	Ranibizumab	Bevacizumab
MOA /class		
Molecular weight	48 kDa	149 kDa
Half-life in the human eye	9 days	6.7 days
Systemic elimination half-life	2 hours	20 days

Development of the RAINBOW Study

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

40%

<5%

- ROP
- Neonate
- Vitreous volume 1.69ml
- Systemic circulation 95ml/kg
- 95ml for 1,000g neonate

Howie SR 2011. WHO; 89: 46-53
Cole TJ et al. 2014. Arch Dis Child Fetal Neonatal; 99: F34-40

Development of the RAINBOW Study

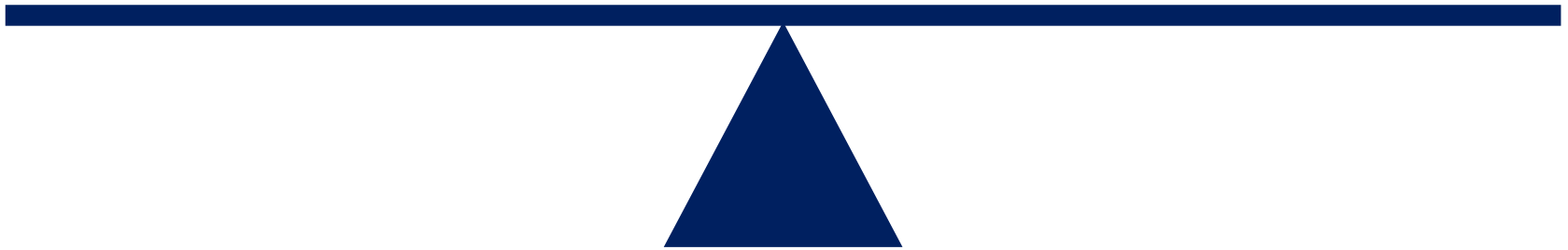
What are the Challenges - Dose selection

<u>Efficacy</u>

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

<u>Safety</u>

- 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

Development of the RAINBOW Study

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 **RA**nibizumab compared with laser therapy for the treatment of **IN**fants **B**orn prematurely **W**ith retinopathy of prematurity

RAINBOW

Core Study H2301

Extension Study H2301E1

Development of the RAINBOW Study

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

- 

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

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PREVENT ROP SHIRE

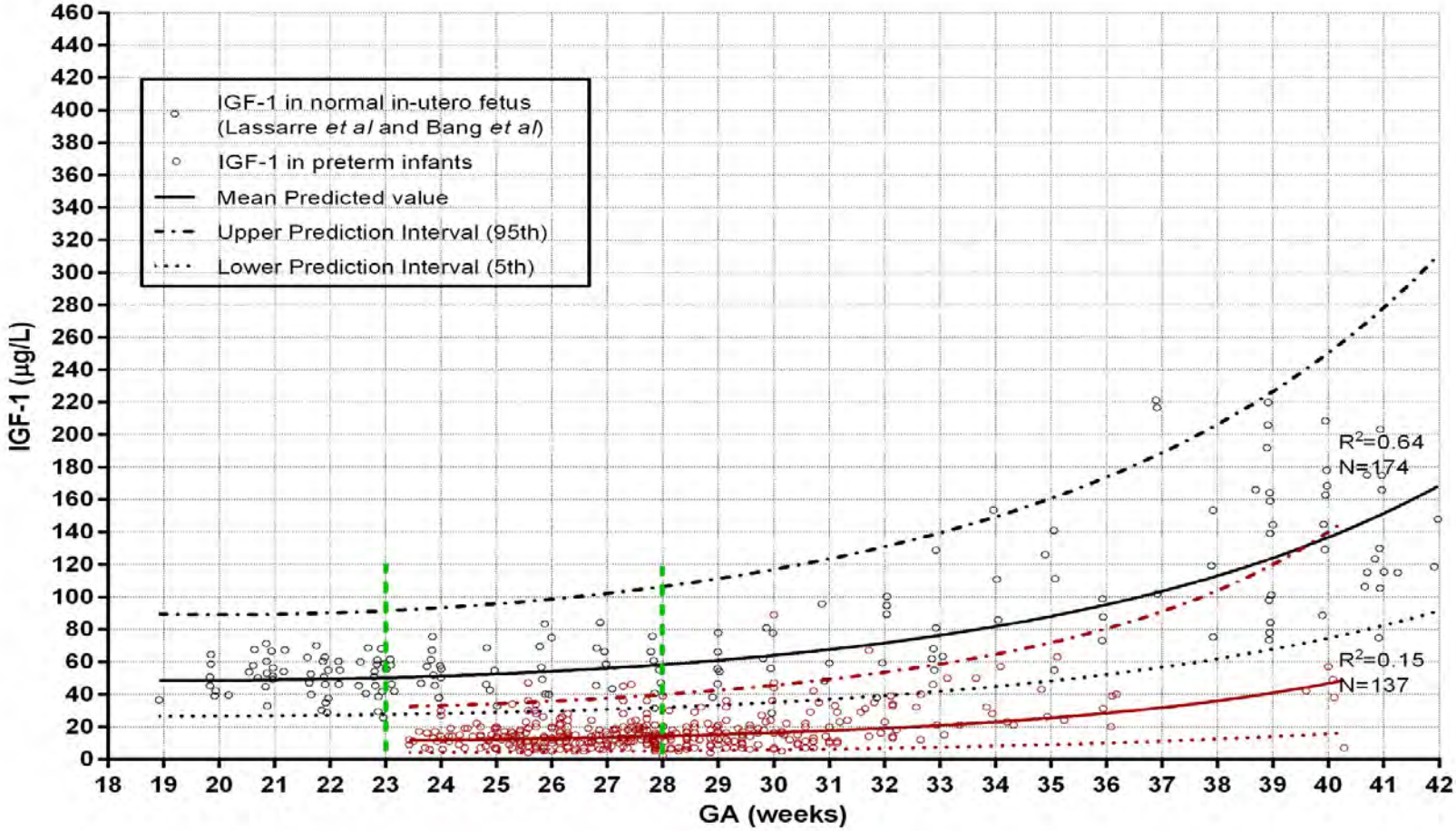
Adina Tocoian
Medical Director Shire

CRITICAL PATH INSTITUTE

IGF-1 target range – healthy in-utero serum level

Shire

IGF-1 target range – 28-109 µg/L

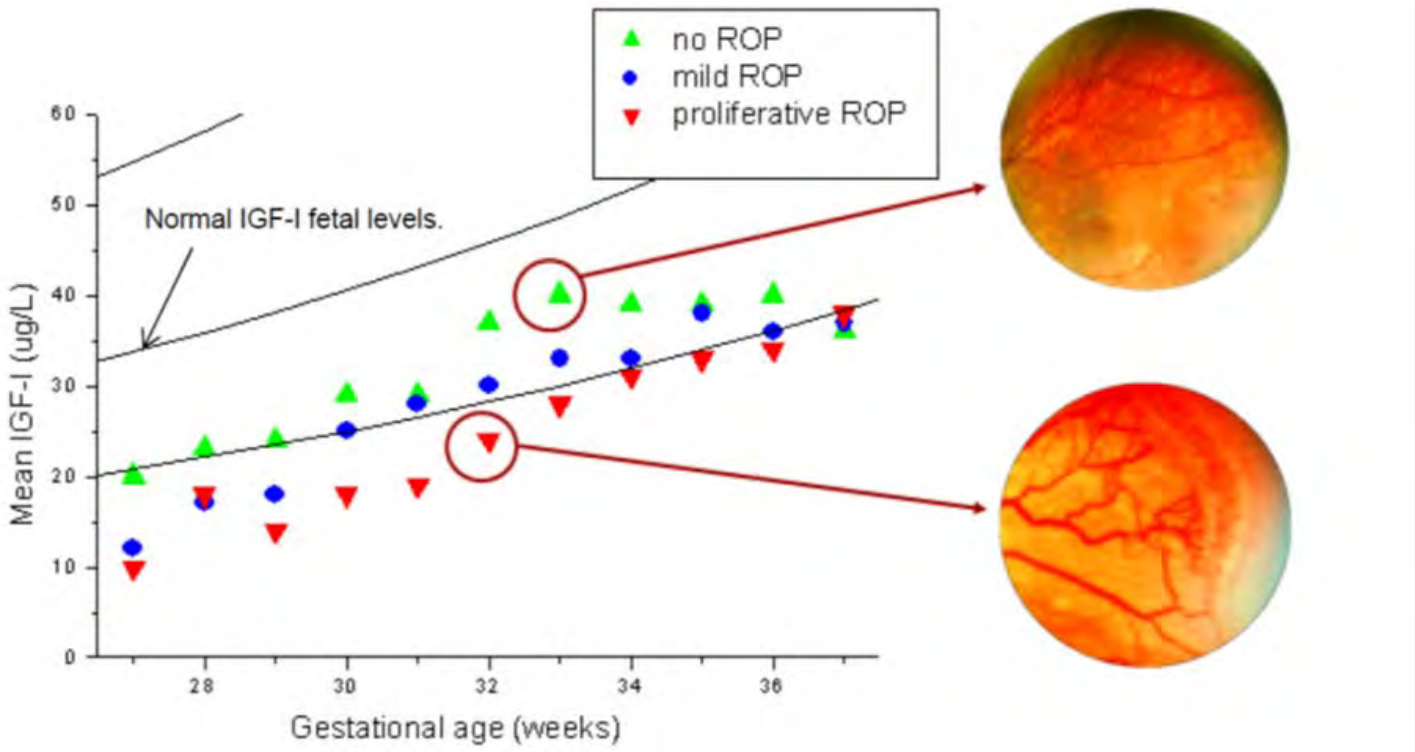


Hellström A, et al. *Acta Paediatrica,* 2016

IGF-1/IGFBP3 for Prevention of ROP

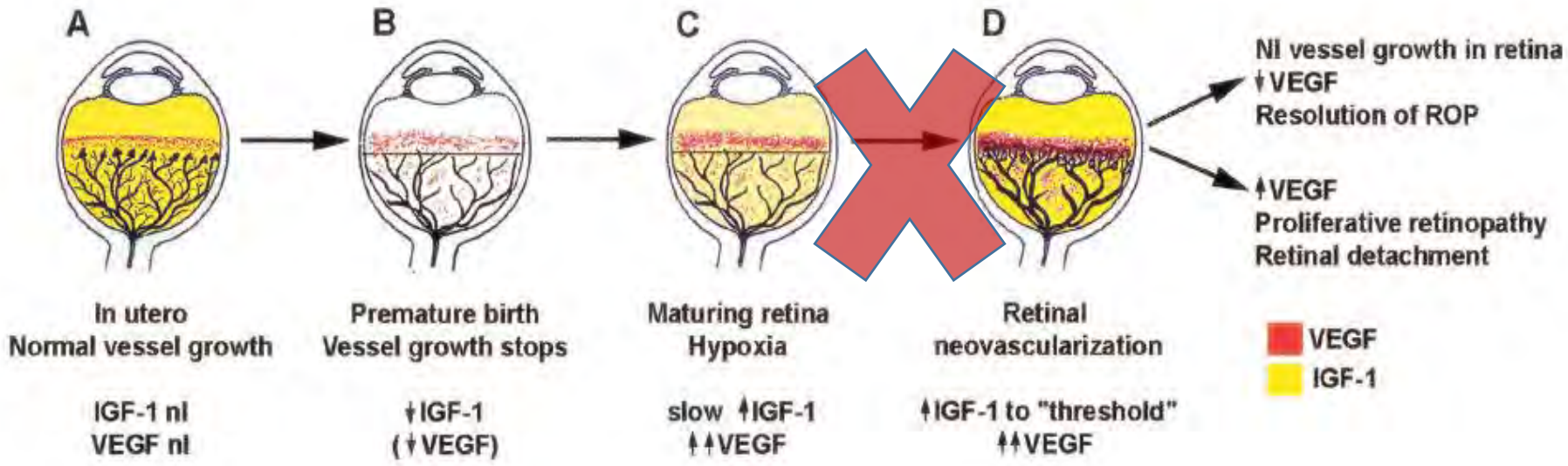
Shire

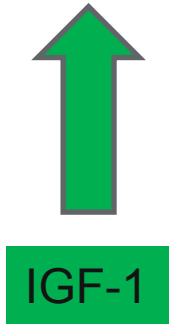
Intra-uterine IGF-1 levels and the correlation between ROP and serum IGF-1 levels in prematurely born infants



ROP: IGF-1 and VEGF roles in development

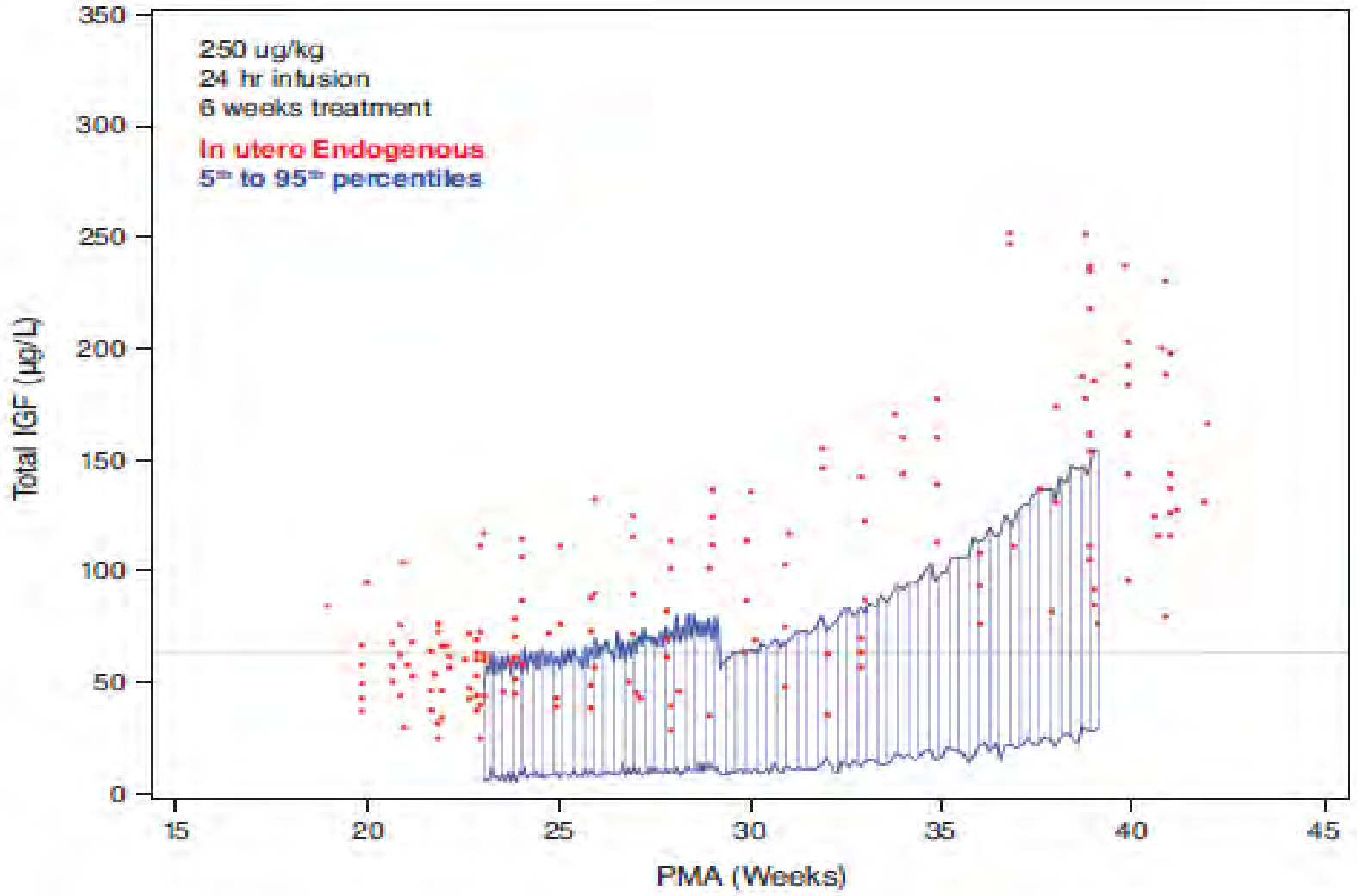
Shire





Simulation of 250 µg/kg/24 h dose over 6 w treatment

Shire



Shire ROPP 2008-01

Shire

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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

Shire ROPP 2008-01

Shire

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

Shire ROPP 2008-01

Shire

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 ≥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

PEDAL

Shire

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

pedal

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)

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Coffee Break
30 minutes

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Coffee Break
30 minutes

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Agenda – ROP Session

9:30 am	Challenges in Conducting Clinical Trials to Treat ROP & Strategies for Overcoming those Challenges Olaf Dammann (Tufts Medical Center)
10:00 am	ROP Panel Melissa Liew (Novartis), Adina Tocoian (Shire)
10:20 am	COFFEE BREAK
10:50 am	ROP Panel (continued) Alistair Fielder (City University London) Ann Hellstrom (University of Gothenburg) Neil Marlow (University College London) Wiley Chambers (US Food and Drug Admin.) Reiko Shimizu (Pharmaceutical and Medical Devices Agency, Japan) Ralph Bax (European Medicines Agency)
12:15 pm	Voting on Priority Projects for ROP
12:30 pm	LUNCH

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Alistair Fielder
City University, London, UK

CRITICAL PATH INSTITUTE

Retinopathy of Prematurity

Alistair Fielder

City University, London, UK

Financial Disclosure

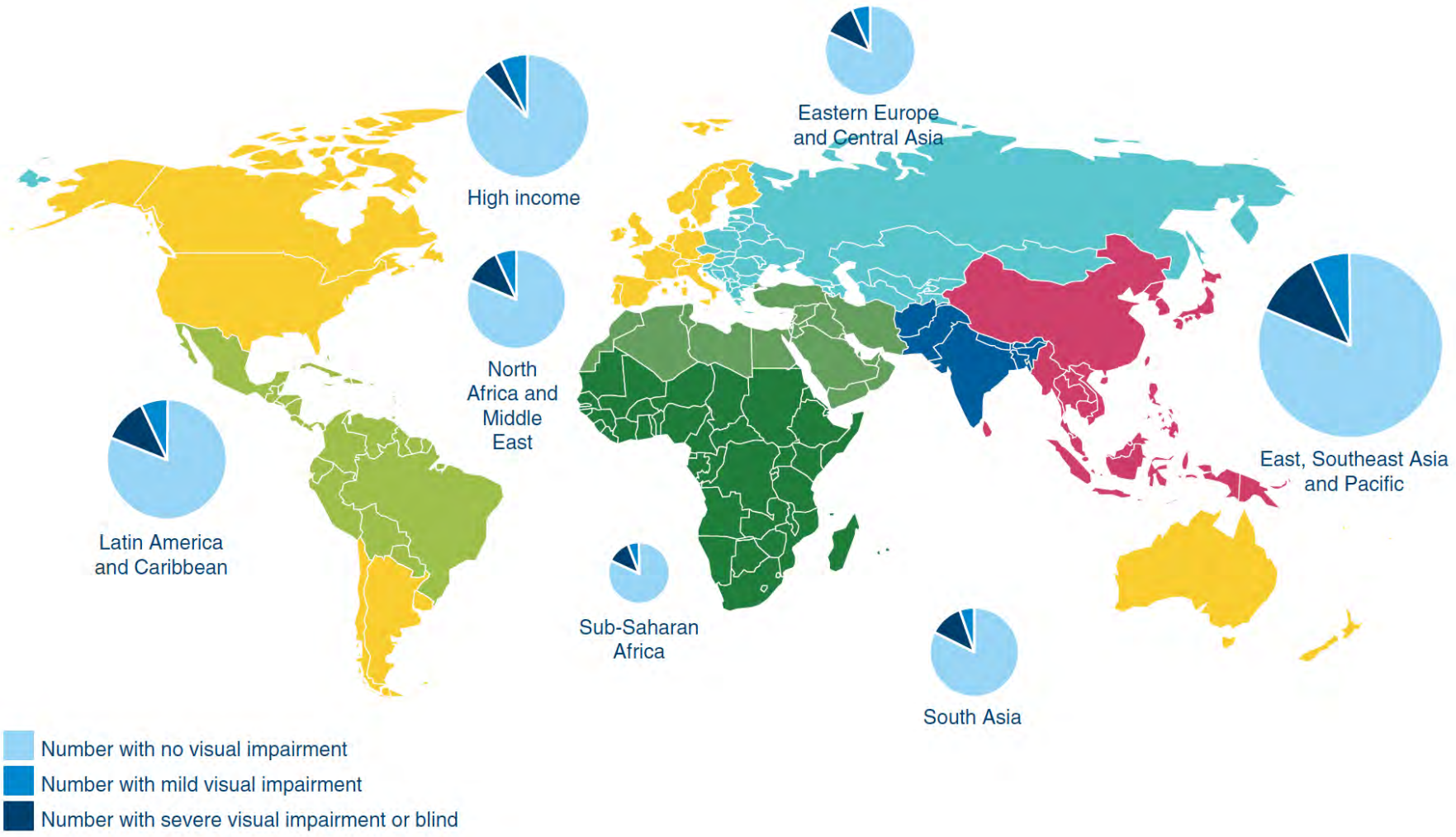
Honoraria from Clarity Medical Systems for presentations at meetings & workshops in Middle East

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*

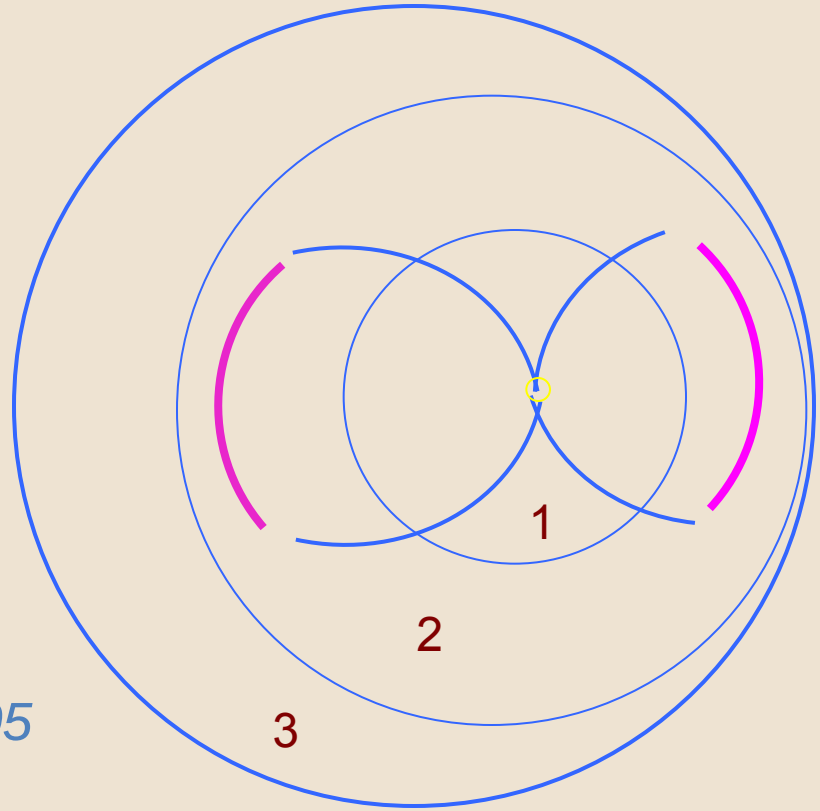
ROP Natural History
Highly Stylised

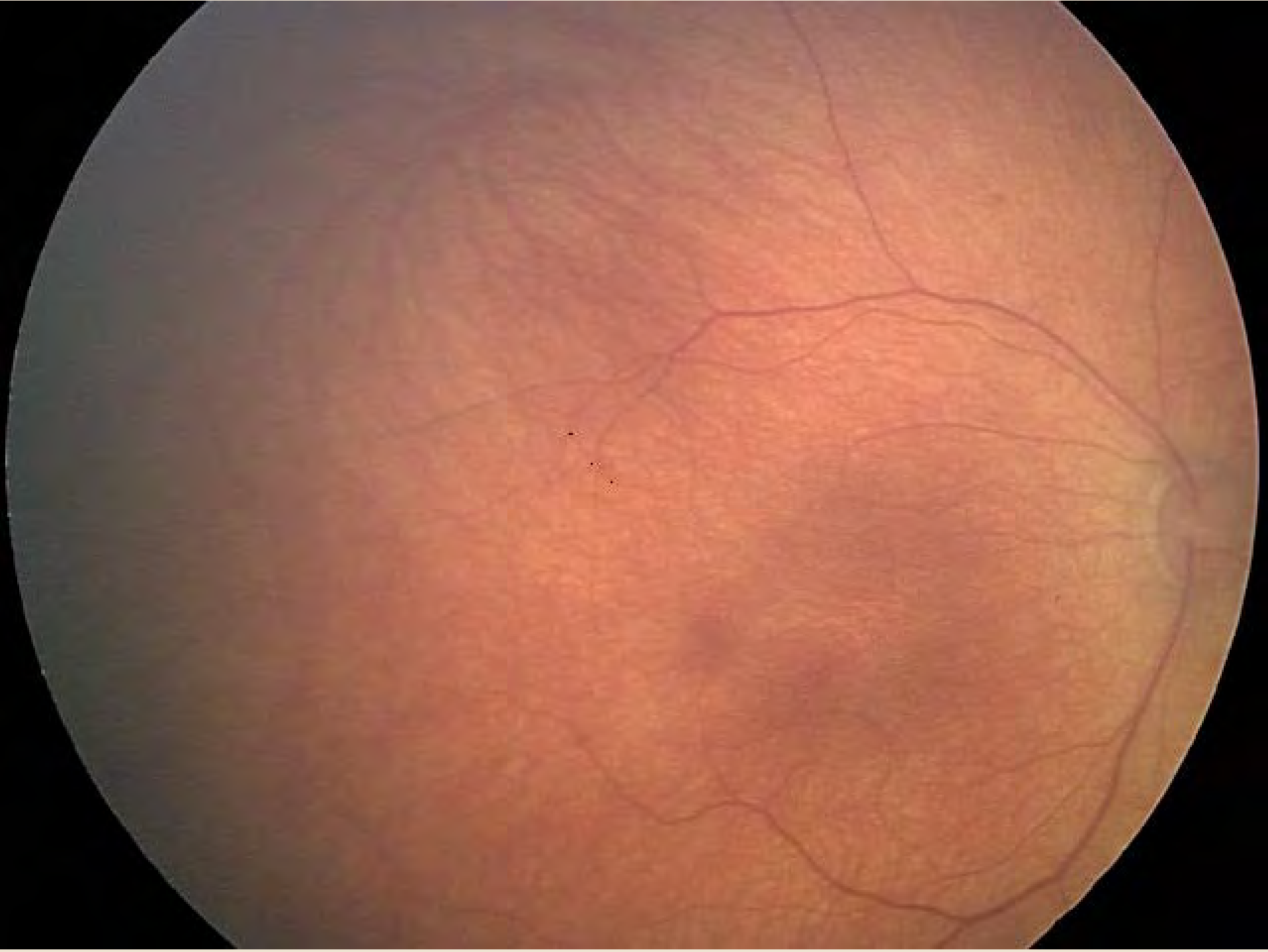
- Clearly described natural history
- Timing of onset & progression largely determined by postmenstrual age & is
- Consistent across ethnic groups & settings
- More mature babies have an earlier postnatal age at onset & more protracted course than the more immature babies

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

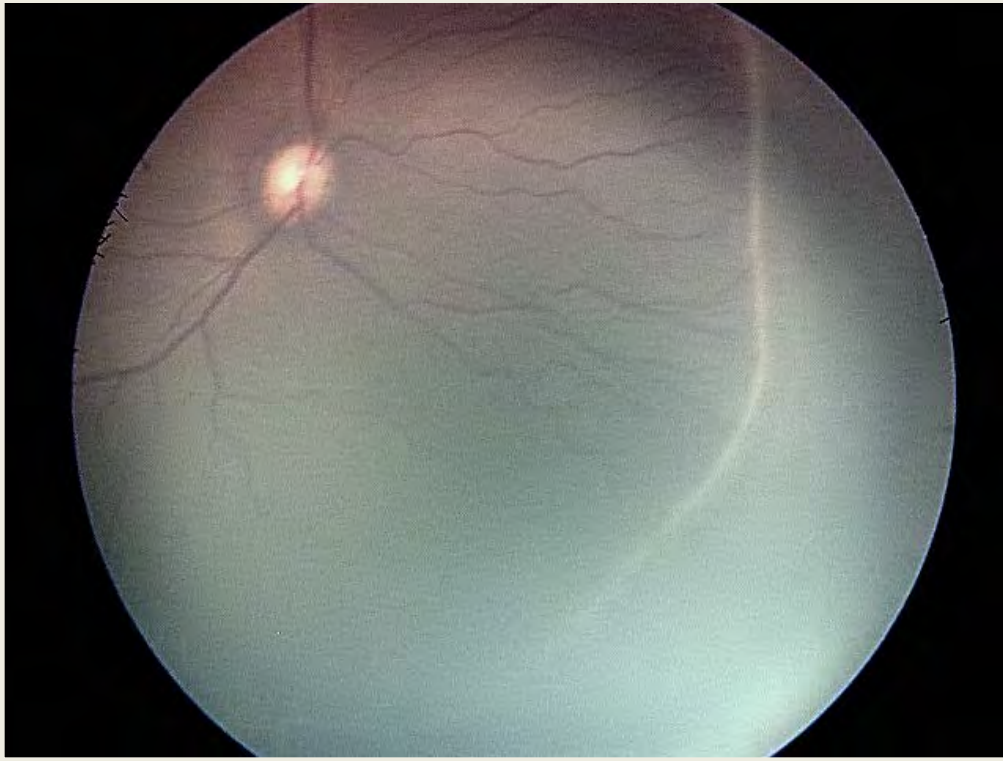
ICROP 1984, 1987 & 2005





ROP Stage 1

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

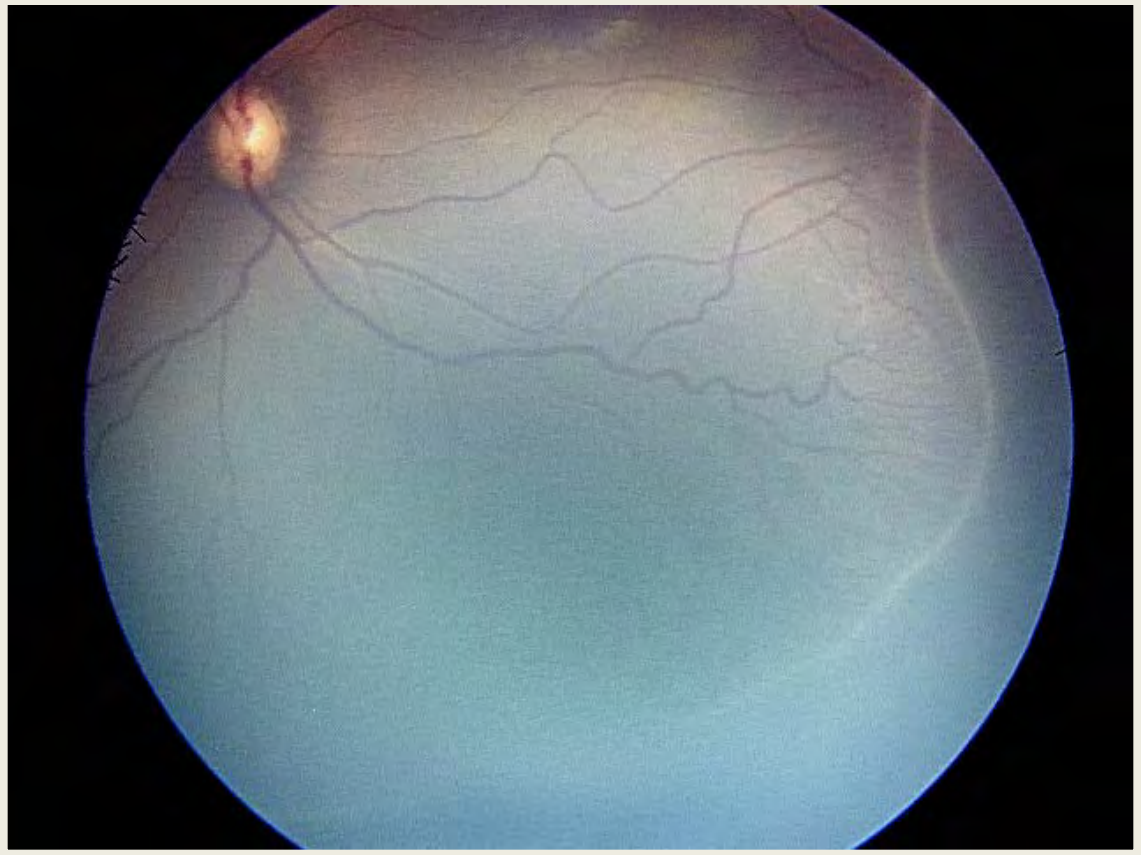


Should 1 & 2 be merged?

& some stage 2 here

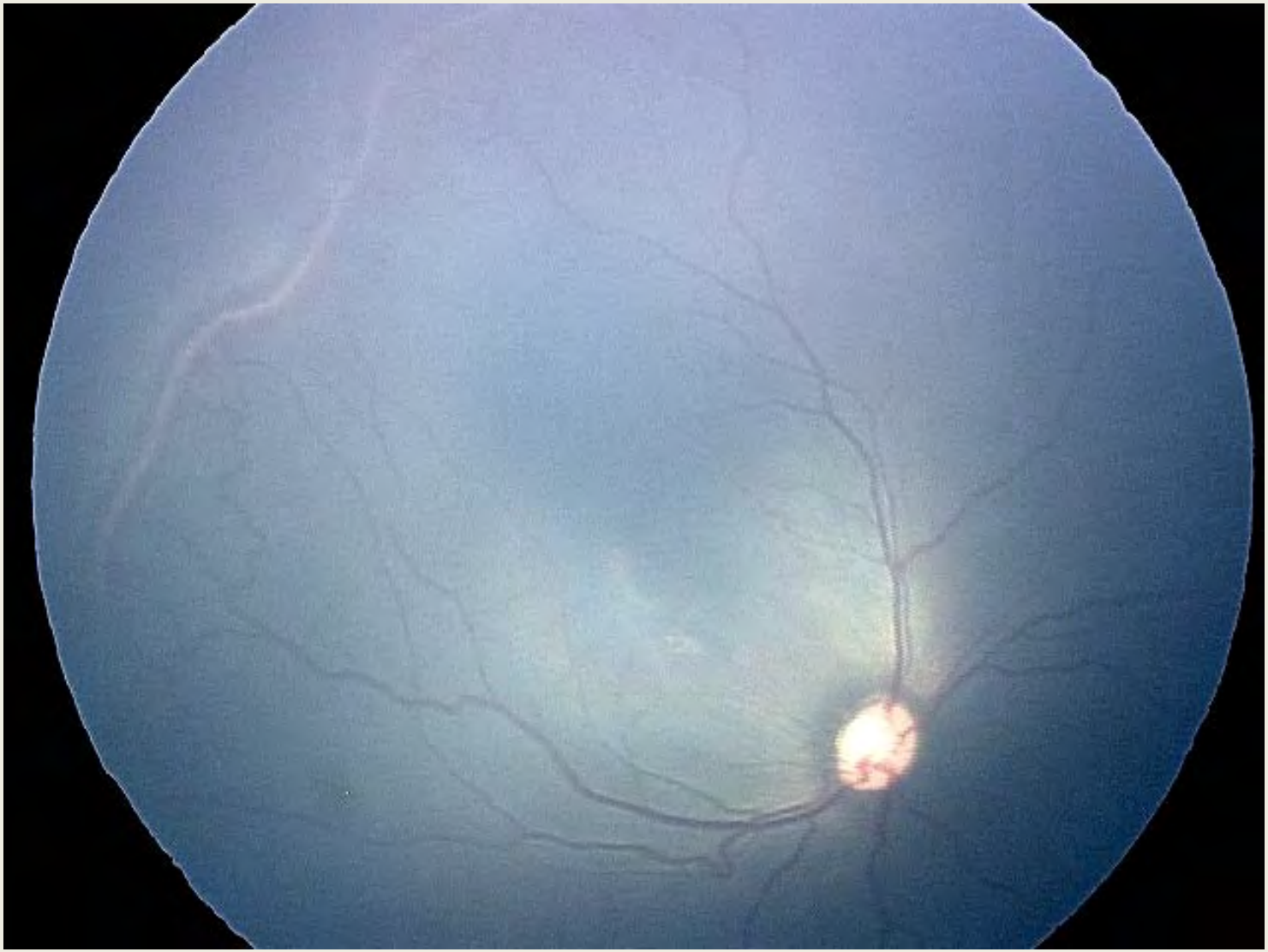
ROP Stage 2

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

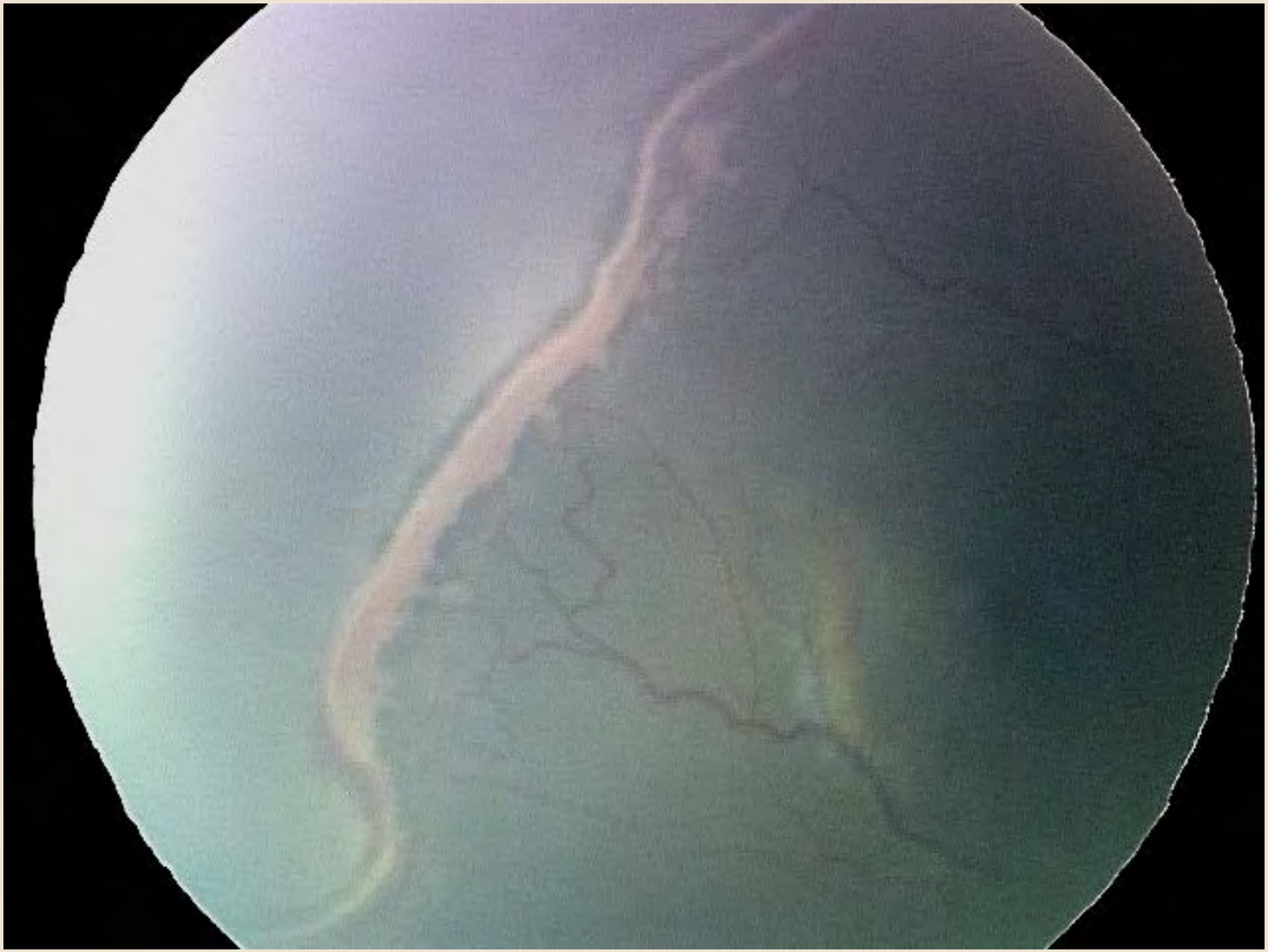


& some stage 1 here

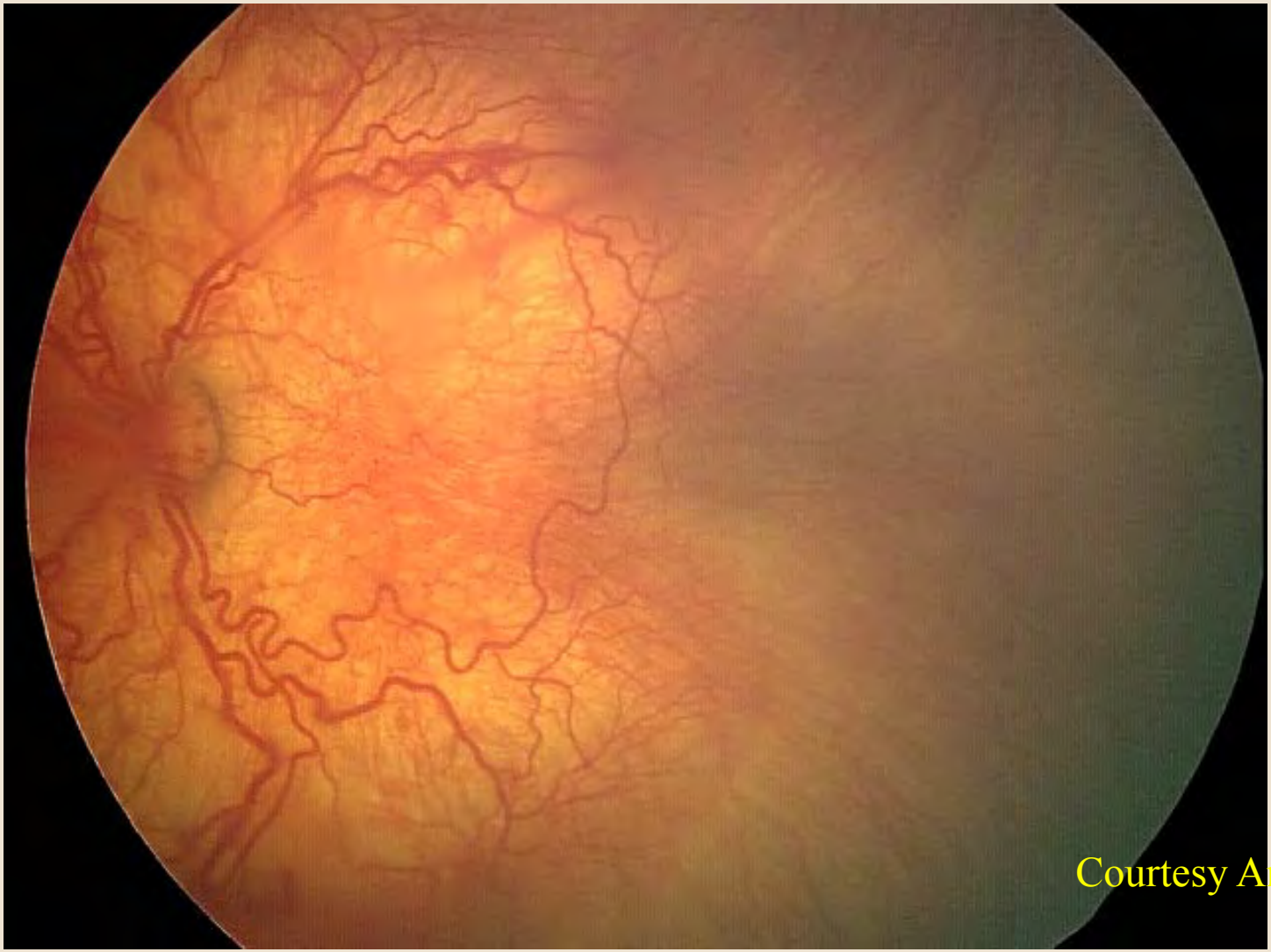
ROP Stage 2



ROP Stage 3

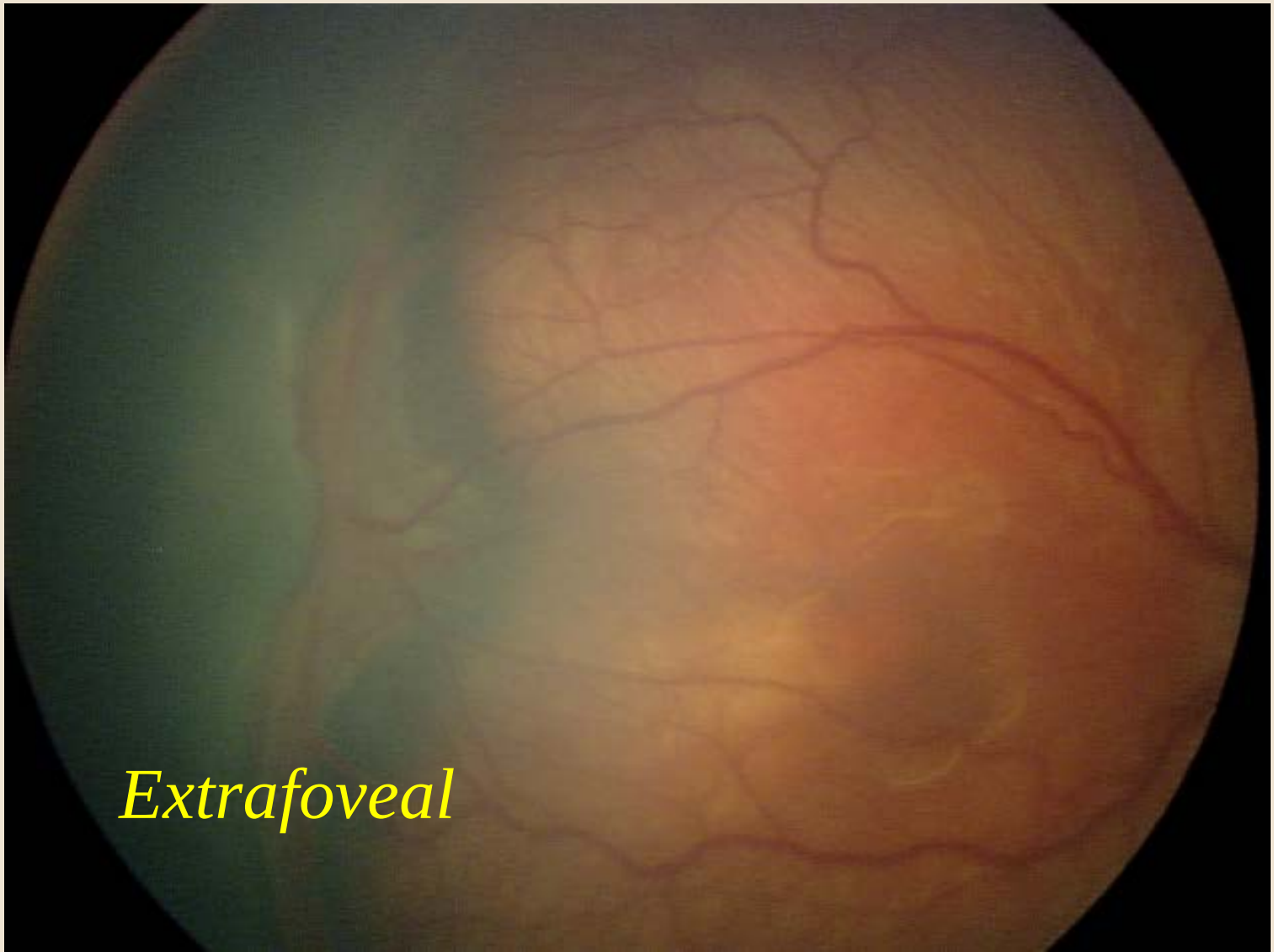


Aggressive Posterior ROP

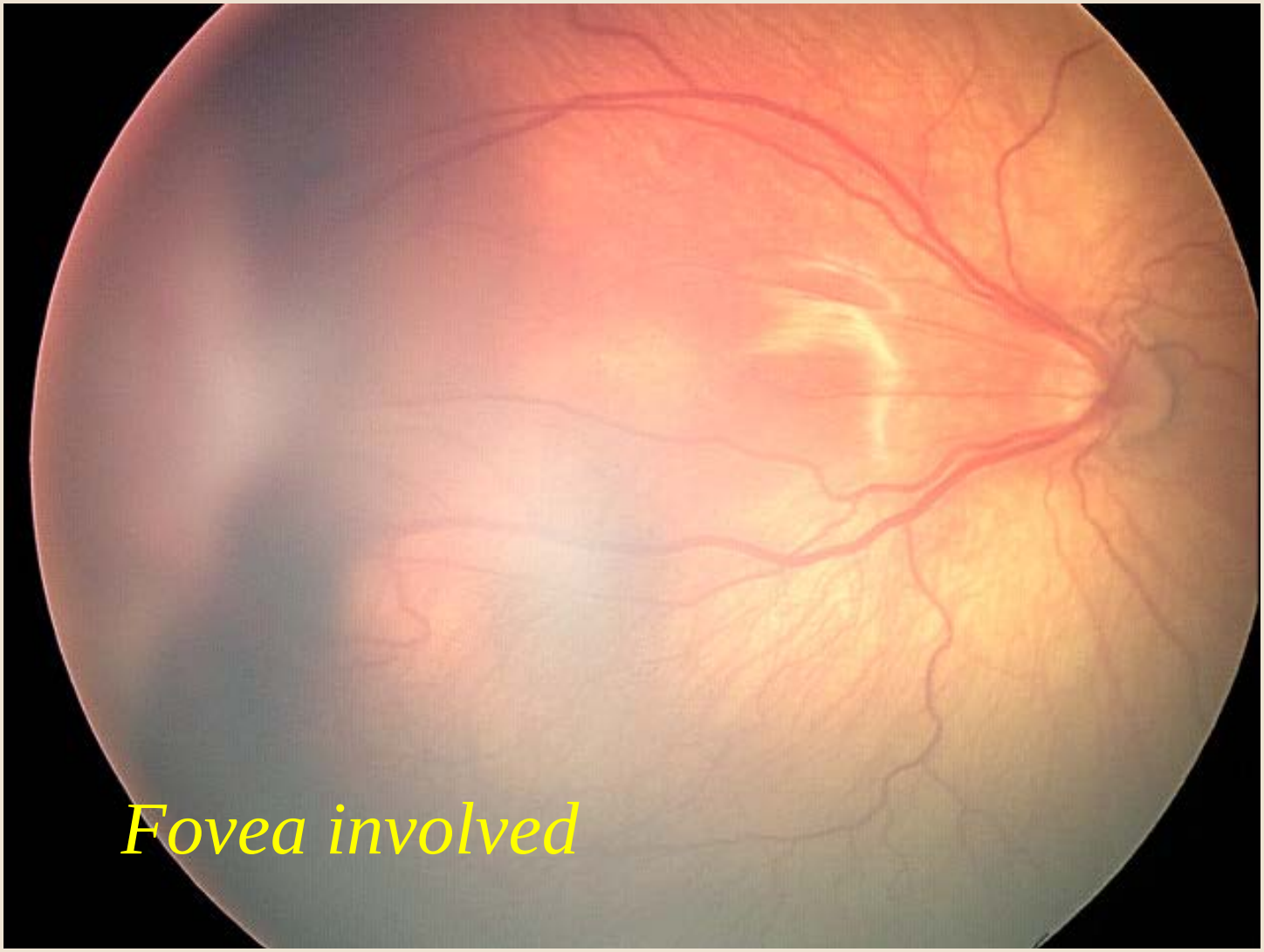


Courtesy Anna Ells

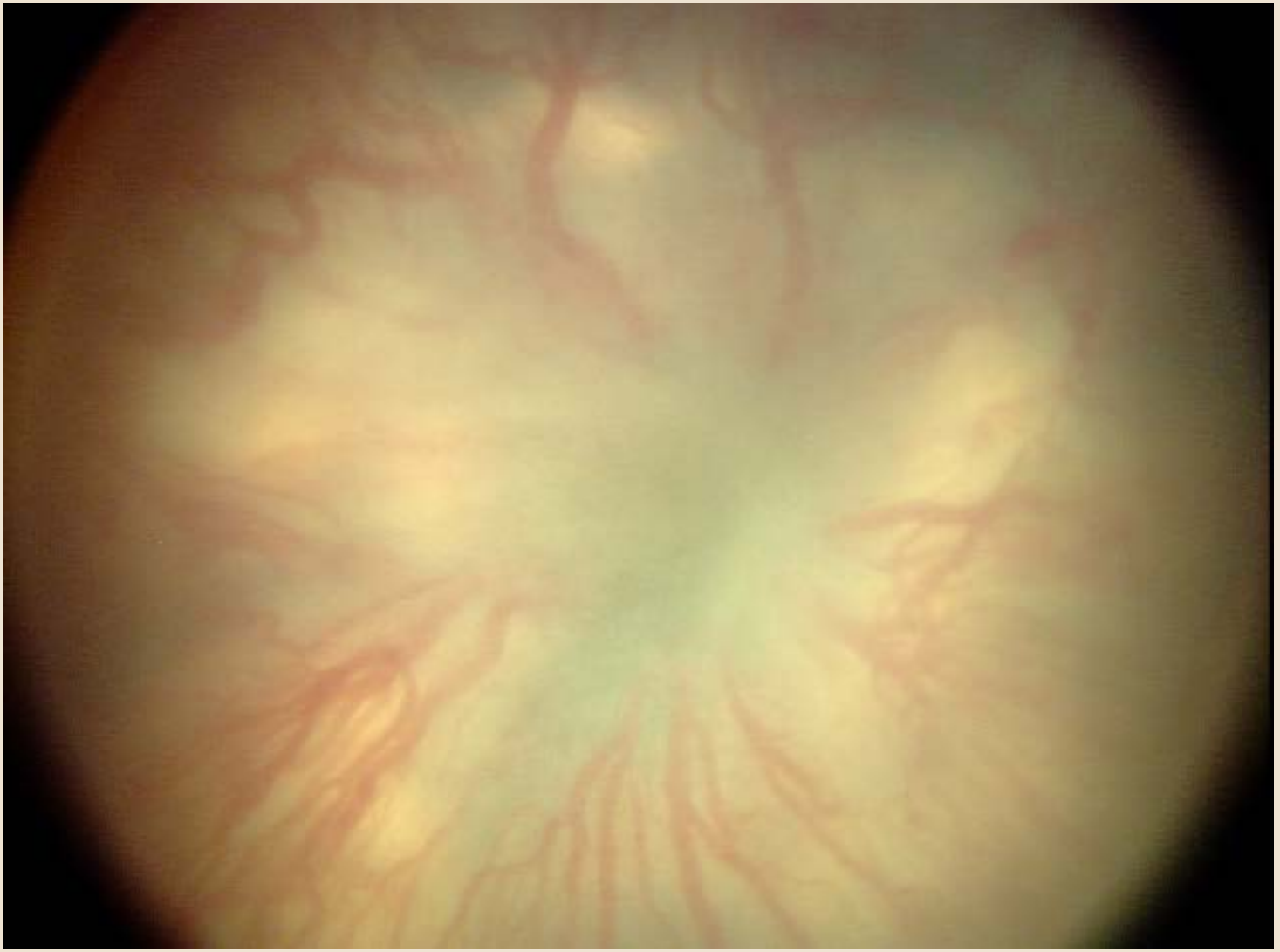
ROP Stage 4a



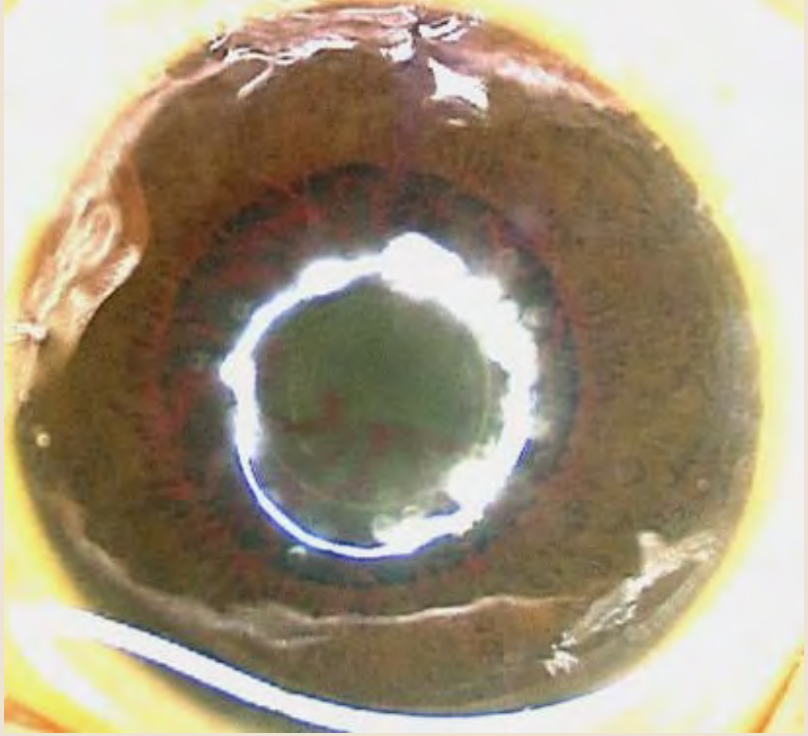
ROP Stage 4b



ROP Stage 5

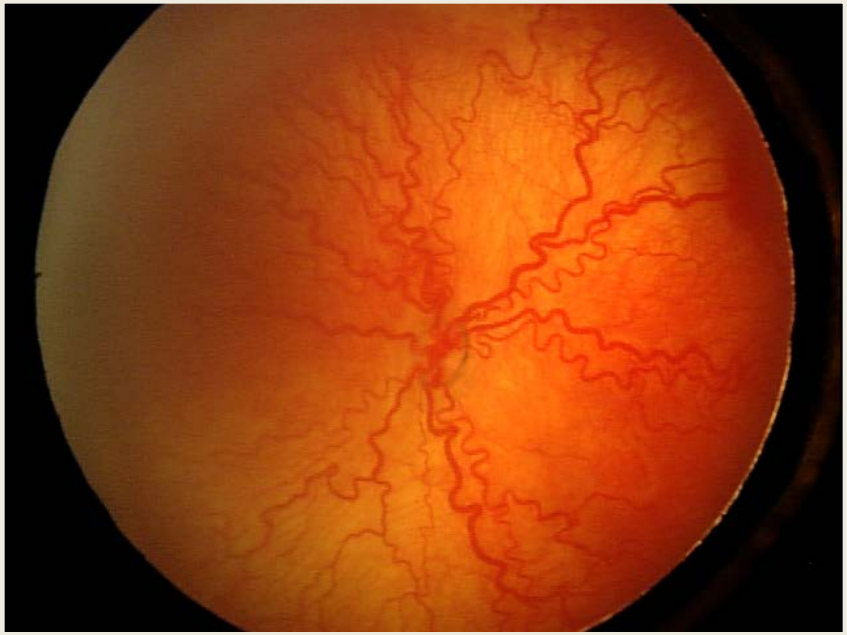


Plus Disease

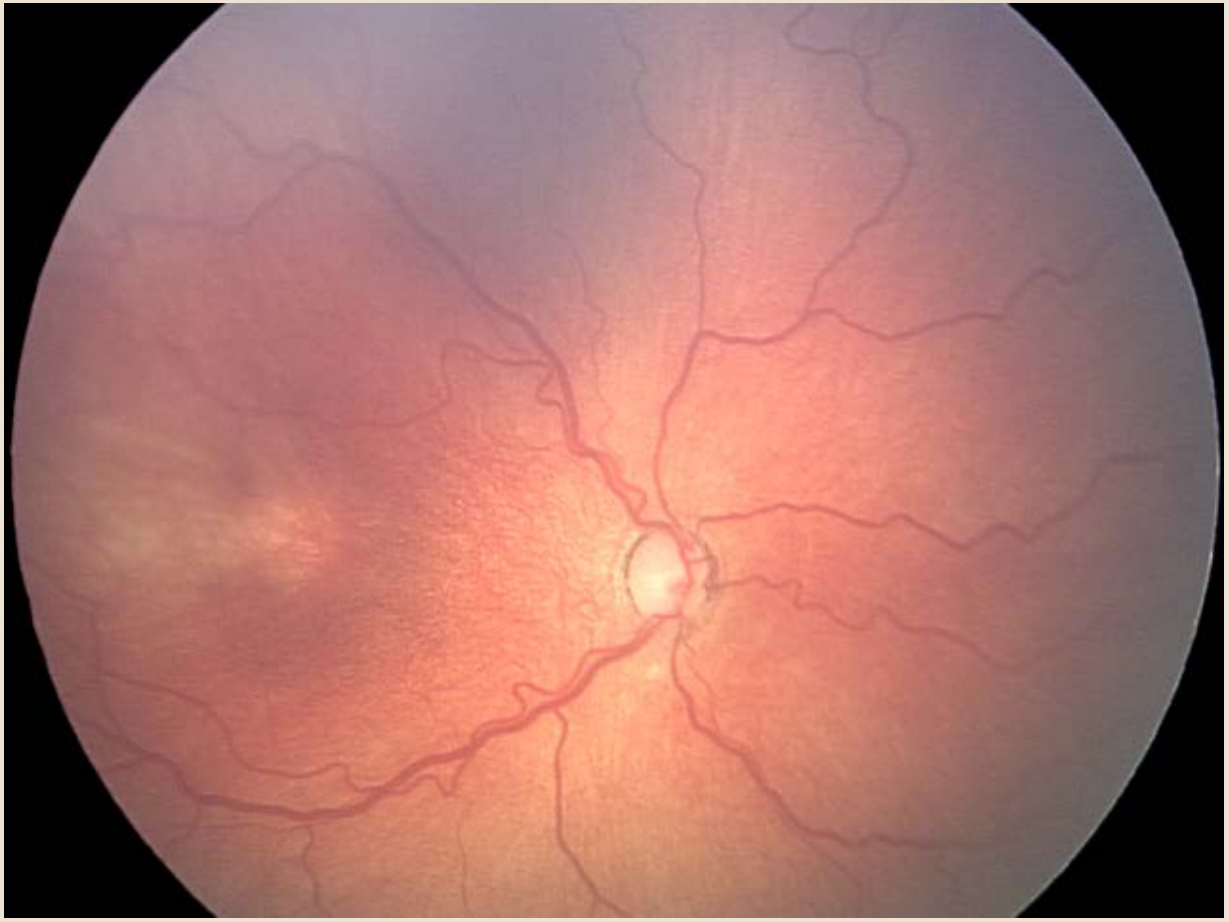


Spectrum of

- 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

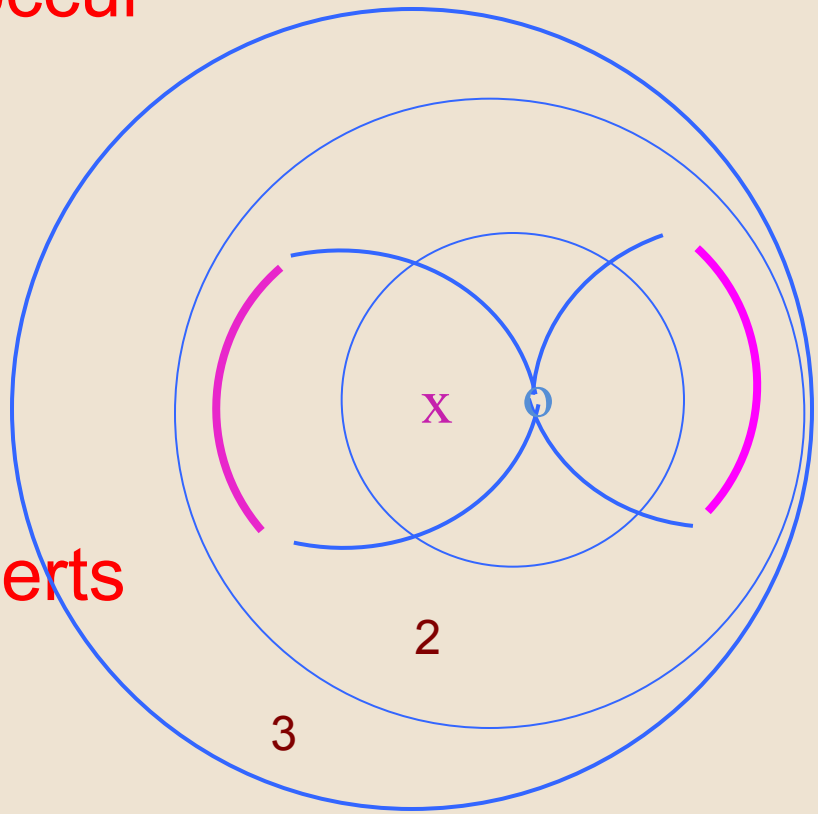
Treatment
ETROP – recommendations 2003

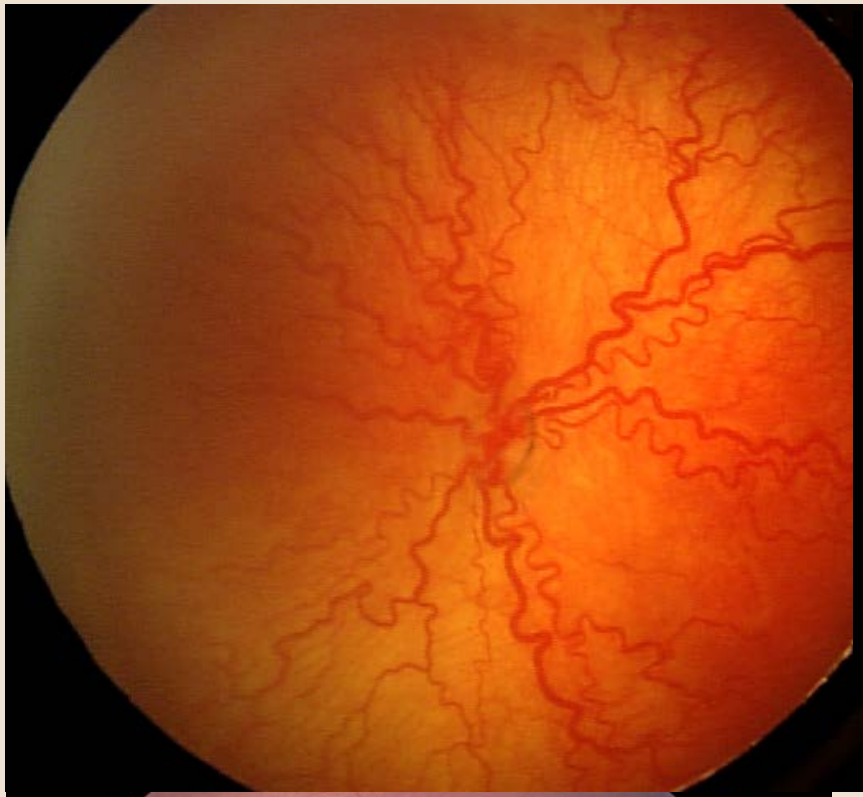
- *Type 1 ROP - Requires Rx*
  - Zone I
    - Any ROP ***with plus***
    - Stage 3 ***with or without plus***
  - Zone II
    - Stage 2 or 3 ROP ***with plus***
    - Stage 2 ***with plus***

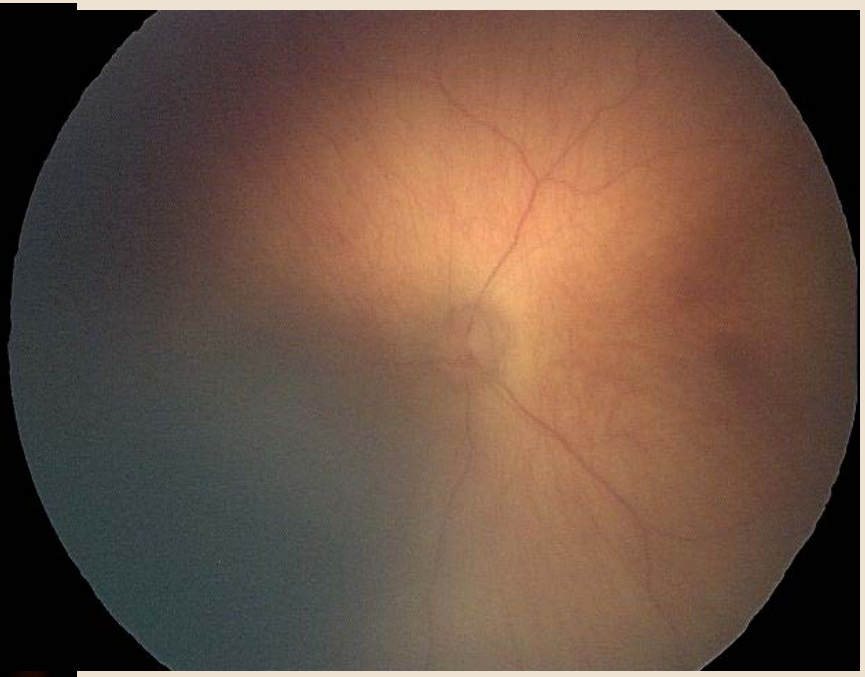

So Far So Good
Excellent classification
Clear treatment indicators
What can go wrong?

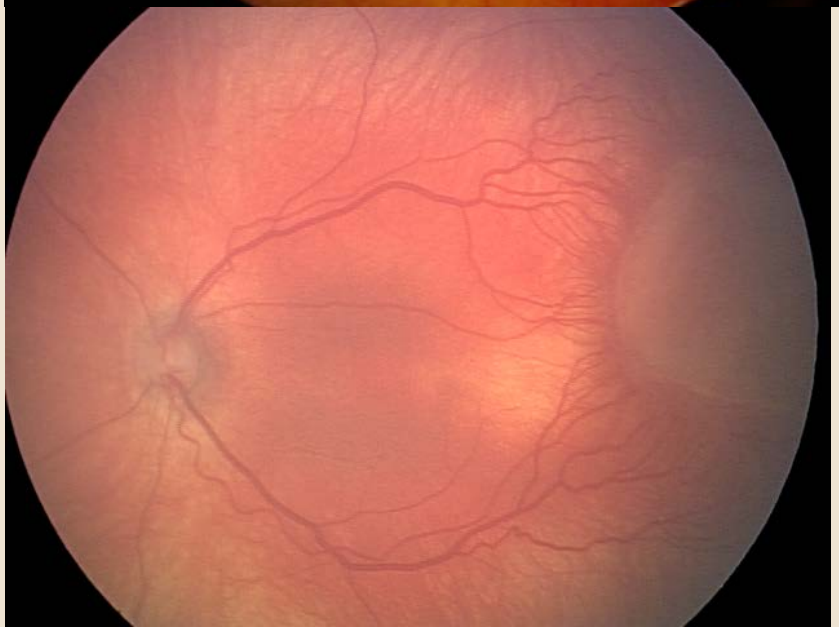
Difficulties with Classification

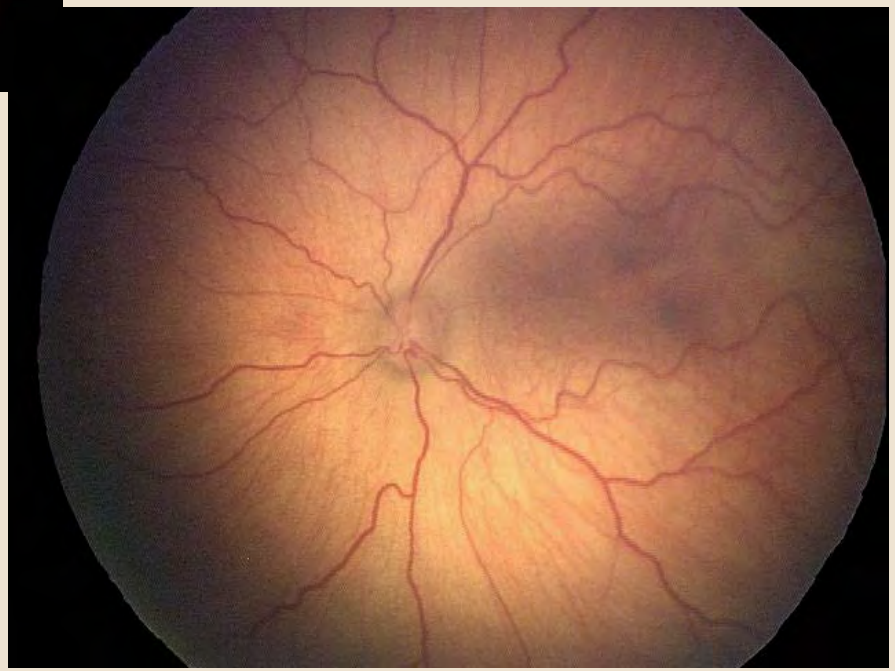
- Zone
  - Described well but errors occur & important in studies
- APROP
  - Overdiagnosed but will not result in overtreatment
- Plus
  - THE major challenge - experts do not agree & leads to variations in treatment

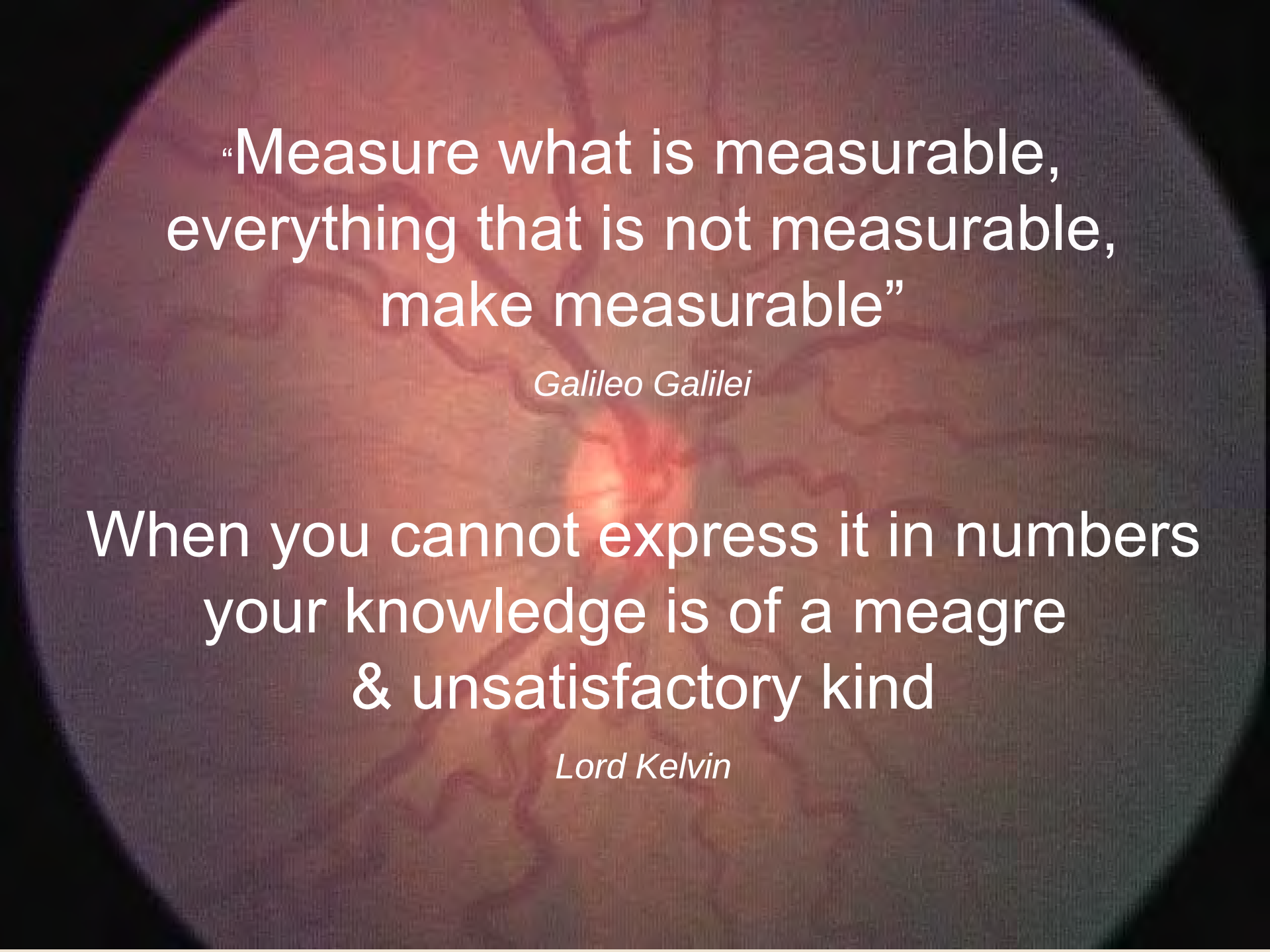











“Measure what is measurable, everything that is not measurable, make measurable”
Galileo Galilei
When you cannot express it in numbers your knowledge is of a meagre & unsatisfactory kind
Lord Kelvin

Issues with changing / improving the classification

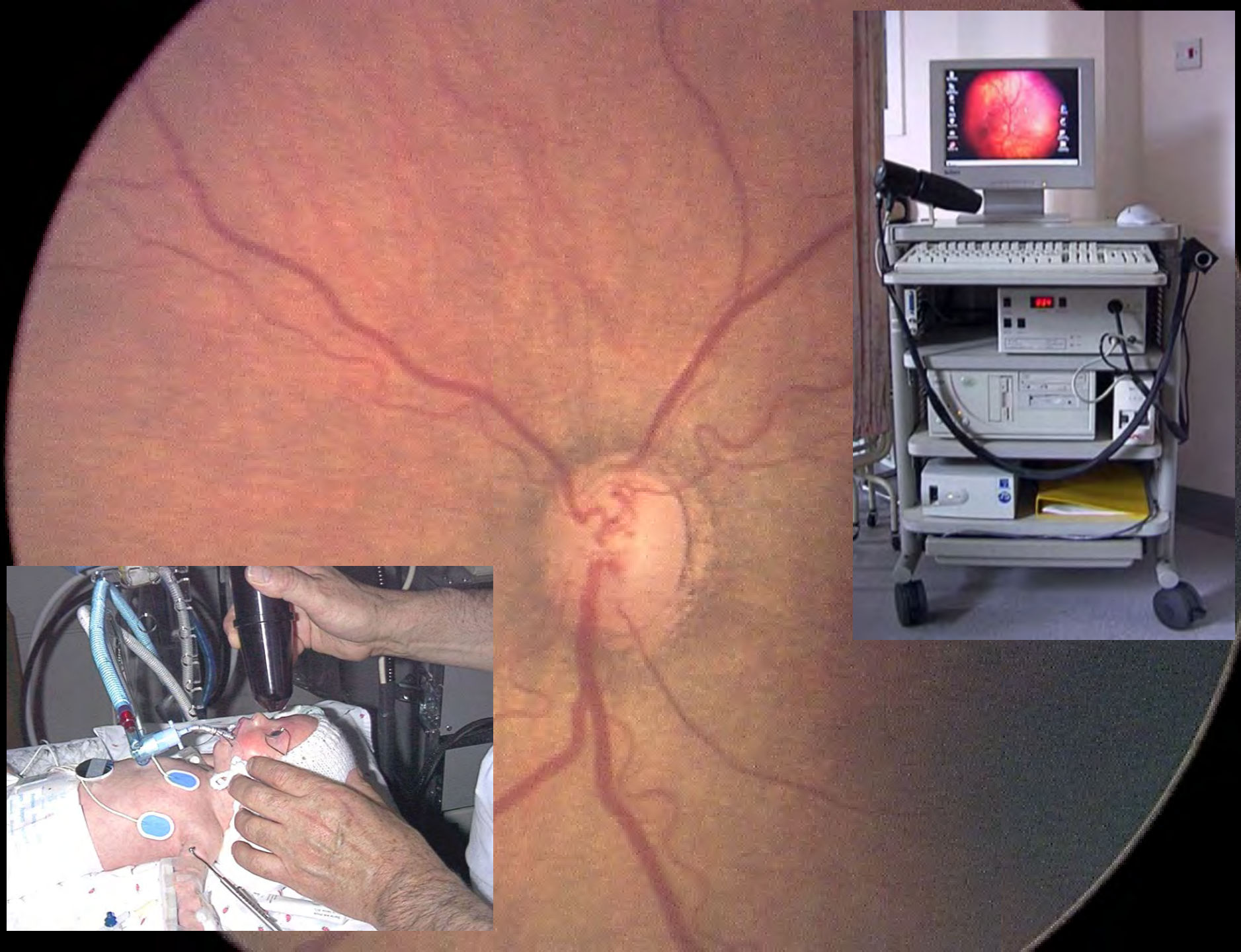
- What type of classification is acceptable to regulators?
- What type of classification is acceptable to clinicians?
  - ICROP I & II - self-selected but internationally agreed
- How should a new / improved classification be decided?
  - How long have you got?
  - Work within but use novel stratification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

Collecting Robust data

The gold standard?

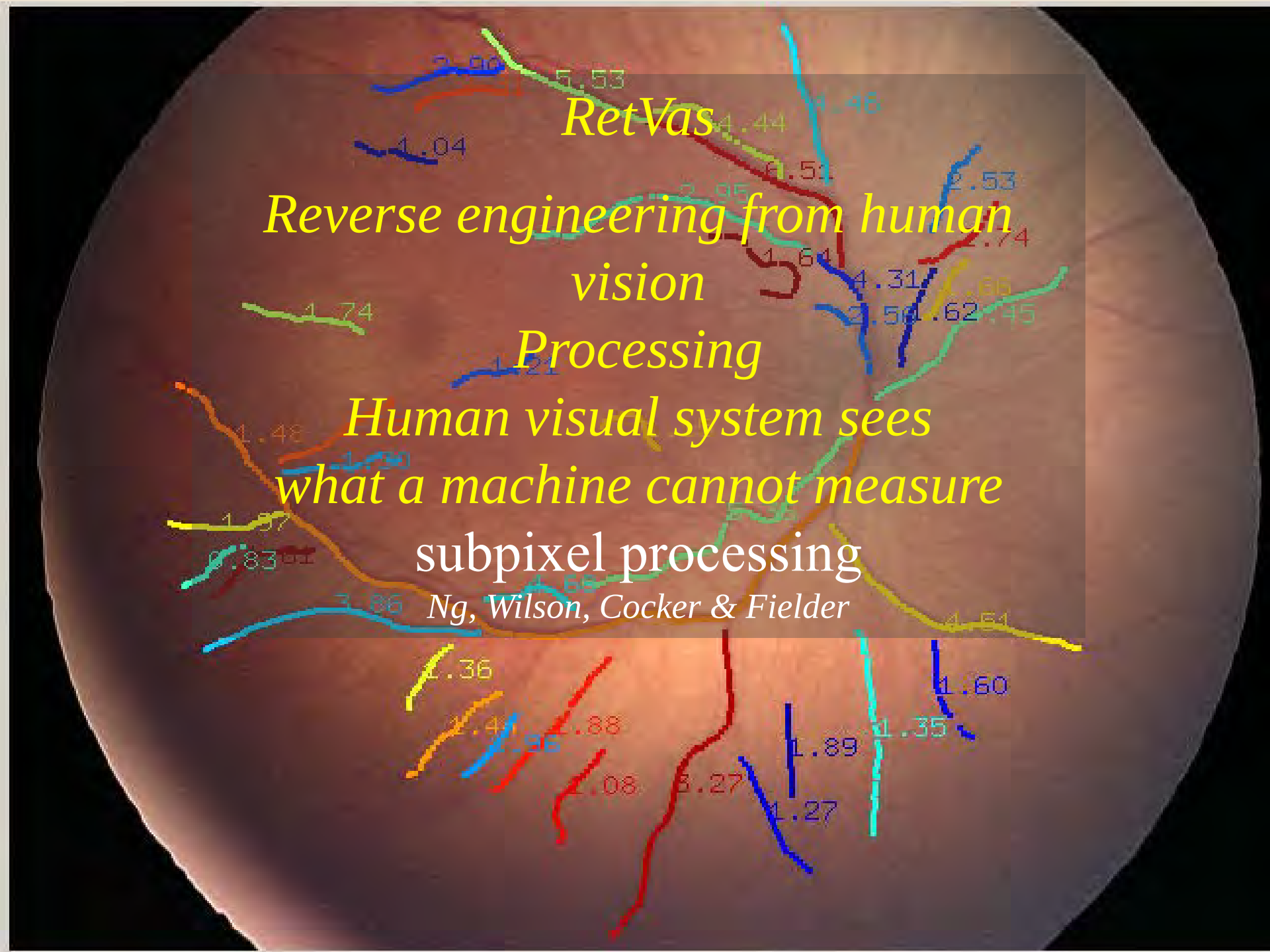

RetCam II
RetCam II
ROP SCREENING

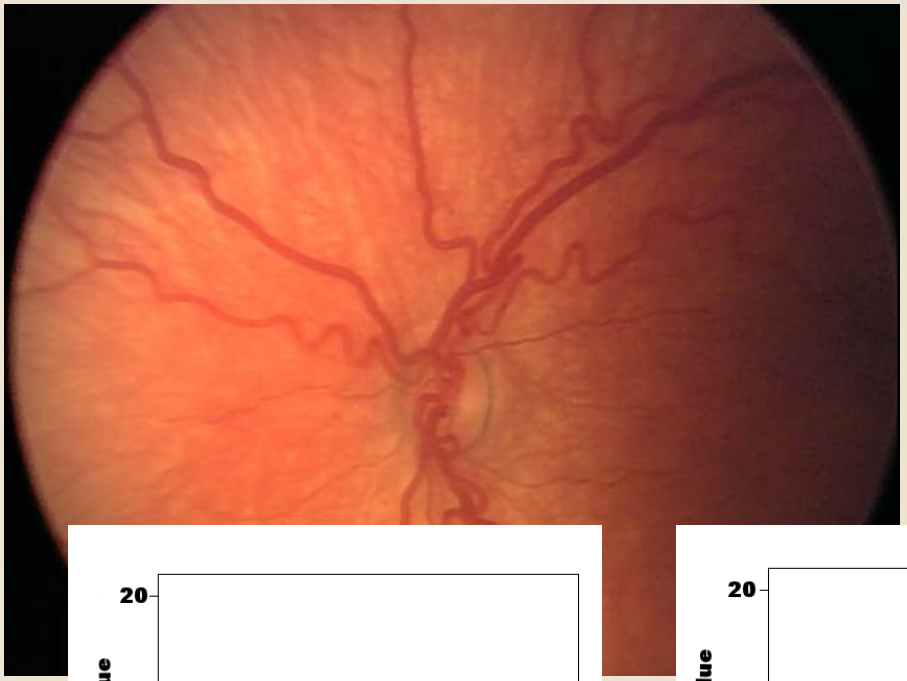

RetCam

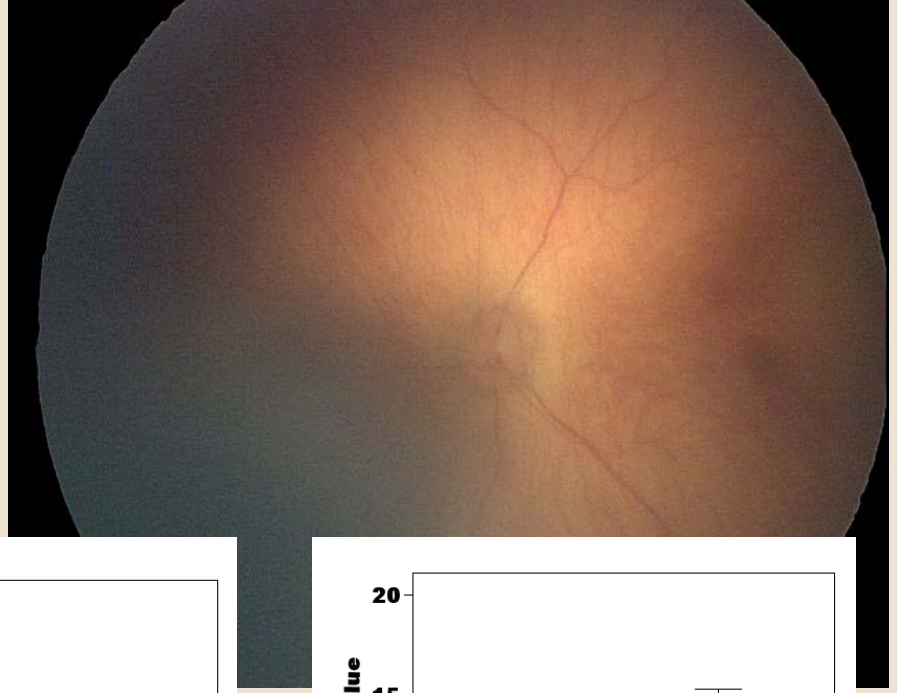


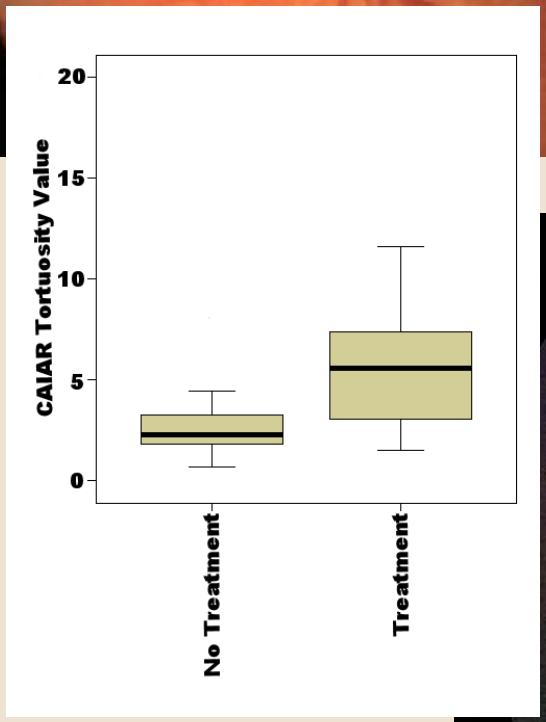
Issues with data standards

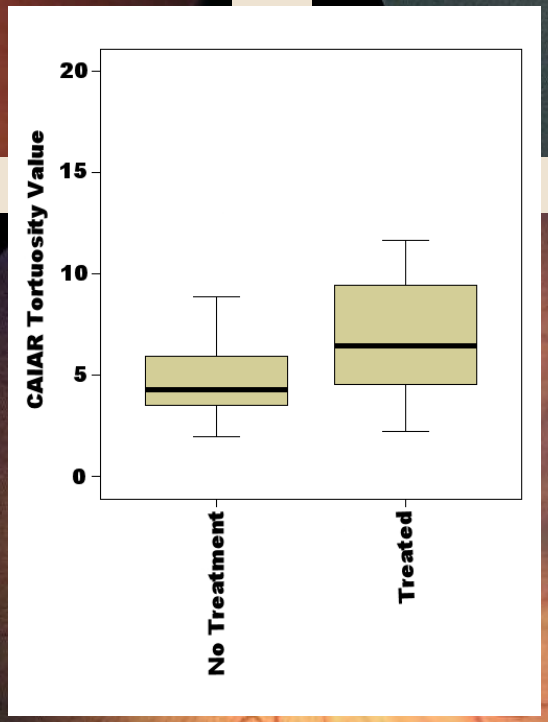
- Who defines the standards?
- How are standards defined?
- What are the technological implications?

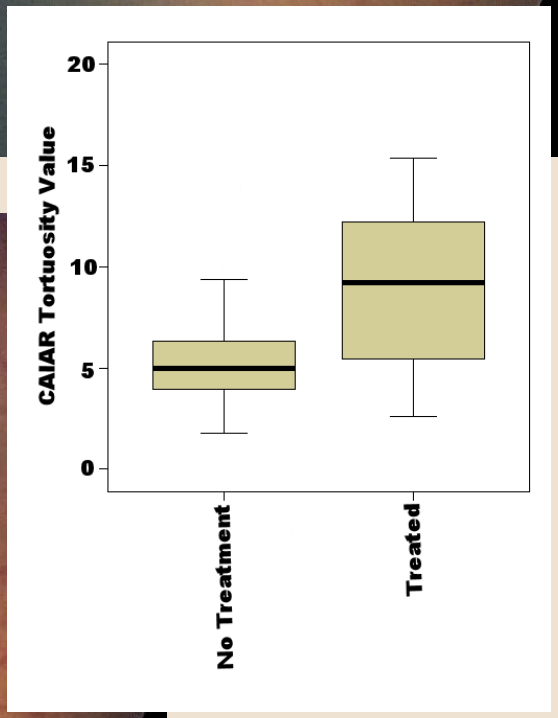

RetVas
Reverse engineering from human vision
Processing
Human visual system sees what a machine cannot measure
subpixel processing
Ng, Wilson, Cocker & Fielder











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

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Ann Hellstrom
University of Gothenburg

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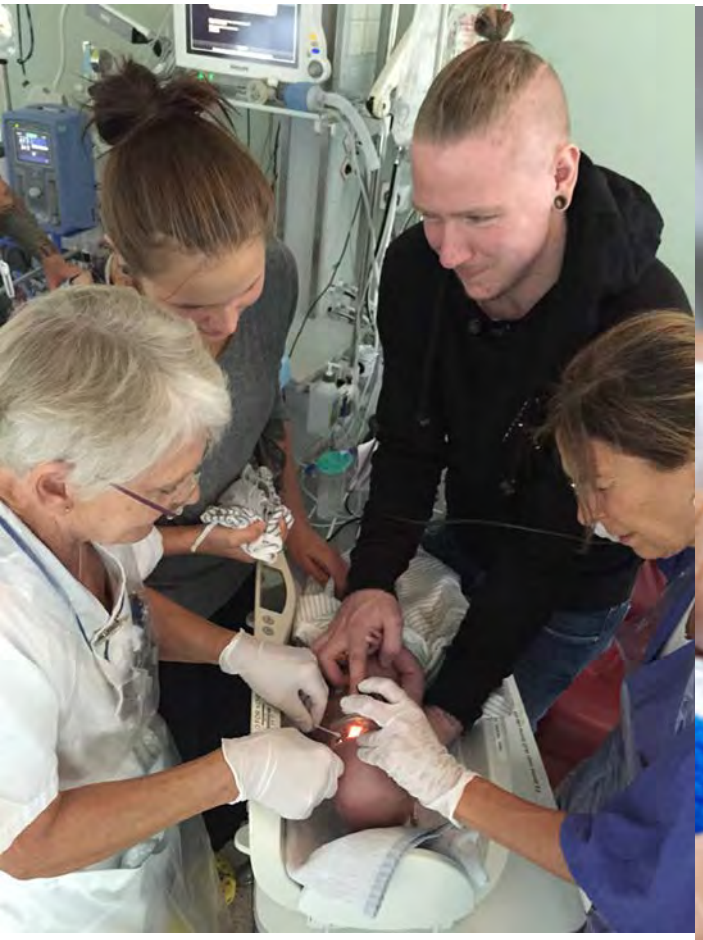
The Sahlgrenska Center for Pediatric Ophthalmology Research

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

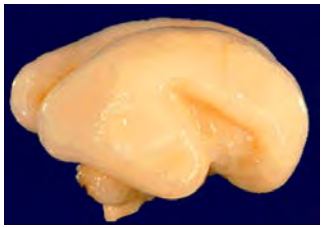
Prevention

Vessel growth stops

Phase 2

Late stage treatment

Retinal vasoproliferation



Brain at birth in baby born at 22 weeks

Chorioamnionitis

Postnatal sepsis

Extrauterine growth retardation

Hyper-hypoxia

Growth factors for angio- and neurogenesis ↓

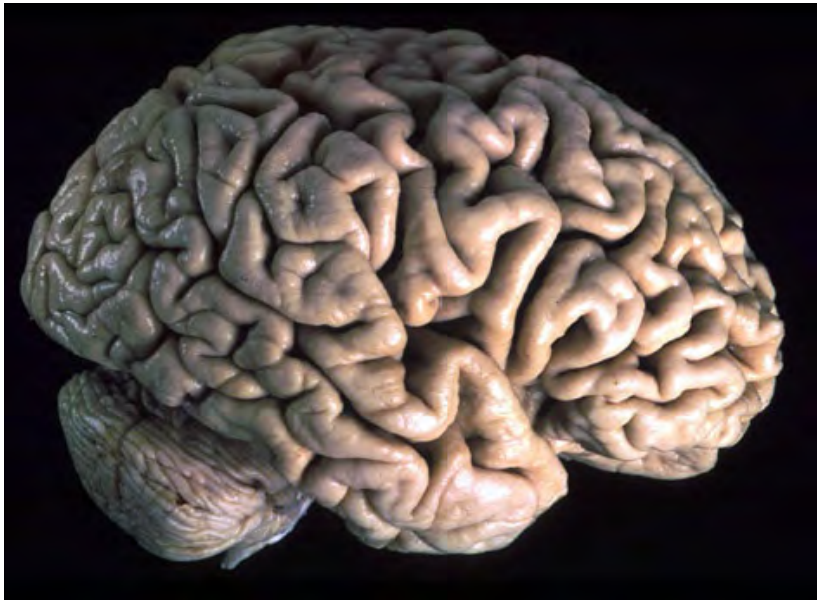
Necrotising enterocolitis

Hyperglycemia

Brain lesions

Suboptimal nutrition

Brain at birth in baby born fullterm



Follow-up variables

Fu

- Visu
- Contrast
- Color vision
- Visual processing
- Electroretinography (E
  - –full field
  - –multifocal

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

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

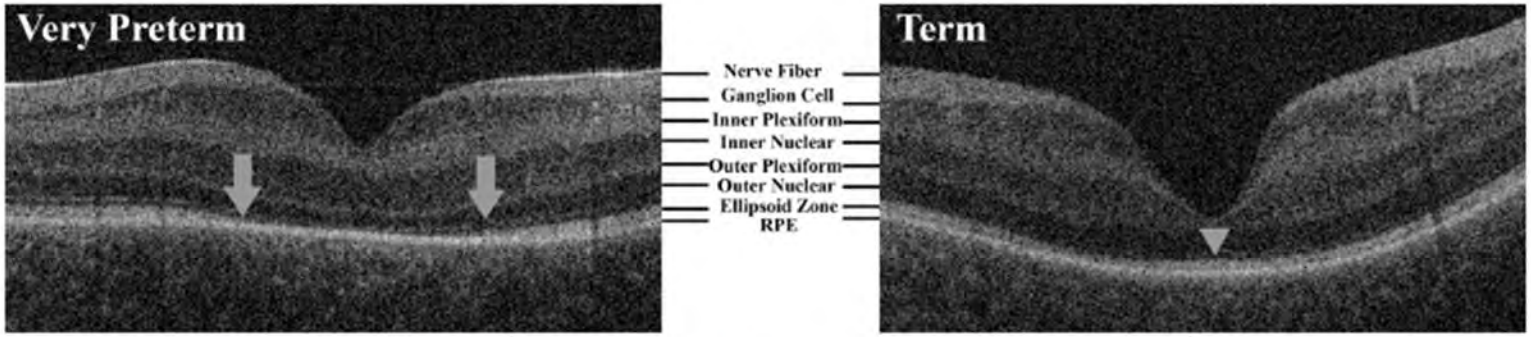


FIGURE 1. The SD-OCT foveal images of a VPT and term infant at 39 weeks PMA. *Gray arrows* indicate the EZ proximity to the foveal center in *left* image, and *gray triangle* indicates presence of the immature EZ at the foveal center in *right* image.

- Fluorescein angiography
  - ✓Choroid
  - ✓Retinal vessels

Fluorescein angiography at 9 months in general anesthesia *Lepore 2014*

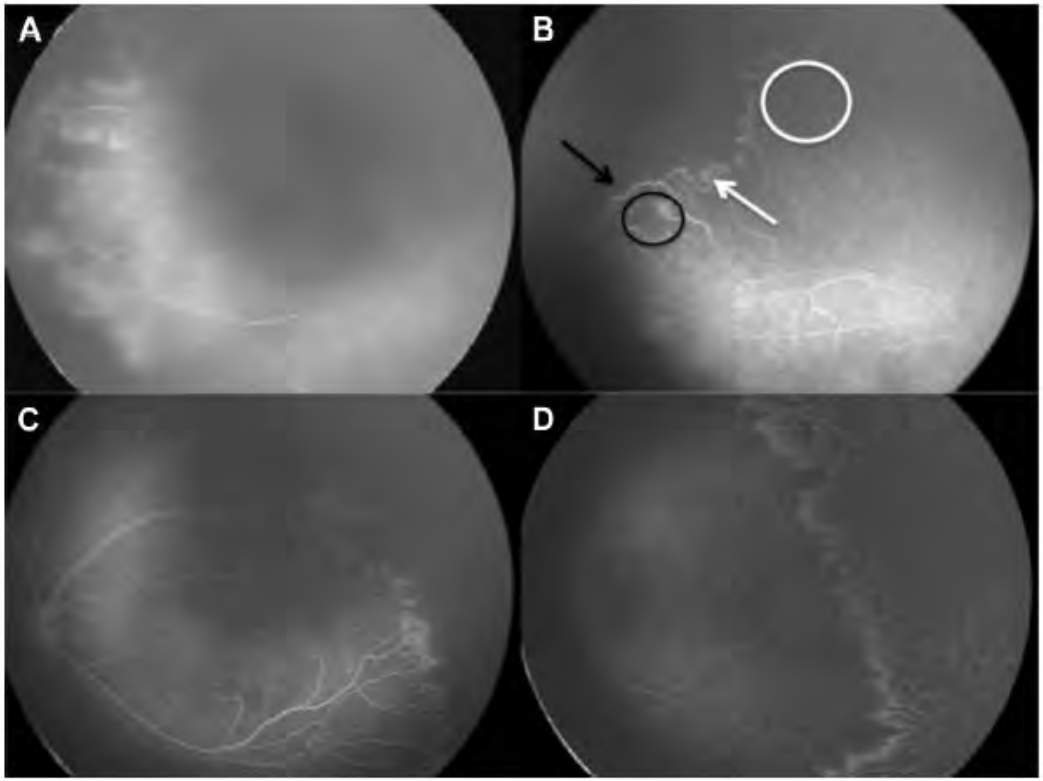


Figure 1. Fluorescein angiographic images before treatment and 9 months after treatment showing the junction between the vascularized and avascular retina in an infant born at 24 weeks' gestational age (**A** and **B**, bevacizumab injected; **C** and **D**, laser treated). There is persistent leakage 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?

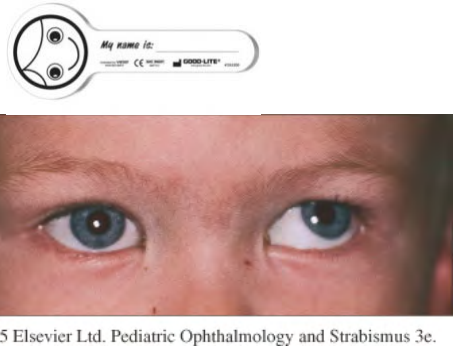
- NB Trials for FDA / EMA may have different end points to trials for HTA agencies
  - Although it is good to include HTA outcomes in trials

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

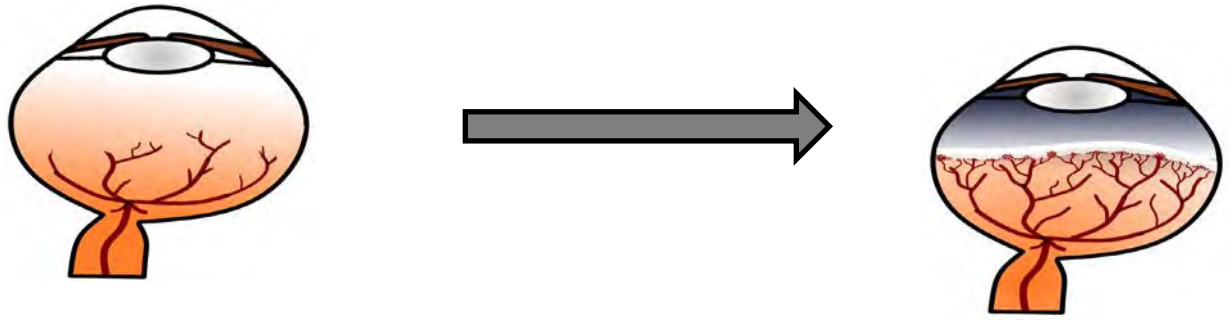
Primary end point for clinical trials?

- How closely are these multiple assessments correlated?
  - Functional tests largely dependent on executive functions

Biomarkers for ROP

Phase 1

Phase 2

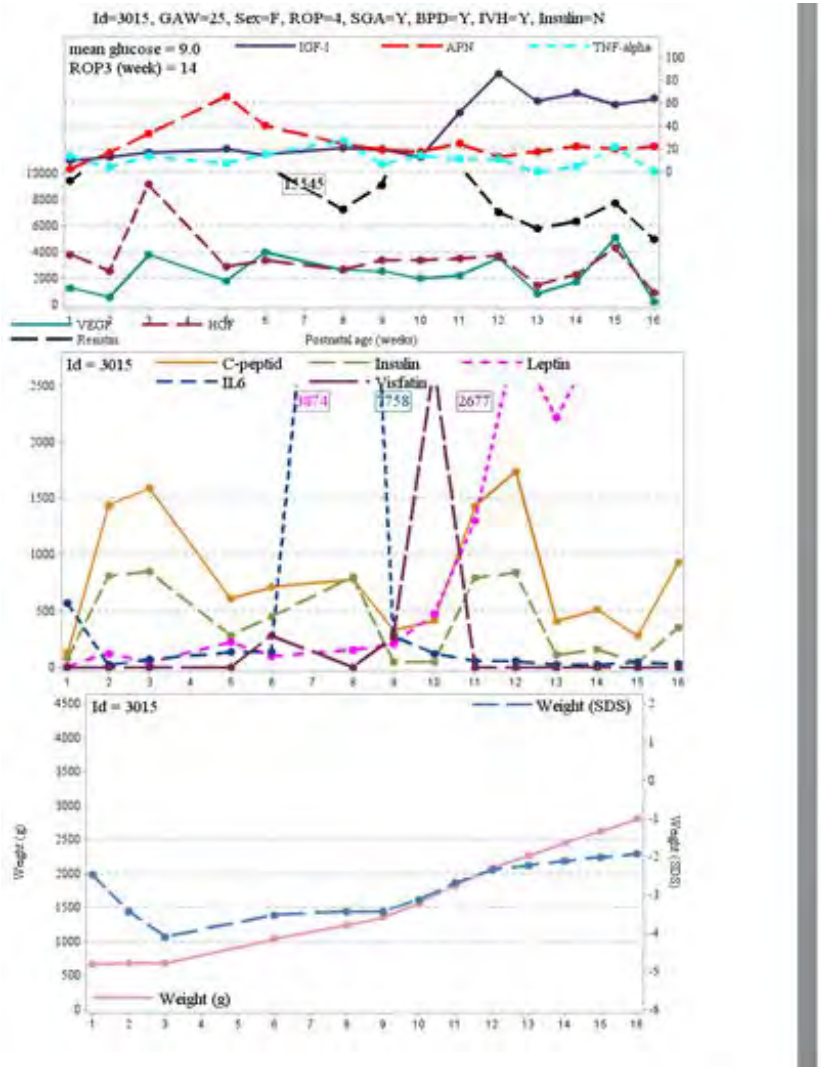


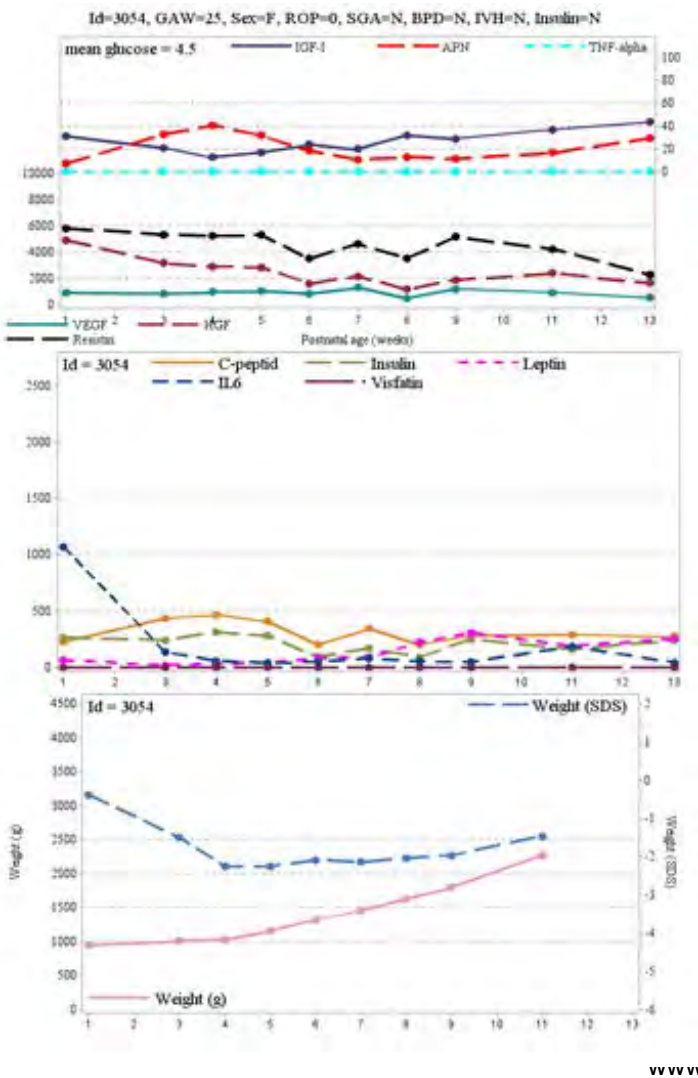
Vessel growth stops

Retinal vasoproliferation

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

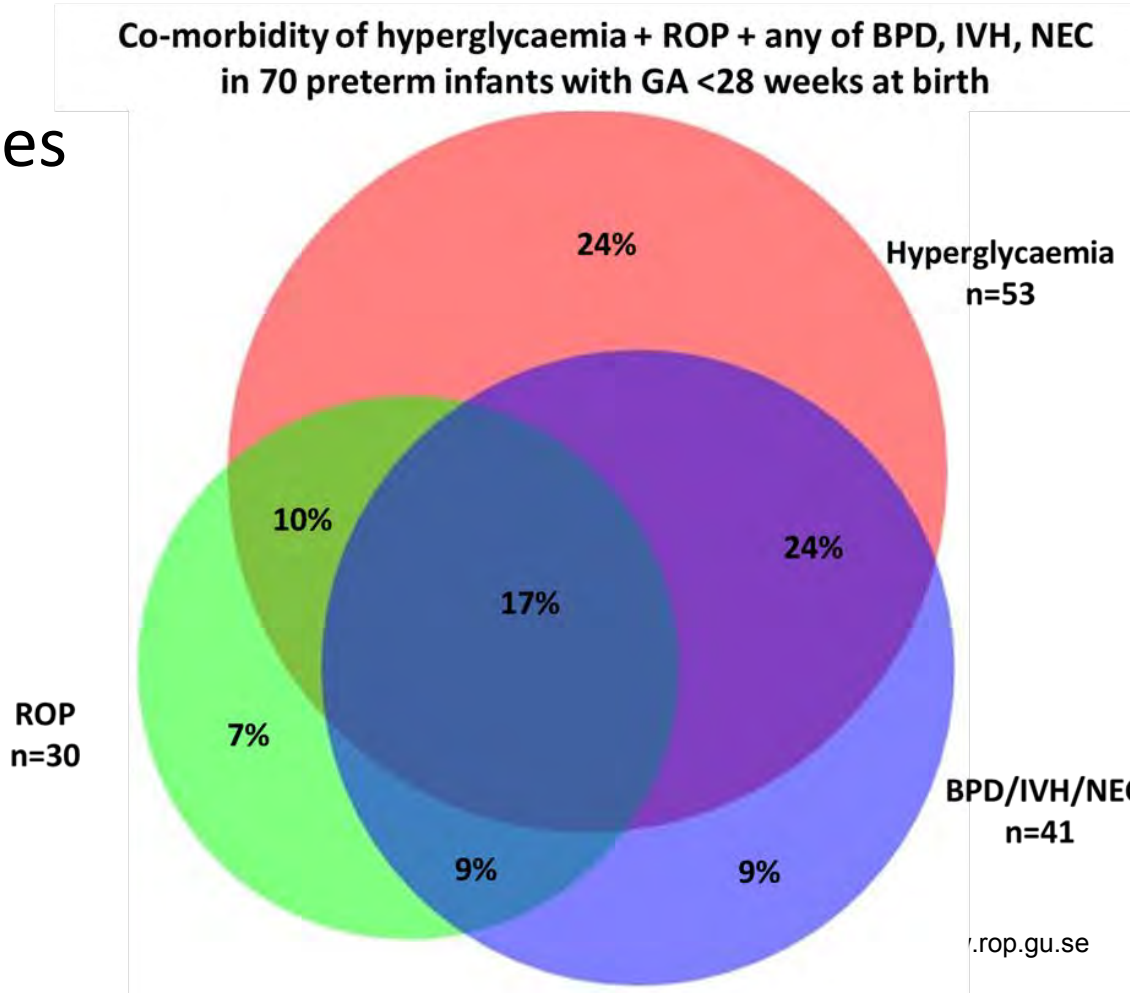
Complex…large variability in many factors





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

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Neil Marlow
University College London

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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 SaO_2 targets
- May be positive or negative
  - 'Developmental arrest'
  - Phase changes after 32w
  - Relative importance of other system effects may be greater

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Wiley Chambers
US Food and Drug Administration

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Reiko Shimizu
Pharmaceutical and Medical Devices Agency, Japan

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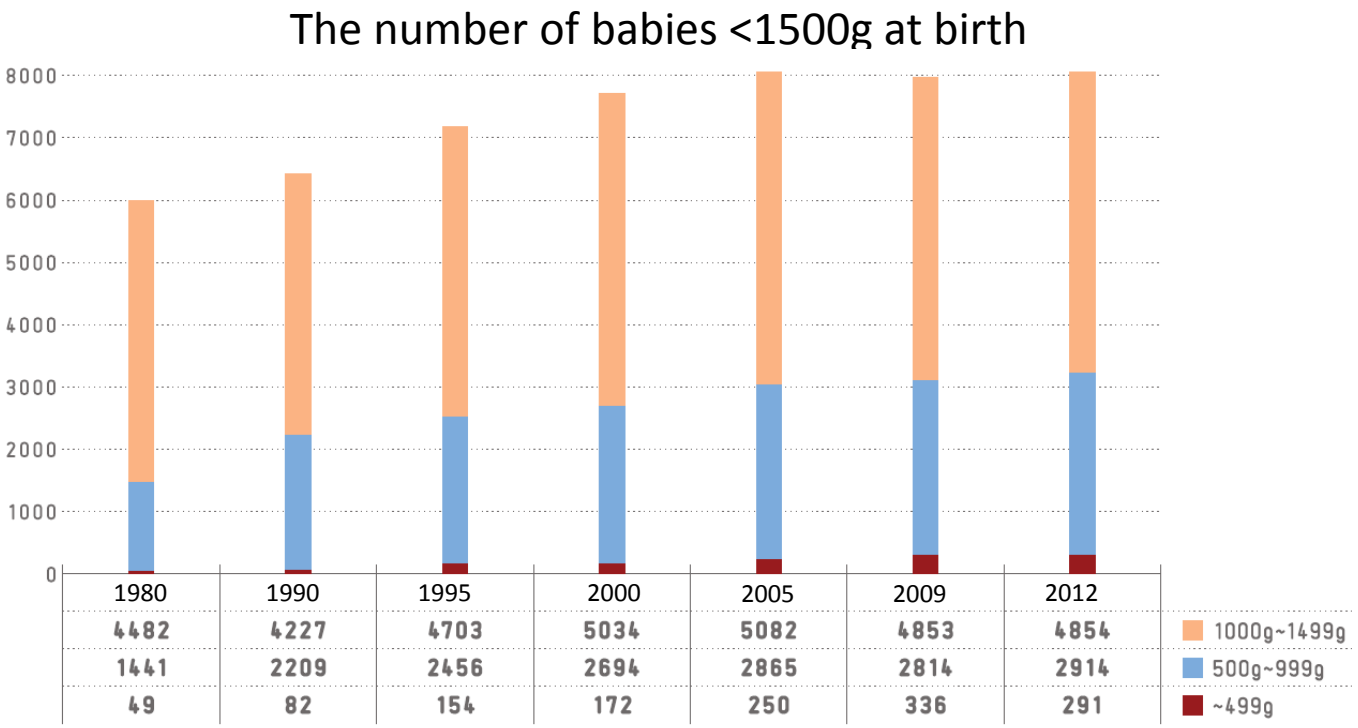
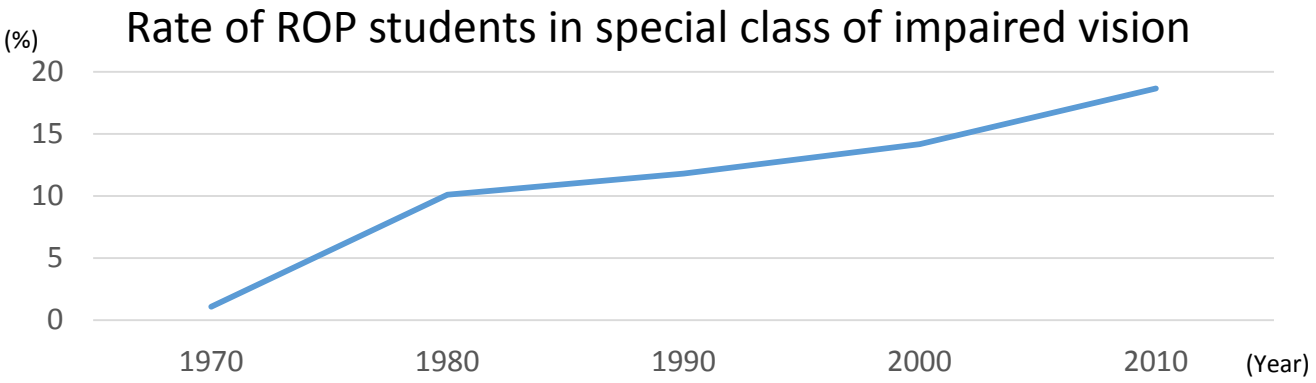
Project 3

Feasibility





Project 3

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

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Ralph Bax
European Medicines Agency

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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:

Project 3 - Defining Outcomes related to ROP

- 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:

ROP Voting Slide 1

- *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*

ROP Voting Slide 2

- *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*

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Lunch
1 Hour

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Second Annual Neonatal Scientific Workshop at the FDA

March 7th, Afternoon

FDA

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

Danny Benjamin
Duke University, Chair

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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 candidasis

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 litereature--Hypertension
- Trial design vs. ‘the answer is’
- Access to data vs. public access

INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Challenges in Conducting Clinical Trials to Treat Infections/NEC and Strategies for Overcoming those Challenges

Karel Allegaert
University of Leuven

CRITICAL PATH INSTITUTE

take home messages

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 ?

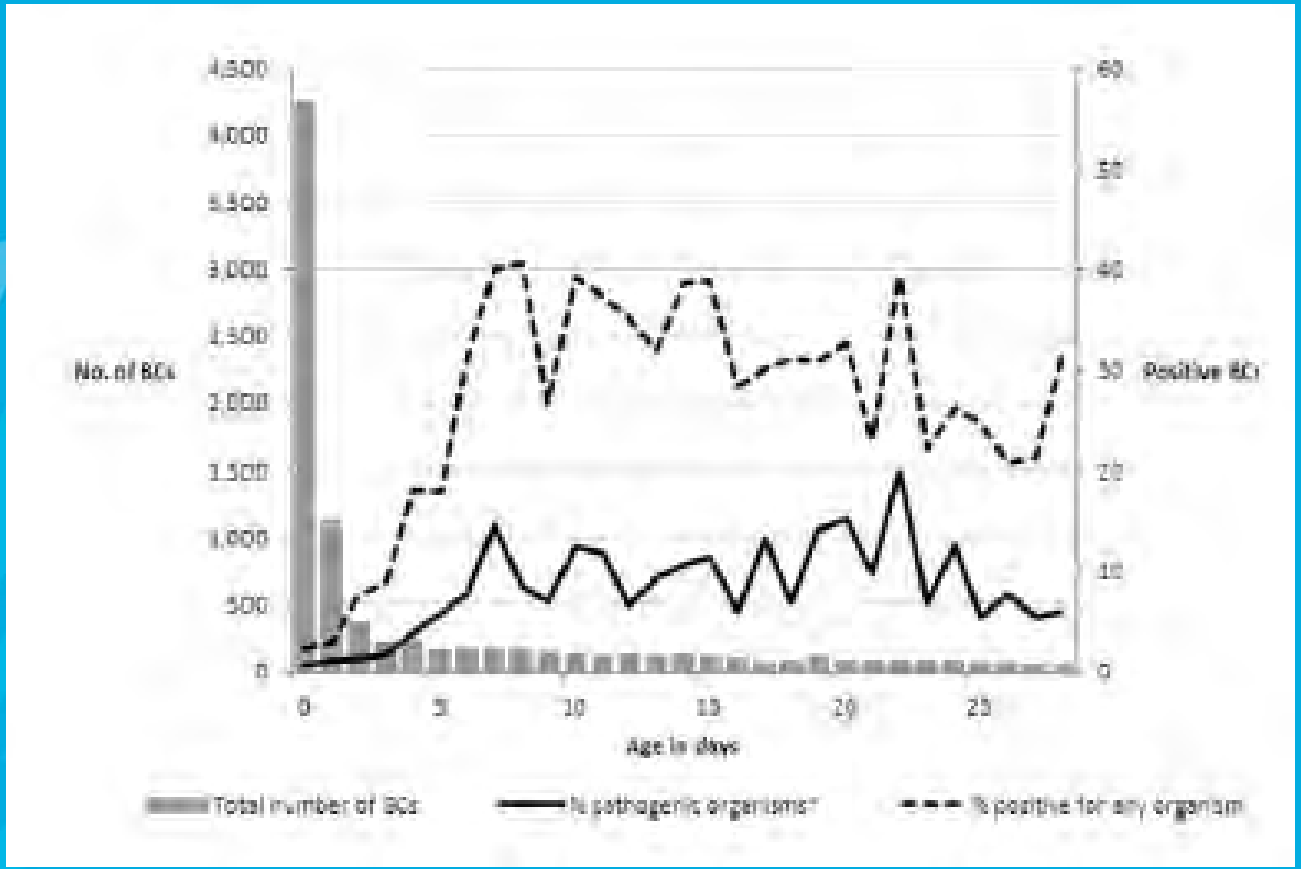
- **do we always need vancomycin**

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

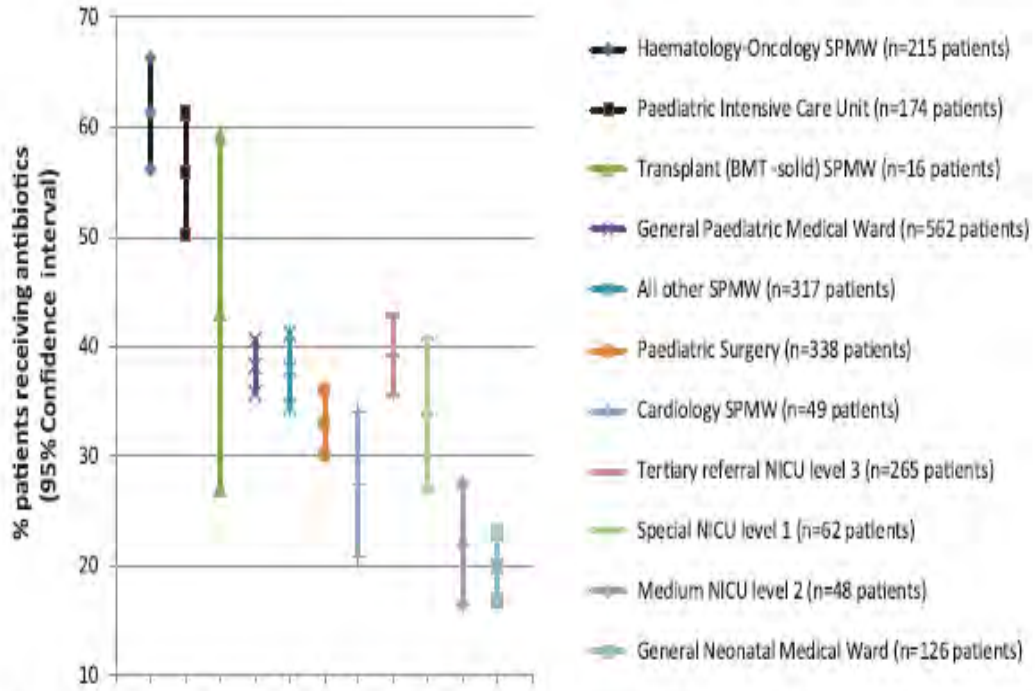


FIGURE 3. Variation in overall proportions of antibiotic use (J01) by ward type (N = 2172 children treated with at least 1 antibiotic, N = 50 European and 23 non-European hospitals). SPMW indicates specialist pediatric medical ward ; BMT-solid, Bone Marrow Transplantation and Solid Organ Transplantation.

ARPEC Study, J Ped Inf Dis 2013

California, 40-fold variability in antibiotic use rate (n=217)

surgical volume

NEC

proven infection

level of care

mortality

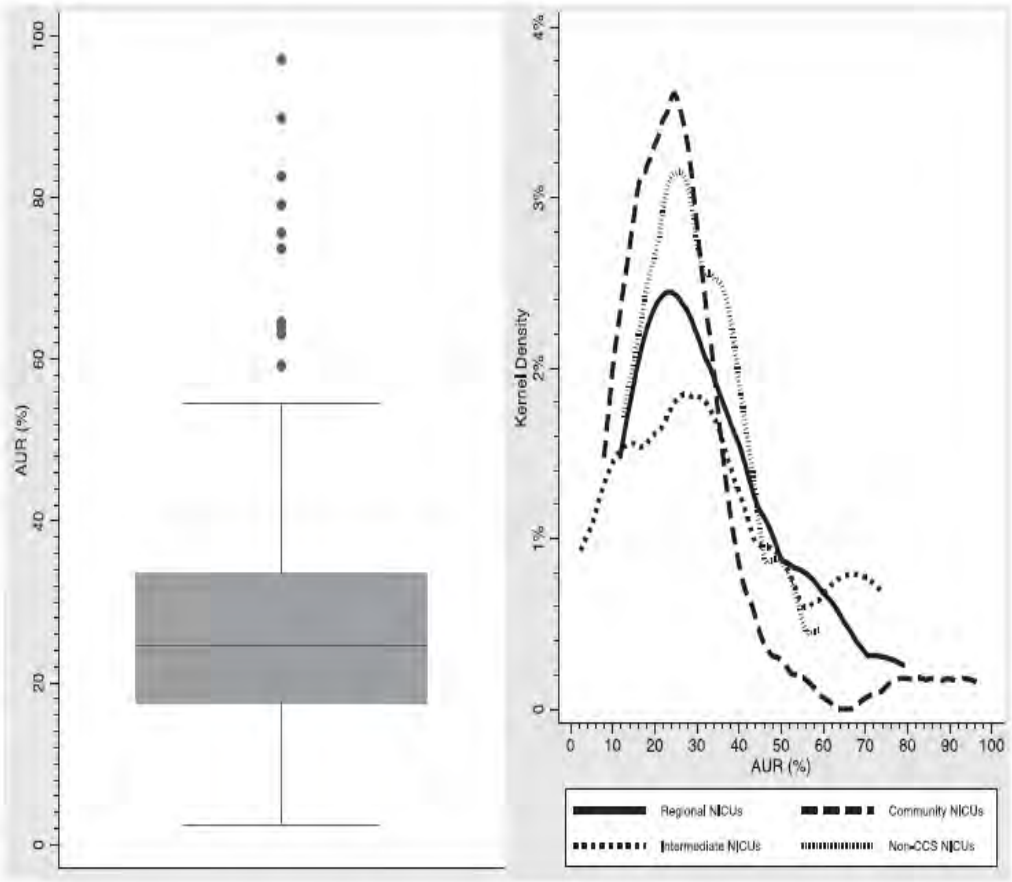


FIGURE 1
Range of AUR values and distribution of AUR values by level of care. Left, Interquartile range and median AUR across all NICUs; lines above or below the box extend further by 1.5 times the interquartile range; dots mark extreme outliers. Right, AUR stratified by NICU level of care. Kernel density is essentially a smoothed frequency distribution histogram.

Schulman et al, Pediatrics 2015

Dosing guidelines amikacin in reference text books

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

UZ LEUVEN

Wide intra- and inter-country variability in drug use and dosage in very-low-birth-weight newborns with severe infections

Chiara Pandolfini · Florentia Kaguelidou · Marco Sequi · Evelyne Jacqz-Aigrain · Imti Choonara · Mark A. Turner · Paolo Manzoni · Maurizio Bonati

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.

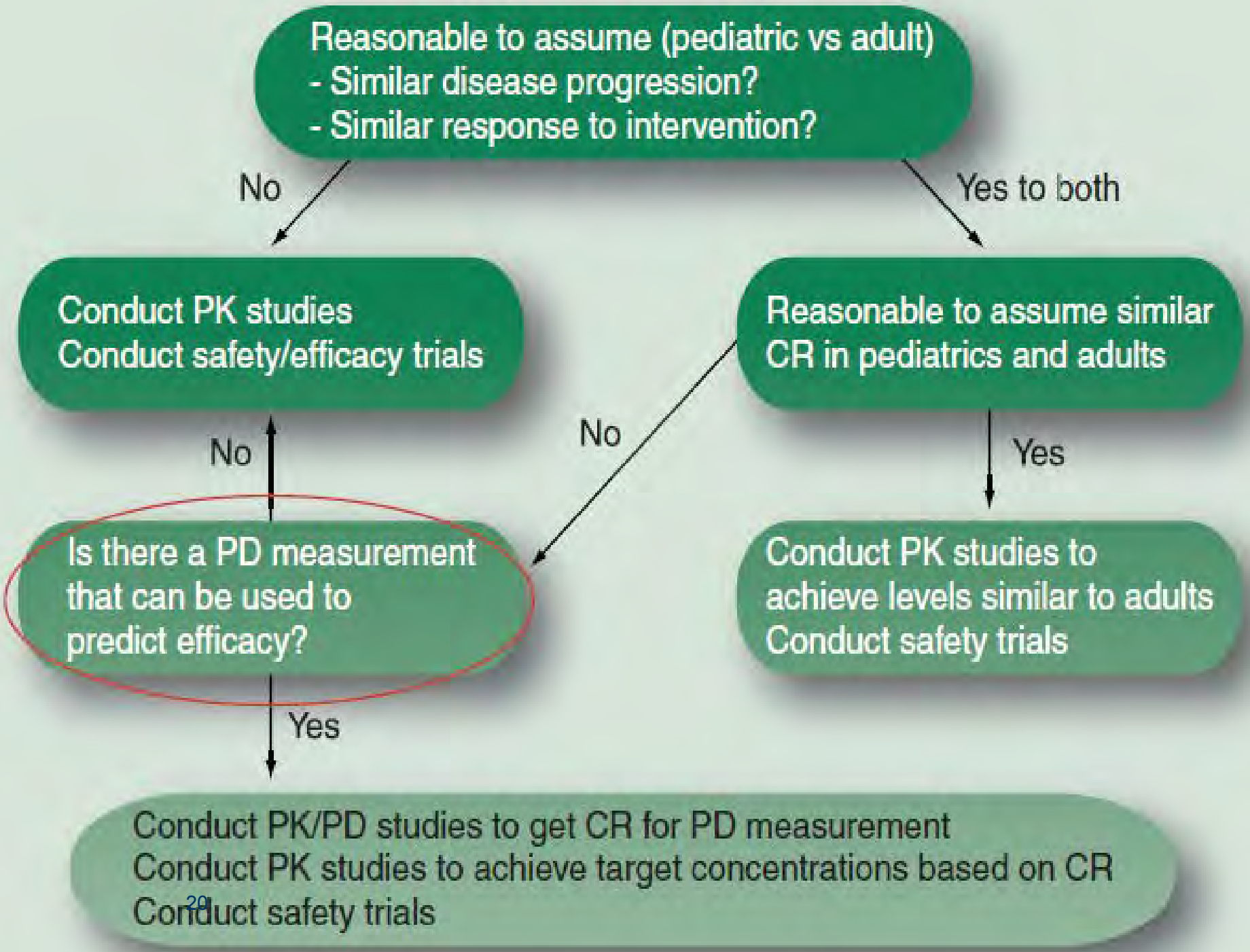
RESULTS

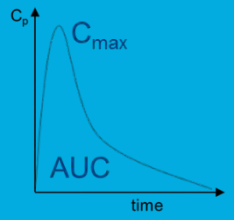
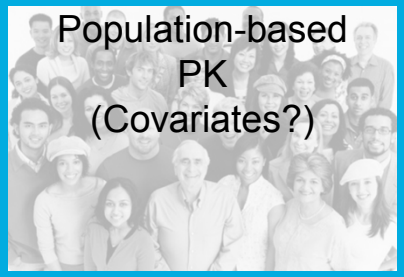
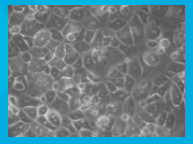
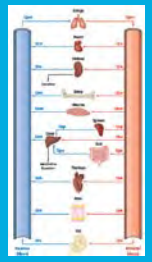
A total of 35 randomized controlled trials were evaluated. The majority were conducted in a single hospital institution, without funding. Median sample size was 63 (34–103) participants. The most frequently evaluated antibiotic was gentamicin. Respectively, 18 (51%) and 17 (49%) trials evaluated the 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

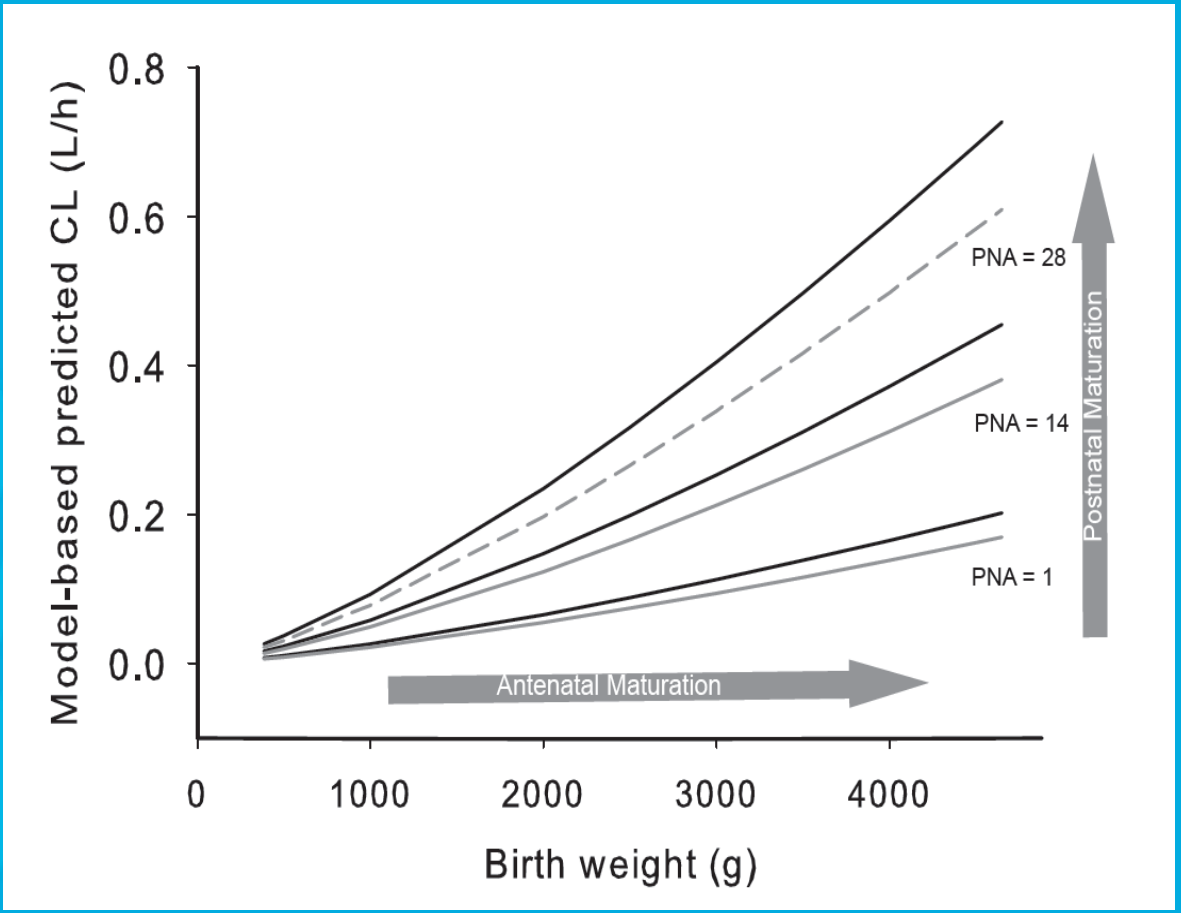
Design and reporting of randomized controlled trials of antibacterial agents in neonates should be improved. Nevertheless, the necessity of implementing such trials when antibacterial efficacy has already been established in other age groups may be questioned and different methods of evaluation should be further developed.

Kaguelidou et al, Br J Clin Pharmacol 2013


Reasonable to assume (pediatric vs adult)
- Similar disease progression?
- Similar response to intervention?
No
Yes to both
Conduct PK studies
Conduct safety/efficacy trials
Reasonable to assume similar CR in pediatrics and adults
No
No
Yes
Is there a PD measurement that can be used to predict efficacy?
Conduct PK studies to achieve levels similar to adults
Conduct safety trials
Yes
Conduct PK/PD studies to get CR for PD measurement
Conduct PK studies to achieve target concentrations based on CR
Conduct safety trials

	Data gathering	Modelling	Clinical implications
"TOP DOWN" Clinic to mechanistic (population-based)	Plasma Data 	Population-based PK (Covariates?) 	Confirming 
"BOTTOM UP" *In vitro* to *In vivo* (IVIVE)	 Demography Physiology Genetics *In vitro* data  	PBPK/IVIVE 	Learning 

Amikacin clearance in neonates: variability in addition to age/weight



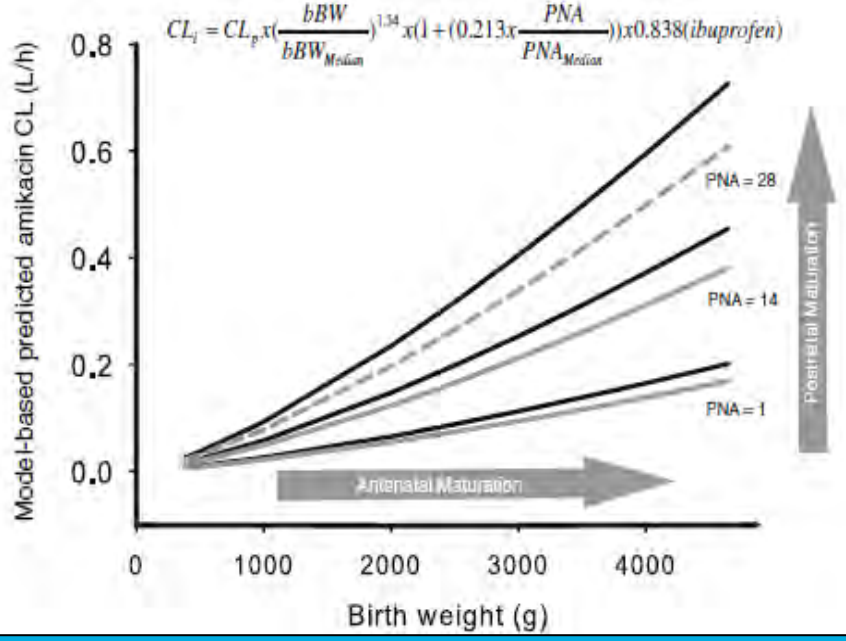
De Cock et al. Clin Pharmacok 2012

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

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

Drug specific property

Amikacin covariate model



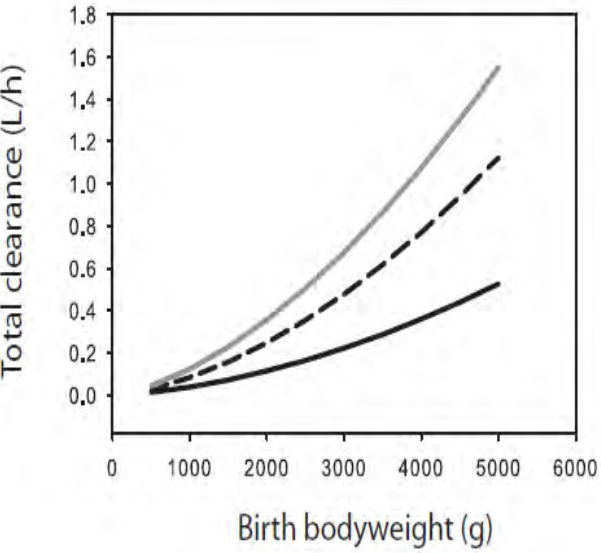
De Cock *et al*. Pharm Res 2014

$$CL_i = \left\{ CL_{p\ amikacin} \times \left(\frac{BWb}{BWb_{Median}}\right)^{1.34} * \left(1 + \left(0.213 * \frac{PNA}{PNA_{Median}}\right)\right) \right\} + \left\{ CL_{p\ cefazolin} \times \text{Covariates} \right\}$$

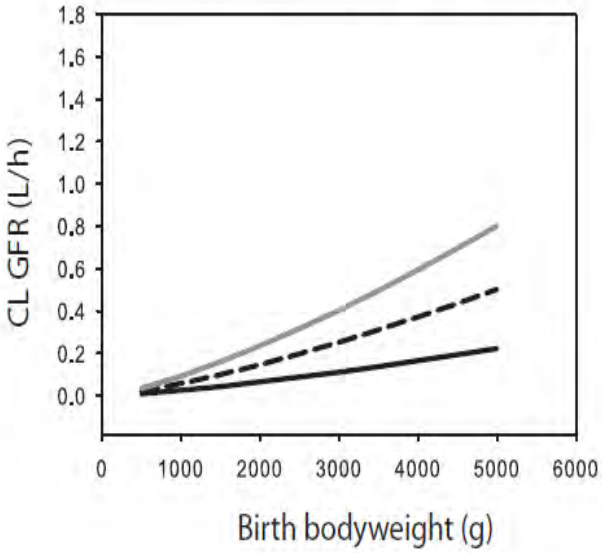
Developmental changes in GFR based on amikacin clearance

Developmental changes in tubular processes

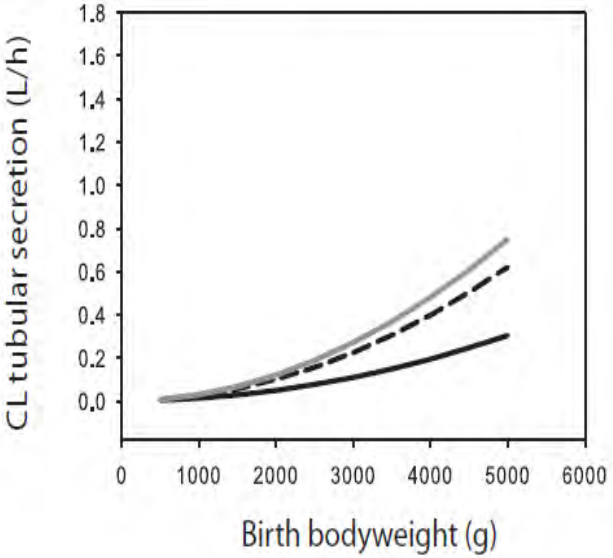
Total clearance of cefazolin



Clearance of cefazolin through GFR



Clearance of cefazolin through tubular secretation



De Cock *et al.* Int J Antimicrobiol Chemother 2014

balance between neonatal physiology and clinical feasibility ?

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

Current body weight (g)	Amikacin dose and interval for[a]: Original model-based dosing regimen (4)		Simplified model-based dosing regimen		Final proposed dosing regimen after prospective validation	
	PNA < 14 days	PNA ≥ 14 days	PNA < 14 days	PNA ≥ 14 days	PNA < 14 days	PNA ≥ 14 days
0–800	16 mg/kg, 48 h (gp 1)	20 mg/kg, 42 h (gp 2)	16 mg/kg, 48 h (gp 1)	20 mg/kg, 42 h (gp 2)	16 mg/kg, 48 h (gp 1)	20 mg/kg, 42 h (gp 2)
800–1,200	16 mg/kg, 42 h (gp 3)	20 mg/kg, 36 h (gp 4)	16 mg/kg, 42 h (gp 3)	20 mg/kg, 36 h (gp 4)	16 mg/kg, 42 h (gp 3)	20 mg/kg, 36 h (gp 4)
1,200–2,000	15 mg/kg, 36 h (gp 5)	19 mg/kg, 30 h (gp 6)	15 mg/kg, 36 h (gp 5)	***18*** mg/kg, ***30*** h (gp 6)	15 mg/kg, 36 h (gp 5)	18 mg/kg, 30 h (gp 6)
2,000–2,800	13 mg/kg, 30 h (gp 7)	18 mg/kg, 24 h (gp 8)	***15*** mg/kg, ***30*** h (gp 7)	18 mg/kg, 24 h (gp 8)	***15*** mg/kg, ***36*** h (gp 7)	18 mg/kg, 24 h (gp 8)
≥2,800	12 mg/kg, 24 h (gp 9)	17 mg/kg, 20 h (gp 10)	***15*** mg/kg, ***24*** h (gp 9)	***18*** mg/kg, ***20*** h (gp 10)	***15*** mg/kg, ***30*** h (gp 9)	18 mg/kg, 20 h (gp 10)

[a] 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.

Smits et al, Antimicrob Agents Chemother 2015

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 Amit[1] & Shai Ashkenazi[3,4]

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

Linder et al. Br J Clin Pharmacol 2012

UZ LEUVEN

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.

Linder et al. Br J Clin Pharmacol 2012

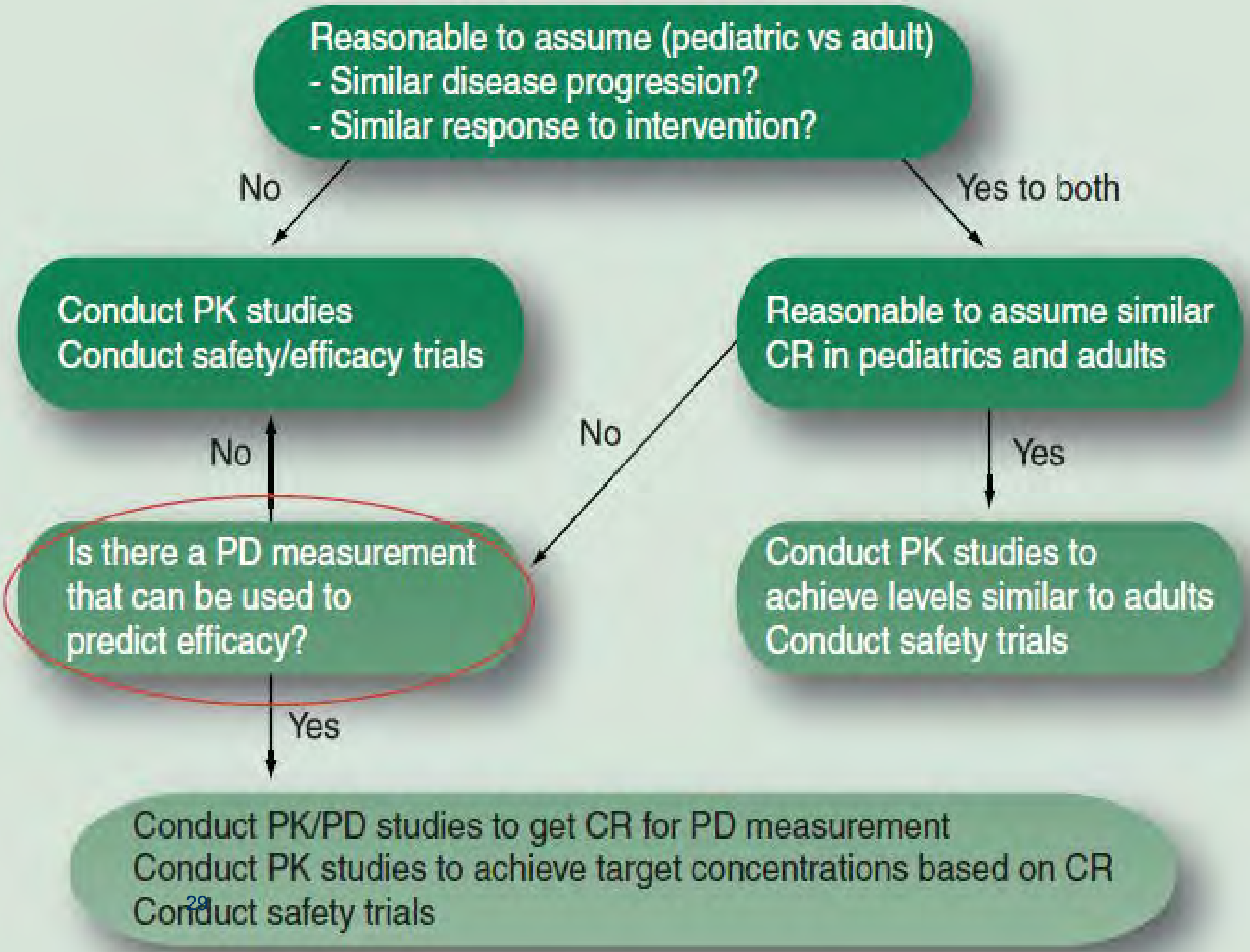

Reasonable to assume (pediatric vs adult)
- Similar disease progression?
- Similar response to intervention?
No
Yes to both
Conduct PK studies
Conduct safety/efficacy trials
Reasonable to assume similar CR in pediatrics and adults
No
No
Yes
Is there a PD measurement that can be used to predict efficacy?
Conduct PK studies to achieve levels similar to adults
Conduct safety trials
Yes
Conduct PK/PD studies to get CR for PD measurement
Conduct PK studies to achieve target concentrations based on CR
Conduct safety trials

Table 6. Effectiveness Results

	GA <32 Weeks		GA ≥32 Weeks		
	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No. (%)	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No. (%)	Total
Evaluable for effectiveness, No.	39	98	28	27	192
Effectiveness success	29 (74)	82 (84)	26 (93)	25 (93)	162 (84)
Death[a]	3 (8)	5 (5)	0 (0)	0 (0)	8 (4)
Presumptive clinical cure score ≥7	35 (90)	90 (92)	27 (96)	27 (100)	179 (93)
Presumptive clinical cure score <7	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Presumptive clinical cure score missing	4 (10)	7 (7)	1 (4)	0 (0)	12 (6)
Change in antibiotic therapy	7 (18)	12 (12)	2 (7)	2 (7)	23 (12)[b]
Cultures negative for bacteria	27 (69)	49 (50)	9 (32)	13 (48)	98 (51)
Cultures not done	12 (31)	49 (50)	19 (68)	14 (52)	94 (49)

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

[a] Death occurring ≤7 days from end of study meropenem.

[b] Of the 23 participants with change in antibiotic therapy, 1 also died and 1 had a presumptive clinical cure score <7.

20-30 mg/kg, q8-12 h, afhankelijk van GA en PNA

Table 4. Frequently Occurring (≥5 Participants) Adverse Events

	GA <32 Weeks		GA ≥32 Weeks		
	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No. (%)	PNA <2 Weeks, No. (%)	PNA ≥2 Weeks, No (%)	Total
No.	39	103	31	27	200
AST increased[a]	0 (0)	3 (3)	0 (0)	2 (7)	5 (3)
Atelectasis	2 (5)	0 (0)	0 (0)	3 (11)	5 (3)
Conjugated bilirubin increased[a]	5 (13)	3 (3)	0 (0)	1 (4)	9 (5)
Hyperglycemia[a]	2 (5)	2 (2)	1 (3)	0 (0)	5 (3)
Hypoglycemia[a]	3 (8)	2 (2)	0 (0)	0 (0)	5 (3)
Hypokalemia[a]	2 (5)	6 (6)	0 (0)	1 (4)	9 (5)
Hypotension[a]	1 (3)	5 (5)	0 (0)	0 (0)	6 (3)
Patent ductus arteriosus	4 (10)	1 (1)	0 (0)	1 (4)	6 (3)
Retinopathy of prematurity	0 (0)	5 (5)	0 (0)	0 (0)	5 (3)
Sepsis	5 (13)	5 (5)	1 (3)	1 (4)	12 (6)
Seizures	4 (10)	3 (3)	1 (3)	2 (7)	10 (5)
Vomiting	0 (0)	1 (1)	4 (13)	0 (0)	5 (3)

Abbreviations: AST, aspartate aminotransferase; GA, gestational age; PNA, postnatal age.

[a] Defined per the local site.

Table 5. Laboratory Evaluations

	Baseline	Days 1–7	Days 8–14	Days 15–21	Days 22–28
Serum creatinine (No.)	181	173	127	85	53
Median (range), mg/dL	0.5 (0.1–1.9)	0.4 (0.0–3.1)	0.4 (0.0–2.7)	0.3 (0.0–2.9)	0.3 (0.0–2.0)
AST (No.)	60	78	68	55	32
Median (range), U/L	37 (12–3358)	33 (9–419)	33 (11–308)	40 (15–567)	50 (19–788)
ALT (No.)	60	80	69	55	30
Median (range), U/L	25 (4–956)	18 (5–140)	16 (4–131)	20 (5–605)	27 (8–168)
Alkaline phosphatase (No.)	64	86	65	52	28
Median (range), U/L	255 (72–1368)	244 (35–967)	321 (104–1103)	412 (101–1600)	508 (123–1145)
Direct bilirubin (No.)	70	71	52	34	14
Median (range), mg/dL	0.6 (0.0–10.8)	0.8 (0.0–10.3)	1.5 (0.0–10.7)	1.7 (0.1–8.5)	3.7 (0.2–6.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

In a multivariate analysis (adjusted for confounding variables) prolonged therapy with antibiotics (≥ 5days) 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 Risk of NEC, death or either with increasing duration of postnatal antibiotics

Outcomes	OR per day of antibiotic use (95% CI), all babies*	OR per day of antibiotic use (95% CI), intubated >7 days*
NEC	1.07 (1.04 to 1.10)	1.09 (1.05 to 1.13)
Death	1.16 (1.08 to 1.24)	1.13 (1.05 to 1.23)
NEC or death	1.04 (1.02 to 1.06)	1.04 (1.01 to 1.07)

*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.*

Cotton CM et al. Pediatrics 2009 and Cotton CM et al. Arch Dis Child 2012

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)*.

Greenwood et al, J Pediatr 2014

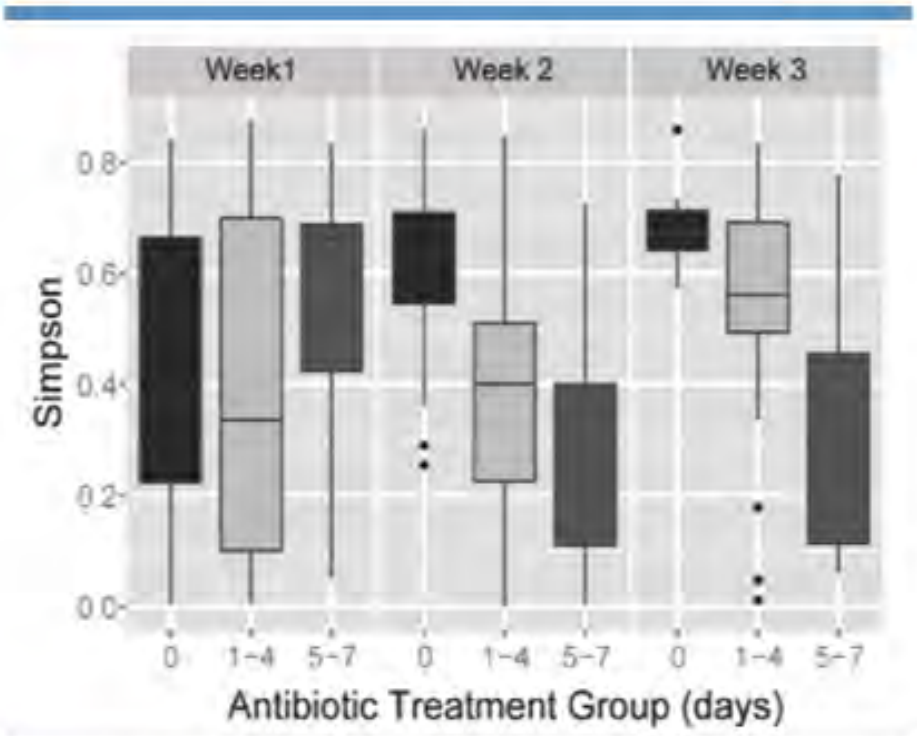


Figure 2. Simpson diversity index depicted in relation to antibiotic receipt (No, 0 days; brief, 1-4 days; or intensive antibiotics, 5-7 days) during the first 3 weeks of life.

Greenwood et al, J Pediatr 2014

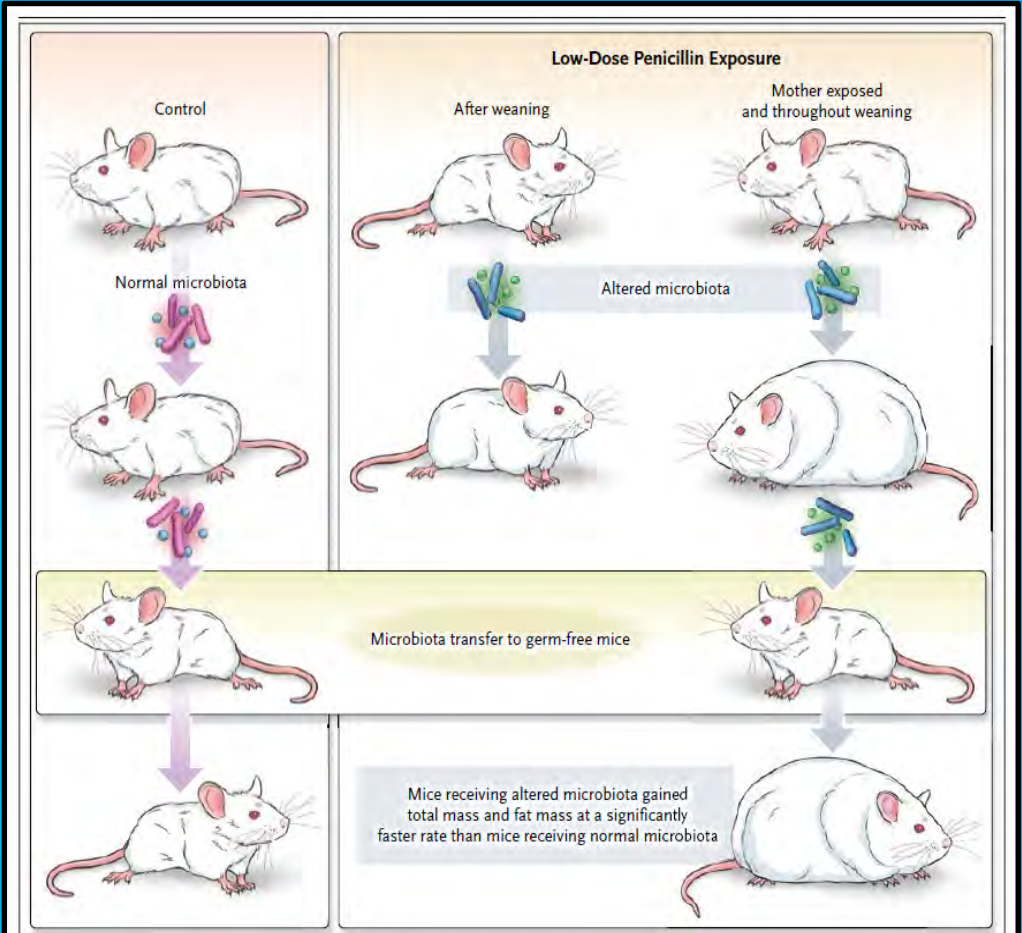


Figure 1. Timing of Low-Dose Penicillin Treatment and Risk of Obesity.

Cox and colleagues[1] 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.

Jess T, NEJM 2014

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.

Saari et al, Pediatrics 2015

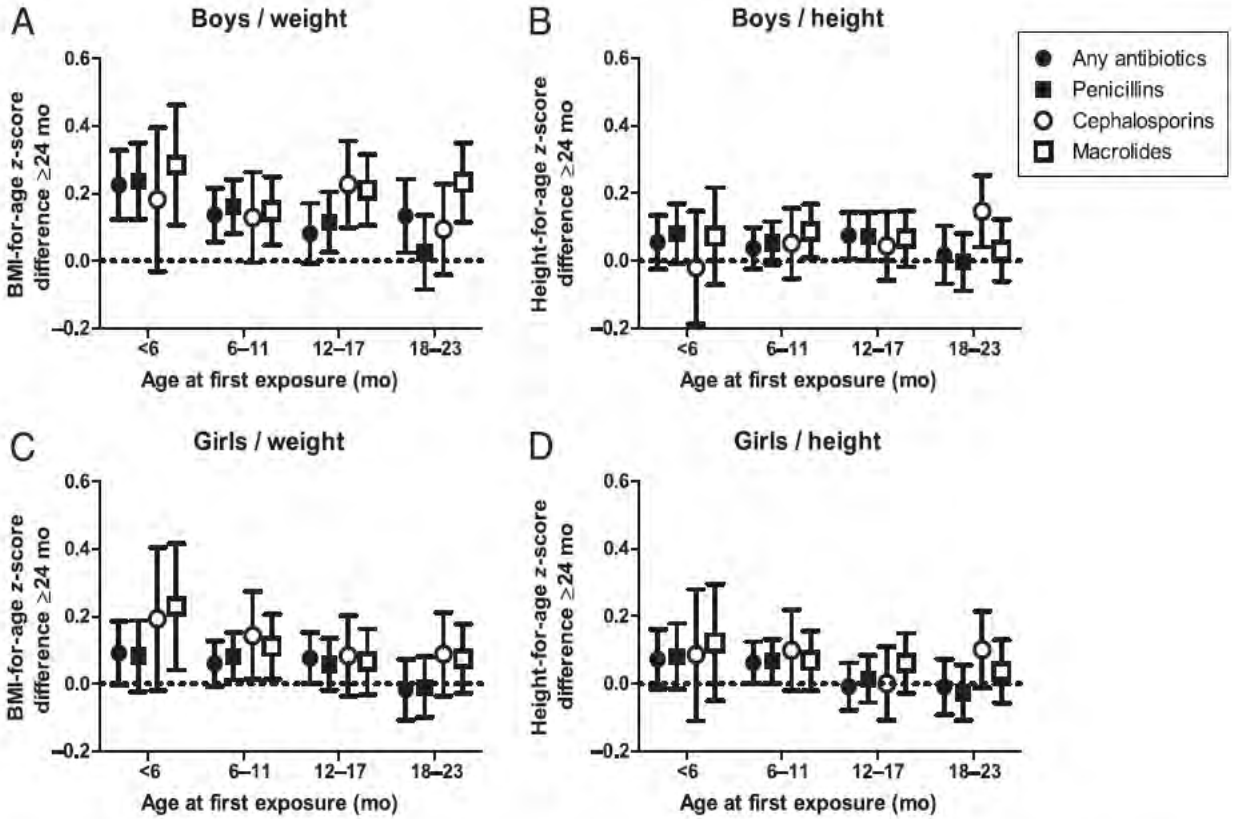


FIGURE 2

Adjusted differences of means (95% CI) for *z*BMI and *z*HFA 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.

Saari et al, Pediatrics 2015

Table 2
Postnatal characteristics of infants associated with retinopathy of prematurity (ROP).

	ROP			ROP occurrence		ROP progression	
				Any ROP vs. None		Grade 3 vs Grade 1/2	
	None	Grade1/2	Grade3	Univariable	Adjusted	Univariable	Adjusted
N (%)	29 (100)	31 (100)	13 (100)				
Systemic Inflammatory Response Syndrome	0	3 (10)	8 (62)	–	–	15 (2.9–76)	15 (2.4–95)
Ductus arteriosus (treated)	0	5 (16)	6 (46)	–	–	4.5 (1.1–19)	2.7 (0.6–12)
Postnatal glucocorticoid	0	4 (13)	5 (38)	–	–	4.2 (0.9–20)	3.8 (0.7–20)
Mechanical ventilation	3 (10)	16 (52)	13 (100)	17 (4.4–65)	12 (2.6–56)	–	–
Hypocarbia	0	9 (29)	4 (31)	–	–	1.1 (0.3–4.5)	0.9 (0.2–3.9)
Catecholamines	1 (3)	9 (29)	12 (92)	26 (3.2–205)	12 (1.3–110)	29 (3.3–260)	24 (2.6–224)

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.

infection

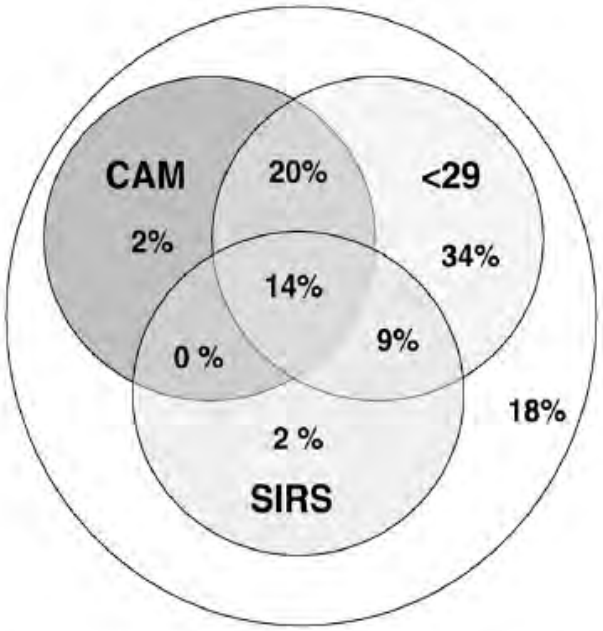
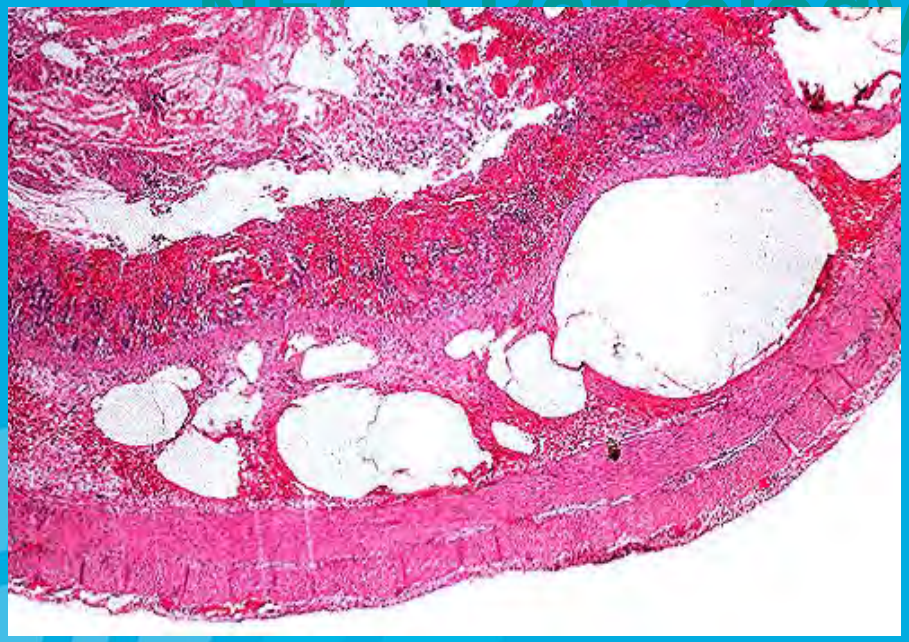


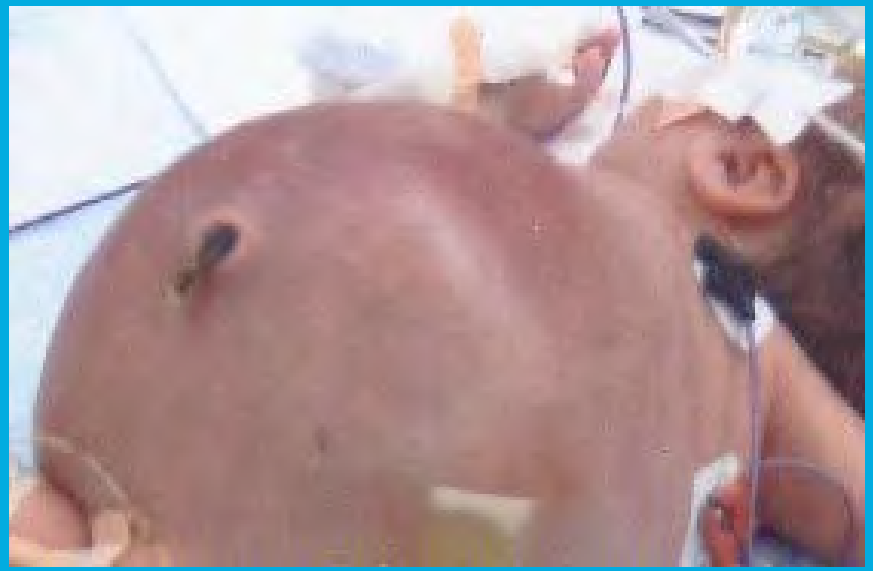
Fig. 2. Venn Diagram of prevalence of risk factors chorioamnionitis (CAM), gestational age <29 weeks, and systemic inflammatory response syndrome (SIRS) among 44 children with ROP (sum not equal to 100% due to rounding).

inflam

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
H_2, 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 Marlow[2]

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

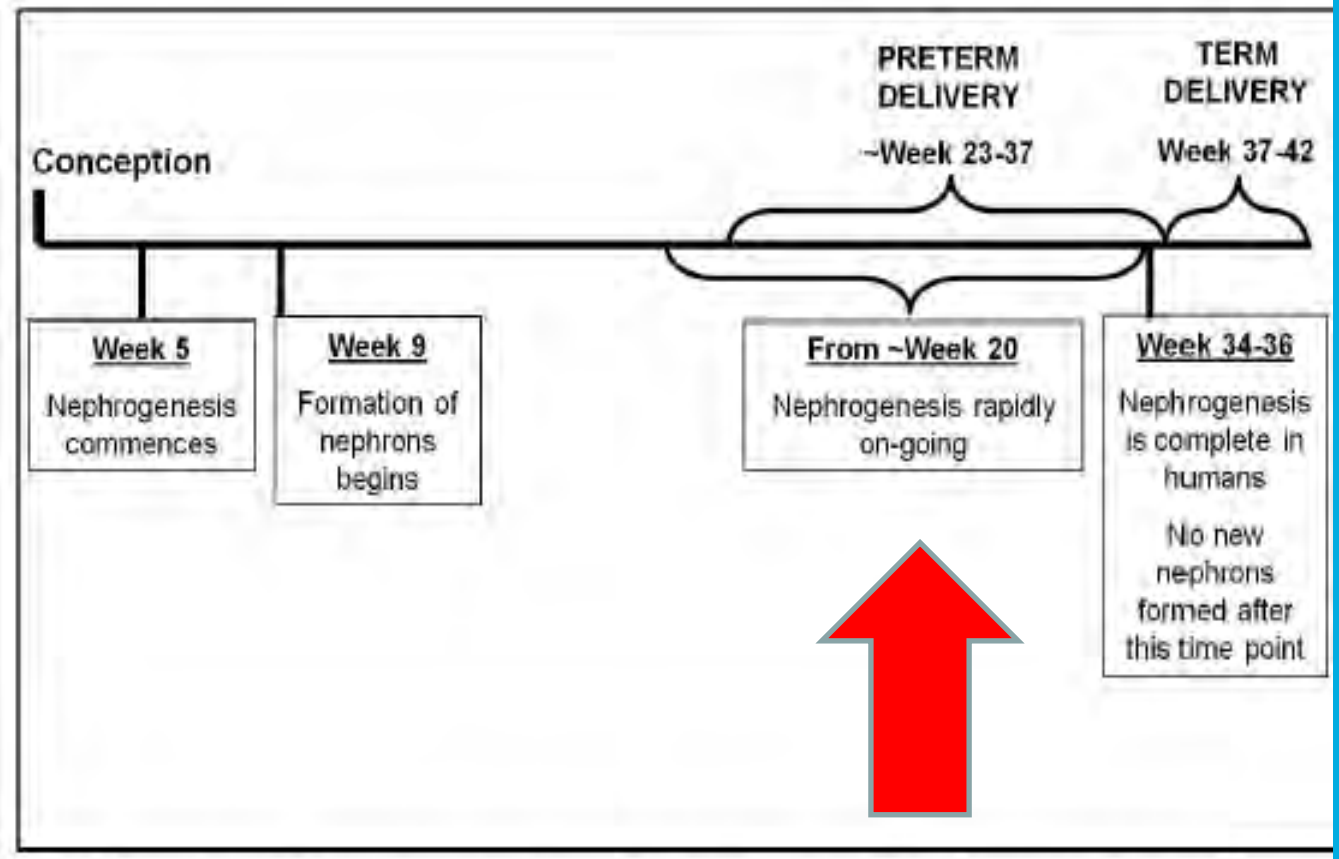


Fig. 1. A timeline of human nephrogenesis during gestation. Nephrogenesis is rapidly on-going at the time when most preterm neonates are delivered.

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Pædiatrica ISSN 0803–5253

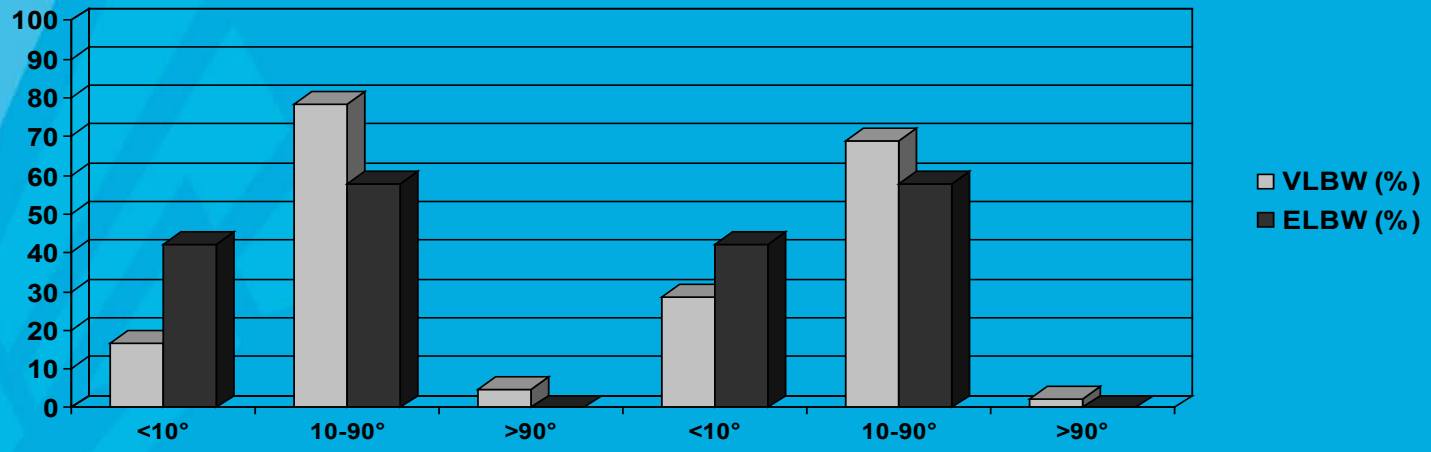
REGULAR ARTICLE

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 Brugnara[1], C Bruno[2], B Franchi[1], G Talamini[3], G Guidi[2], L Cataldi[4], P Biban[5], R Mella[1], V Fanos[6]

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



developmental renal toxicology: aminoglycosides or 'penicillines' ?

Antibiotics and renal branching morphogenesis: comparison of toxicities

Ruud R.G. Bueters[1], Lisanne J.A. Kusters[1], Annelies Klaasen[1], Lambertus P. van den Heuvel[1] and Michiel F. Schreuder[1]

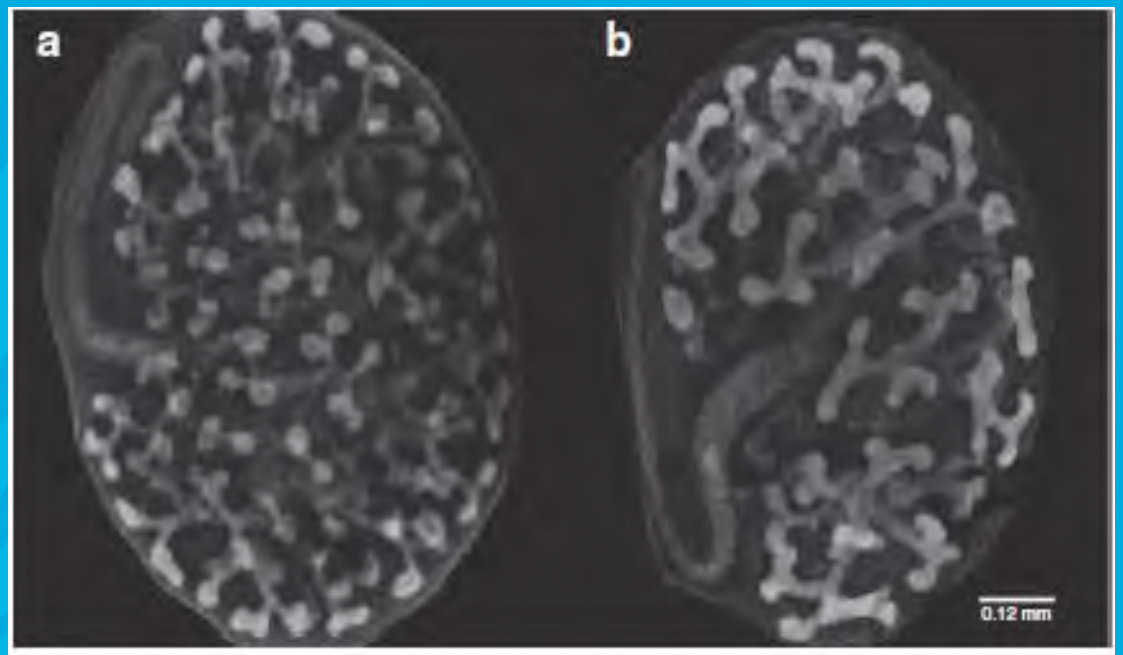


Figure 3. Representative immunohistochemic staining of ureteric bud development in metanephroi cultured for 24 h in media with (**b**) 2,000 µmol/l ceftazidime or (**a**) vehicle control.

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.)

werstern 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)

UZ LEUVEN


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.
AIFA
CLEARCHANNEL

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International Neonatal Consortium

Coffee Break
30 minutes

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Expert Panel on Infections

Raafat Bishai
AstraZeneca

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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

International Neonatal Consortium

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

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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

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Michael Caplan
University of Chicago

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Kelly Wade
Children's Hospital Philadelphia

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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

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Mark Turner
University of Liverpool

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EnprEMA Working Group on Paediatric Infections

- **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

BJCP British Journal of Clinical Pharmacology

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 Langhendries[10] & Evelyne Jacqz-Aigrain[1,2]

[1]Department of Paediatric Pharmacology and Pharmacogenetics, INSERM CIC9202, APHP, Hopital Robert Debré, 75019 Paris, [2]Sorbonne Paris Cité, Univ Paris Diderot, 75019 Paris, France, [3]Department of Women's and Children's Health, University of Liverpool, Neonatal Unit, Liverpool Women's Hospital, Liverpool L8 7SS, [4]Academic Division of Child Health, University of Nottingham, Derbyshire Children's Hospital, Derby, UK, [5]Division of Paediatric Clinical Pharmacology, Children's National Medical Center, Washington, DC, [6]Departments of Paediatrics, Pharmacology and Physiology, George Washington University School of Medicine and Health Sciences, Washington, DC, USA, [7]Intensive Care, Erasmus Medical Center-Sophia Children's Hospital, Rotterdam, the Netherlands, [8]Neonatology and NICU, S. Anna Hospital, Torino, Italy, [9]Department of Clinical Epidemiology, INSERM CIE5, APHP, Hopital Robert Debre, 75019 Paris, France and [10]NICU, CHC-Site St Vincent, 4000 Rocourt-Liège, Belgium

35 trials

Jadad score [median (Q1–Q3)]	2 (1–2)
= 0	1 (3%)
= 1	12 (34%)
= 2	16 (46%)
= 3	4 (11%)
= 4	2 (6%)
Risk of bias	
Low	3 (9%)
Unclear	9 (25%)
High	23 (66%)
Primary outcome	
Defined§	23 (66%)
Not defined	12 (34%)
Power calculation	
Stated	14 (40%)
Not stated	21 (60%)

35 trials

Domains	Risk of bias assessments – *n* (%) High	Unclear	Low
Sequence generation	1 (3%)	21 (60%)	13 (37%)
Allocation concealment	1 (3%)	19 (54%)	15 (43%)
Blinding	7 (20%)	9 (26%)	19 (54%)
Incomplete data	3 (9%)	6 (17%)	26 (74%)
Selective reporting	13 (37%)	9 (26%)	13 (37%)
Other sources of bias	11 (31%)	17 (49%)	7 (20%)

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

J Antimicrob Chemother 2013; **68**: 2733–2745
doi:10.1093/jac/dkt297 Advance Access publication 30 July 2013

Journal of Antimicrobial Chemotherapy

Clinical trials in neonatal sepsis

Clarissa Oeser[1]*, Irja Lutsar[2], Tuuli Metsvaht[3], Mark A. Turner[4], Paul T. Heath[1] and Mike Sharland[1]

[1]Paediatric Infectious Diseases Research Group, St George's, University of London, London, UK; [2]Institute of Microbiology, Tartu University, Tartu, Estonia; [3]Paediatric Intensive Care Unit, Clinic of Anaesthesiology and Intensive Care, Tartu University Clinics, Tartu, Estonia; [4]Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Inclusion criteria	Baseline parameters
suspected infection	PNA, ethnicity, wt, sex
not specified	PNA, wt, sex
'clinical and/or laboratory evidence of sepsis': positive blood culture + clinical manifestation (not further defined)	PNA, wt
infection, severe enough to warrant penicillin/aminoglycoside combination	PNA, sex
suspected or proven bacterial infection	wt, sex, GA, type of delivery, previous episodes of sepsis, maternal antenatal history
definite sepsis: clinical features + positive blood/urine culture	
probable sepsis: presence of ≥2: pneumonia on X-ray, WCC <500, immature to total neutros >0.2, CRP above reference range, GBS antigen in blood	
proven or signs of sepsis, high risk of developing sepsis	GA, PNA, wt, sex, presenting abnormalities
suspected sepsis, fulfilling septic score >10	GA, wt, sex
suspected sepsis or meningitis	GA, PNA, wt, sex

Clinical outcome criteria

Respiratory	Cardiovascular
respiratory problems	haemodynamic changes
apnoea, ventilator therapy	bradycardia, unexplained sudden collapse, disseminated intravascular coagulation
apnoea (cessation of breathing >15 s, resulting in bradycardia and cyanosis)	poor perfusion (CRFT >5 s)
apnoea, increased oxygen requirement	bradycardia spells, hypotension
increasing oxygen demand, new requirement for ventilatory support	not specified
unexplained respiratory distress	poor peripheral circulation

Laboratory parameters

WCC	Neutrophils	CRP
not specified	immature to total neutros >0.2	CRP >20 mg/L
'high' WCC ± positive culture from other site	not specified	not specified
WCC <5000/mm^3	immature to total neutros >0.2	CRP above reference range
not specified	immature to total neutros >0.2	not specified
WCC <5000 or >20000/mm^3	immature to total WCC ratio >0.2	CRP >10 mg/L
not specified	neutrophilia, neutropenia,	'high' CRP
not specified	neutropenia, high band count	not specified
leucopenia, leucocytosis, left shift	not specified	not specified

Primary endpoints

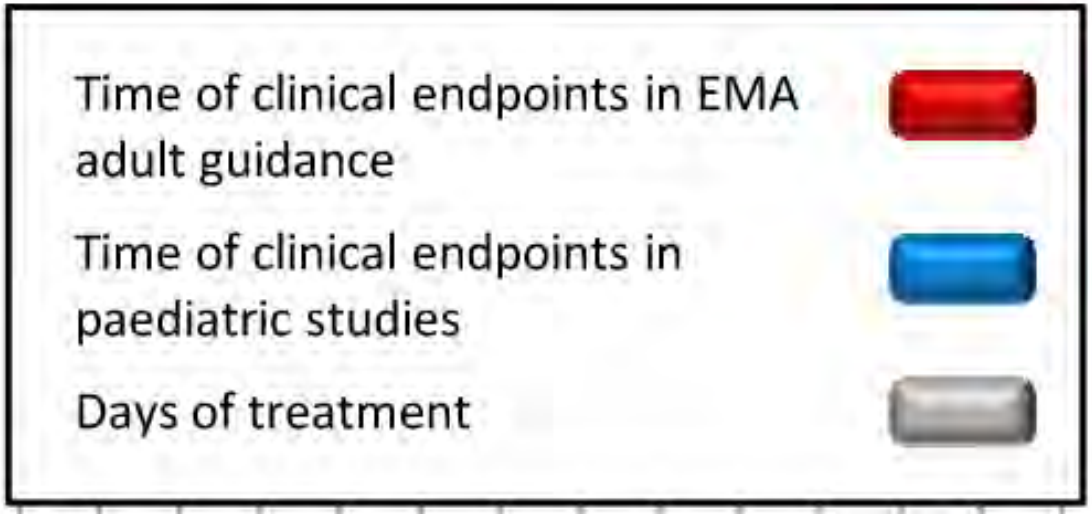
Primary endpoints
cure/improvement: clinical recovery with eradication of original pathogen without subsequent superinfection, sufficient clinical improvement that further antibiotic therapy was deemed unnecessary, no recurrence of clinical signs after cessation of treatment
failure: death due to infection,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

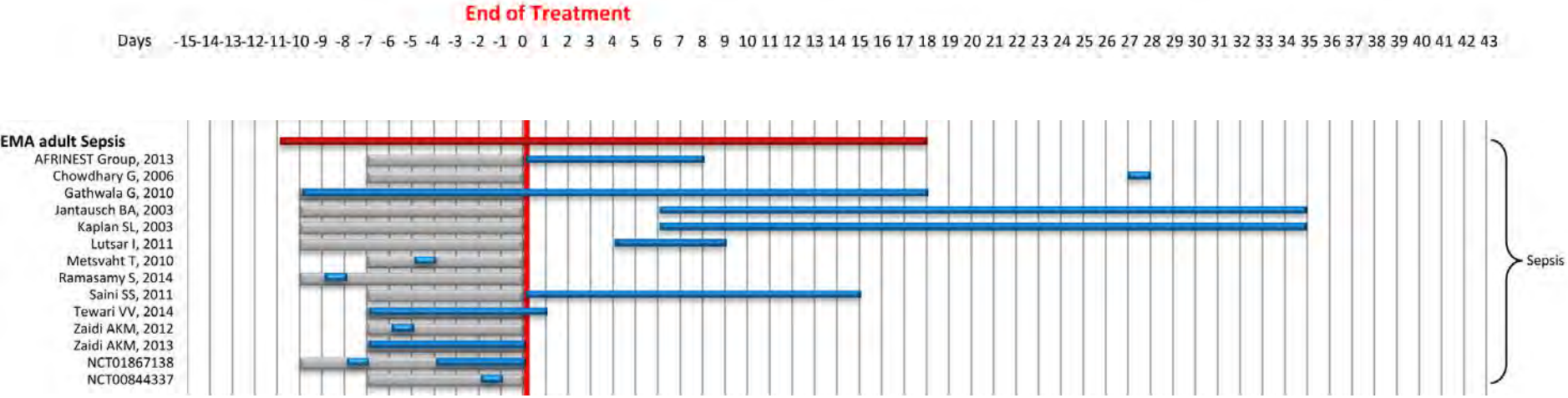
Comparison with regulatory standards

LACK OF HARMONISATION IN STUDY DESIGN AND OUTCOMES IN PAEDIATRIC ANTIBIOTIC CLINICAL TRIALS REPORTED FROM 2000-2015: A SYSTEMATIC REVIEW

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

In press, Lancet Infectious Diseases


Time of clinical endpoints in EMA adult guidance
Time of clinical endpoints in paediatric studies
Days of treatment


End of Treatment
Days -15 -14 -13 -12 -11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43
EMA adult Sepsis
AFRINEST Group, 2013
Chowdhary G, 2006
Gathwala G, 2010
Jantausch BA, 2003
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Lutsar I, 2011
Metsvaht T, 2010
Ramasamy S, 2014
Saini SS, 2011
Tewari VV, 2014
Zaidi AKM, 2012
Zaidi AKM, 2013
NCT01867138
NCT00844337
Sepsis

One way forward

Table 7. Suggestions for some core elements of a neonatal sepsis trial design

Criteria for Neonatal **S**epsis **T**rials of **A**nti**M**icrobials
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**
Neonatal data to record	**Gender, gestational age at birth, chronological age, birth weight, current weight, concomitant conditions and medications**
Assessments	**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**
Endpoints	**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, $f\%T_{>MIC}$ 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

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Expert Panel on Infections

Sumathi Nambiar
US food and Drug Administration

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Ensuring New Antibiotics Address the Needs of NICU Patients

Daniel Keene
Health Canada

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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:

Infections Voting Slide 1

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

Infections Voting Slide 2

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

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Thank You

CRITICAL PATH INSTITUTE

International Neonatal Consortium

Second Annual Neonatal Scientific Workshop

Welcome

March 8th, Morning

Agenda – 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
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Mark Turner (University of Liverpool), Chair

Second Annual Neonatal Scientific Workshop

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

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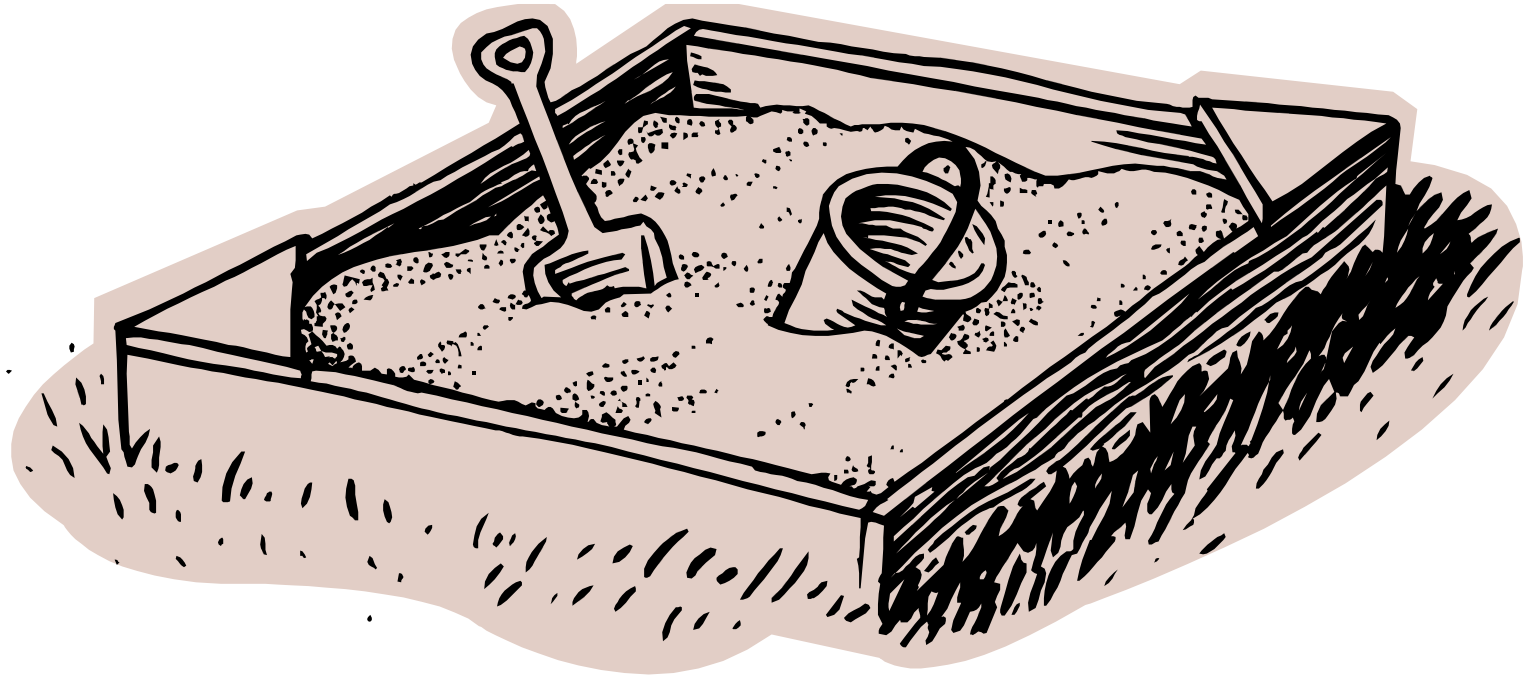
SHARI TARGUM (US Food and Drug Administration)
RALPH BAX (European Medicines Agency)

Sharing and Collaboration



"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.

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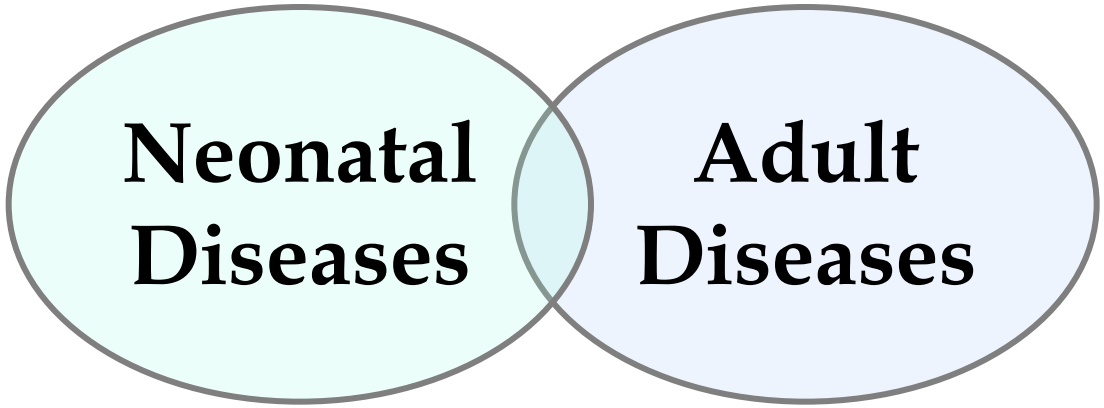
International Neonatal Consortium

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

Drug Development Disconnect

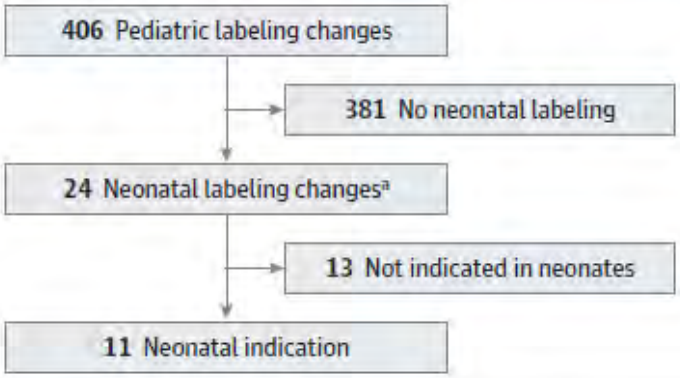
Majority of drugs used are off-label

Very few new therapies are being developed specifically for neonates



Pediatric Plans to include neonates

Figure. Neonatal Labeling Changes Under Legislation From 1997 to 2010 and Exposure of Neonates to Drugs With a Neonatal Indication



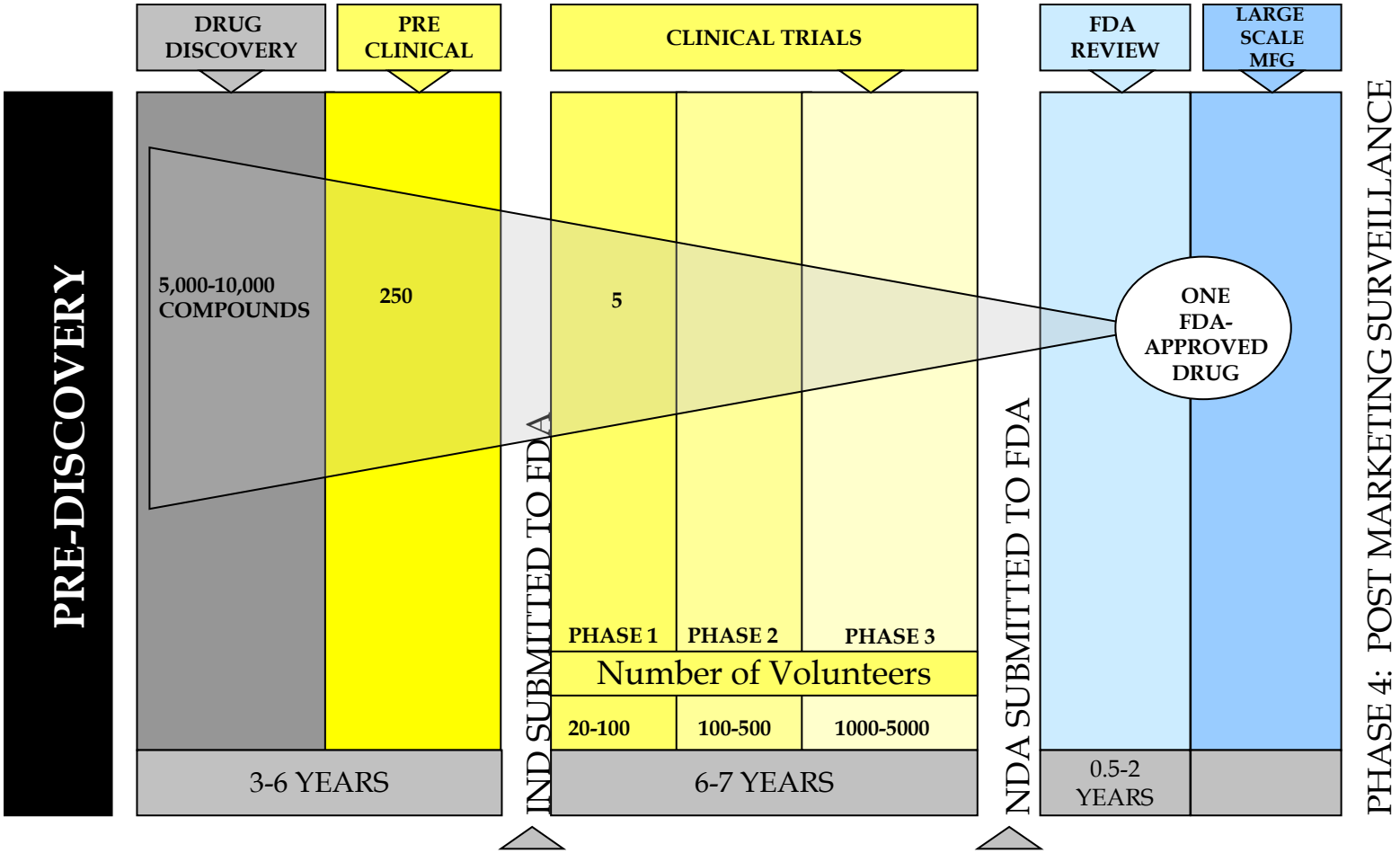
[a]There are 24 neonatal labeling changes involving 23 drugs. Linezolid has 2 labeling changes.

28 drugs studied in neonates

- **46% not used in NICUs**
- **29% used in fewer than 60 neonates**

Laughon MM, Avant D, Tripathi N et al. 2014. Drug labeling and exposure in neoates. *JAMA Pediatr.*168:130-136.

Research and Development Process



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

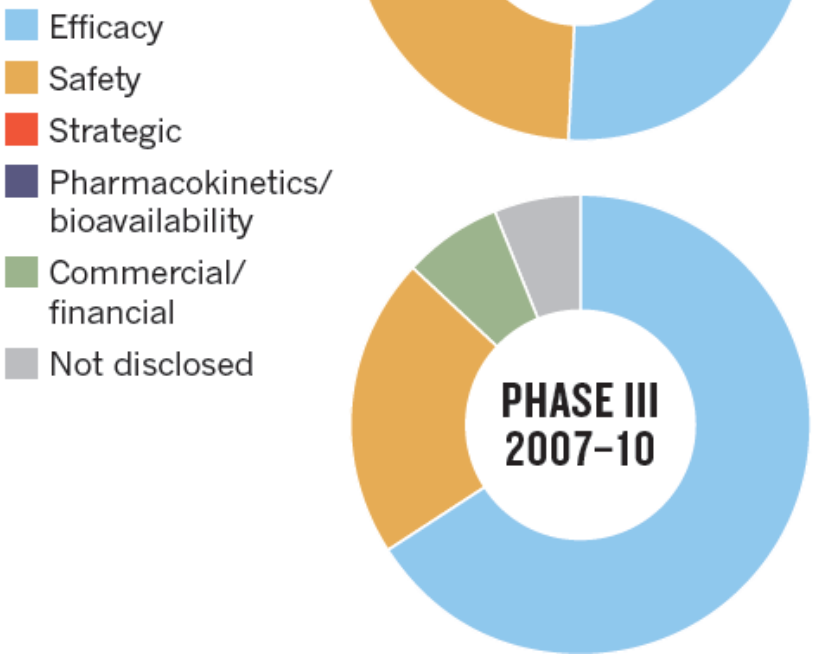
	This study (2013) all indications		This study (2013) lead indications		DiMasi *et al.*[6] lead indications		Kola *et al.*[8] lead indications		Abrantes-Metz *et al.*[9] lead indications	
	Phase success	Phase LOA	Phase success	Phase LOA	Phase success	Phase LOA	Phase success	Phase LOA	Phase success	Phase LOA
Phase 1 to phase 2	64.5%	10.4%	66.5%	15.3%	71%	19%	68%	11%	80.7%	NA
Phase 2 to phase 3	32.4%	16.2%	39.5%	23.1%	45%	27%	38%	16%	57.7%	NA
Phase 3 to NDA/BLA	60.1%	50.0%	67.6%	58.4%	64%	60%	55%	42%	56.7%	NA
NDA/BLA to approval	83.2%	83.2%	86.4%	86.4%	93%	93%	77%	77%	NA	NA
LOA from phase 1[a]		10.4%		15.3%		19%		11%	26.4%[c]	NA
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.



http://www.nature.com/news/2011/110928/full/477526a.html

Right Drug

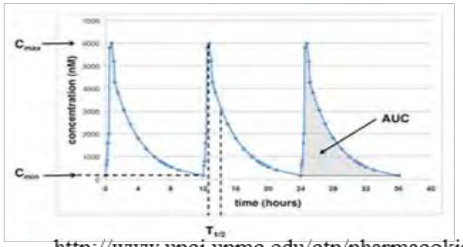




Right Population

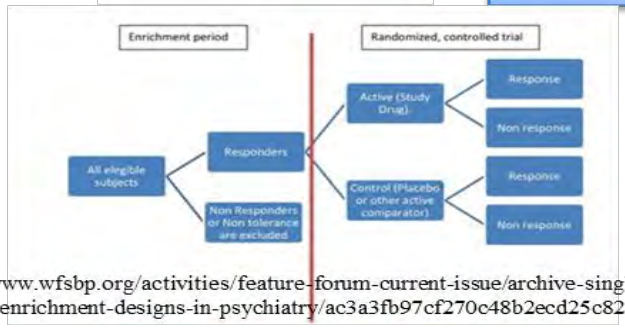


Right Dose

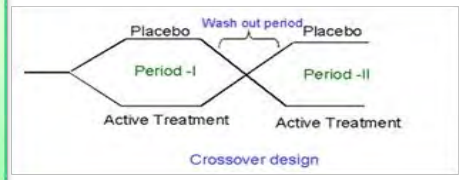



http://www.upci.upmc.edu/ctp/pharmacokinetics.cfm

Right Trial Design

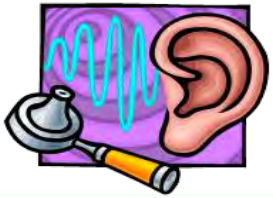


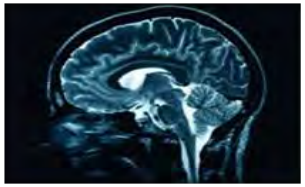
http://www.wfsbp.org/activities/feature-forum-current-issue/archive-single/should-we-accept-enrichment-designs-in-psychiatry/ac3a3fb97cf270c48b2ecd25c825ee9b.html



http://accp1.org/pharmacometrics/theory.htm

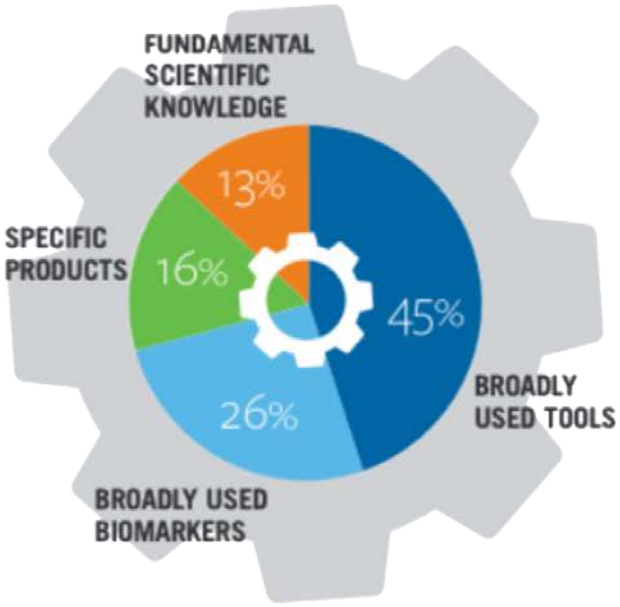
Right Endpoints



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
  - **B**iomarkers, **E**ndpoint**S**, and other **T**ools
  - 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

http://www.ncbi.nlm.nih.gov/books/NBK326791/

BEST Biomarker Categories

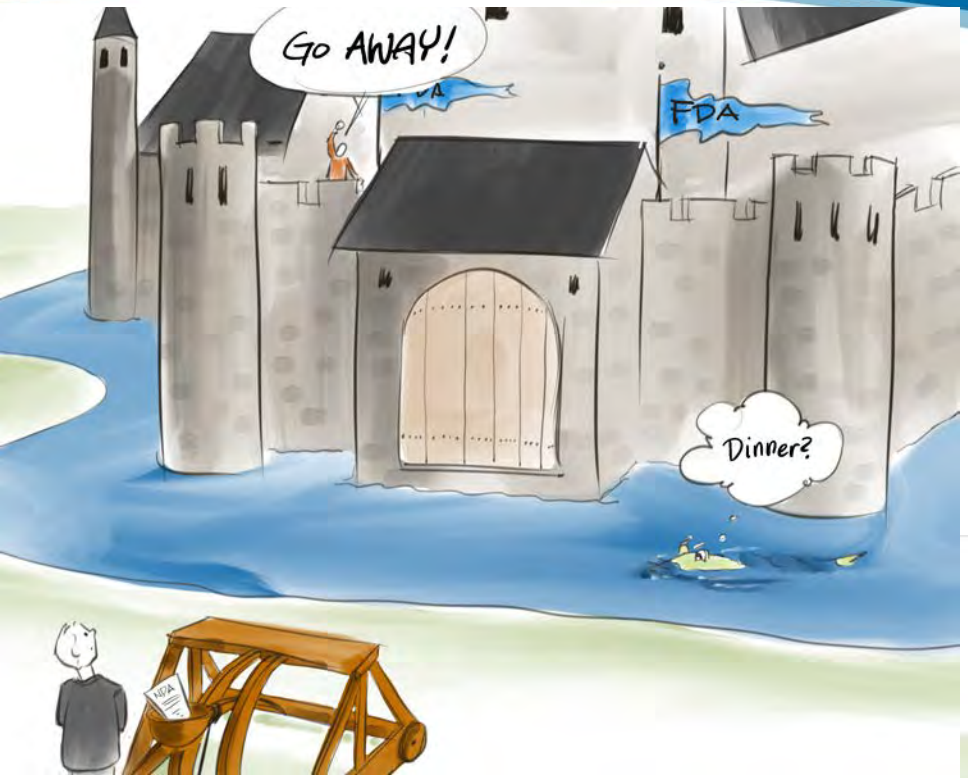
- Susceptibility/risk biomarker
- Diagnostic biomarker
- Prognostic biomarker
- Predictive biomarker
- Monitoring biomarker
- Pharmacodynamic/response biomarker
- Safety biomarker

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

Communication with FDA



Then

Now

Concept: S.McCune
Graphic: T.Benthin

Summary of ROP and Infection Polling

Results of ROP Discussion

N=73	First	Second
A. Enrichment Strategies	5%	14%
B. Data Standards	4%	7%
C. ROP-specific Outcomes	25%	26%
D. Multiple Outcomes	14%	19%
E. Standardizing in Trials Targeting Systemic Inflammation	4%	7%
F. Combination B and C	48%	24%

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	First	Second
A. Make the most of existing data	19%	22%
B. Standard protocol for new studies	44%	29%
C. How to assess efficacy in the CNS	36%	48%

Online – 5 votes
First A=3; B=1; C=1
Second A=1; B=2; C=2

March 8, 2016

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Regulatory Science for Neonates

Janet Woodcock
US Food and Drug Administration

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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

CRITICAL PATH INSTITUTE

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

Regulatory Science

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*

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- *Drug / indication*
- *Biomarker Qualification*

The rational use….

Rational use:

- Assumptions
- Model
- Predictions
- Data
- Test model and validate predictions
- Conclusions

Rigour

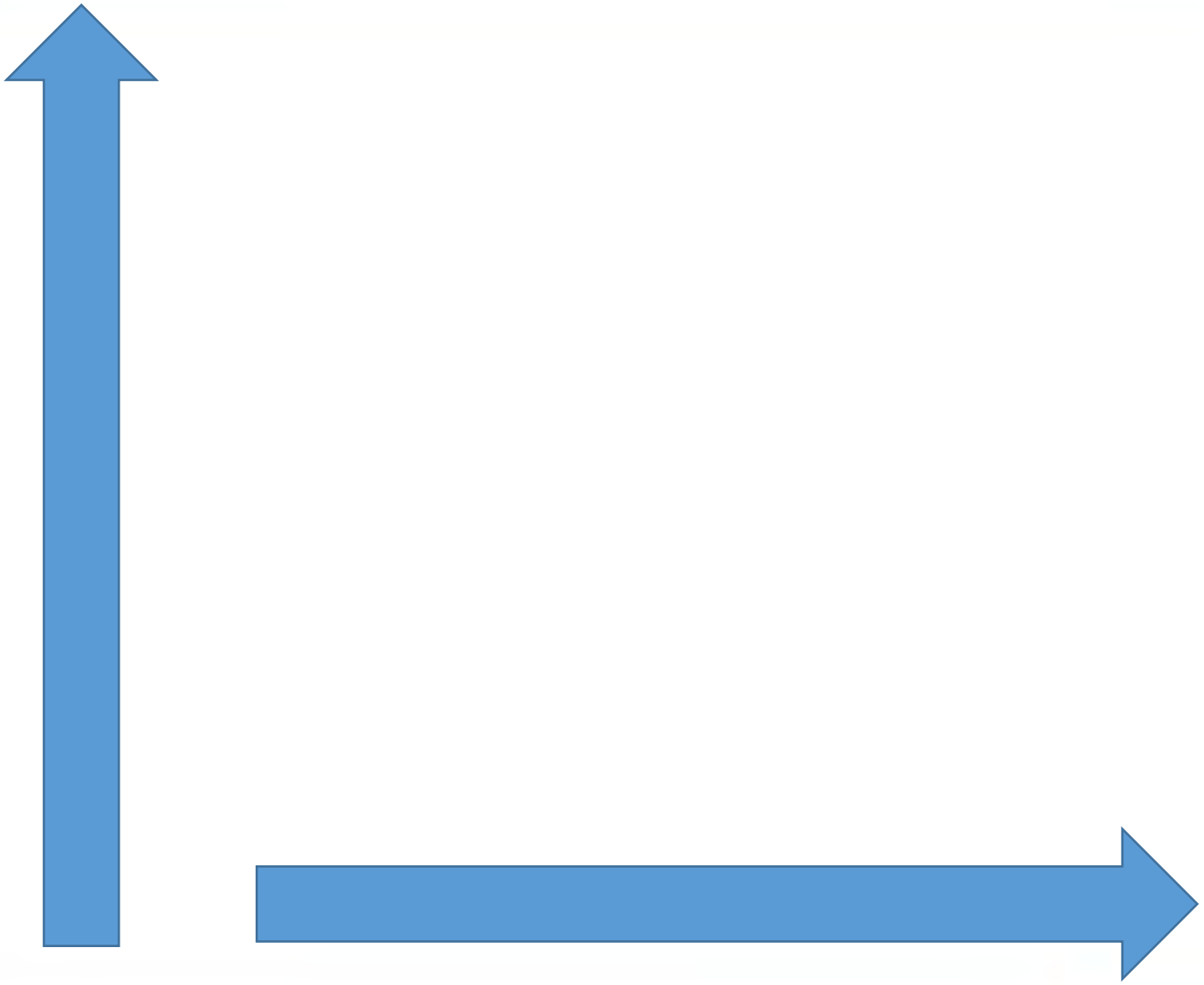
…of data…

Data:

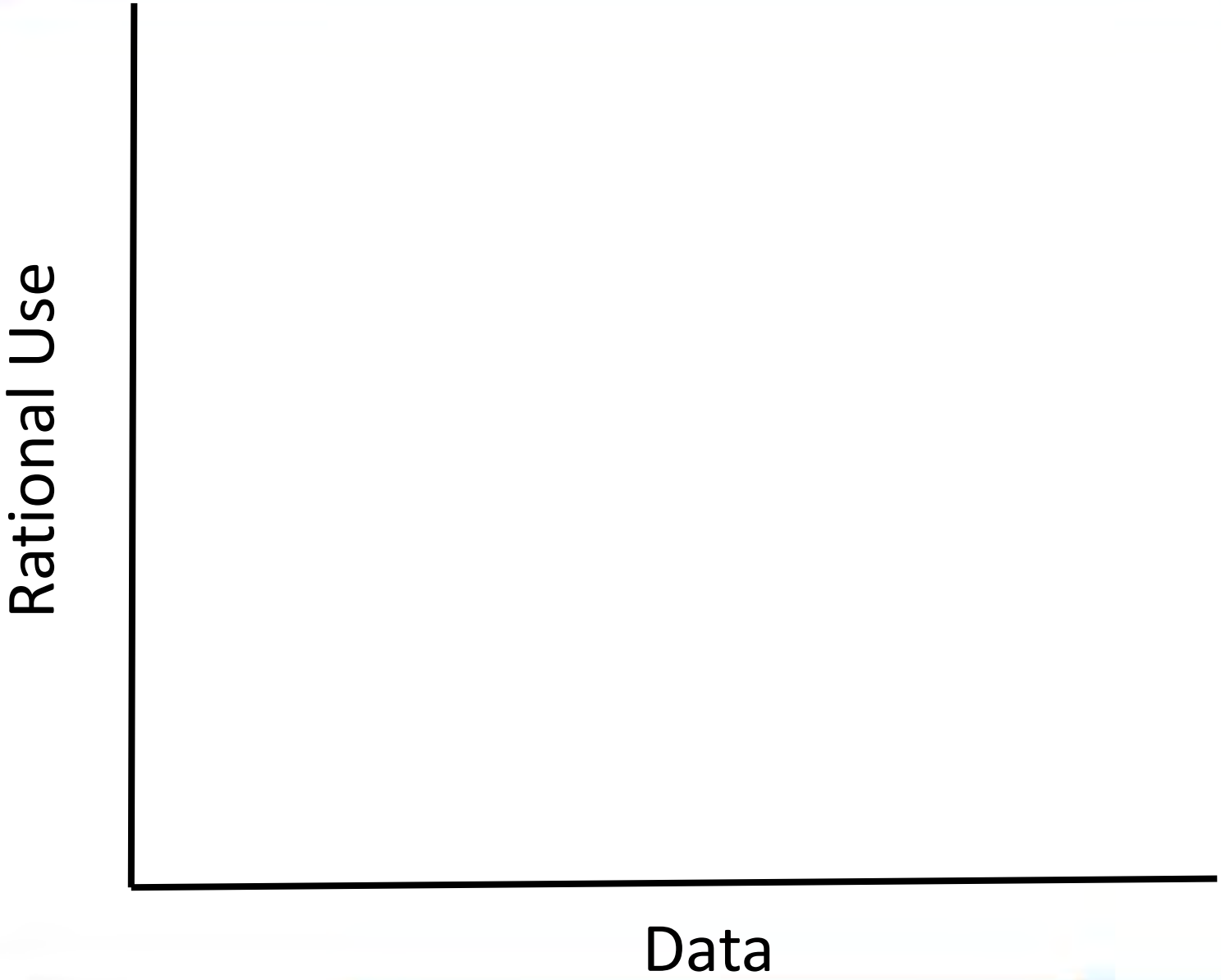
- Reliable measurements
- Reliable collection

Stringency

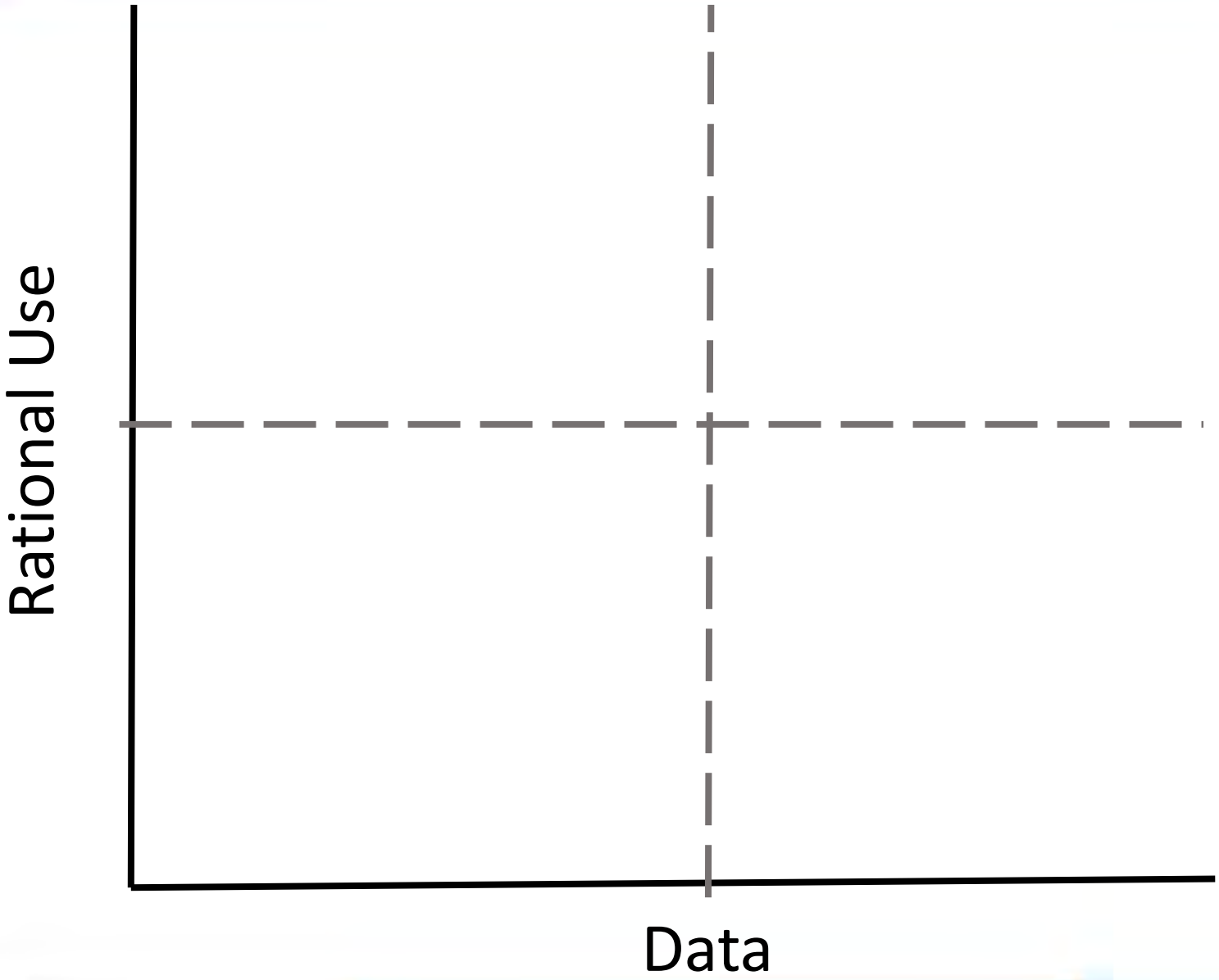
Regulatory Readiness



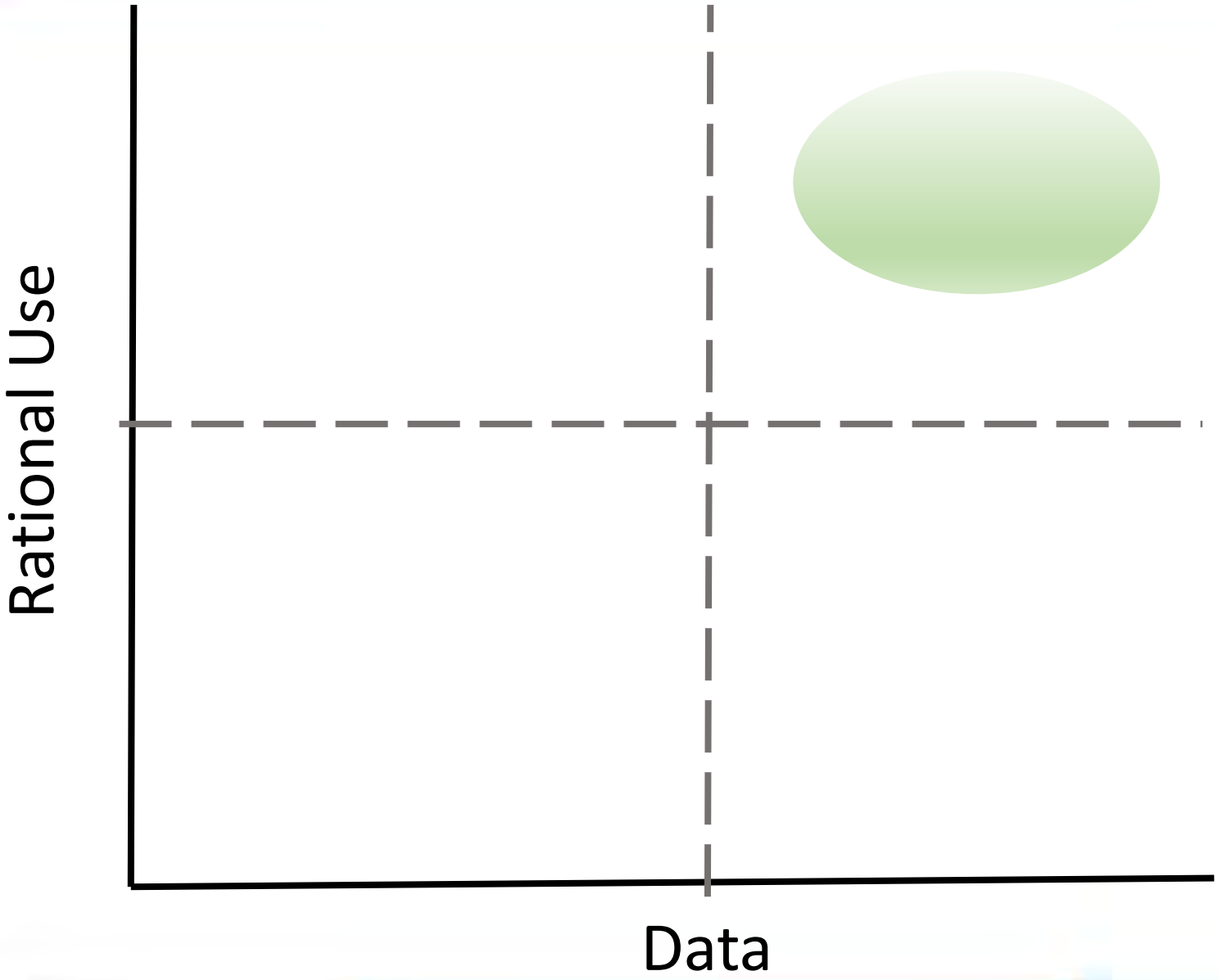
Regulatory Readiness



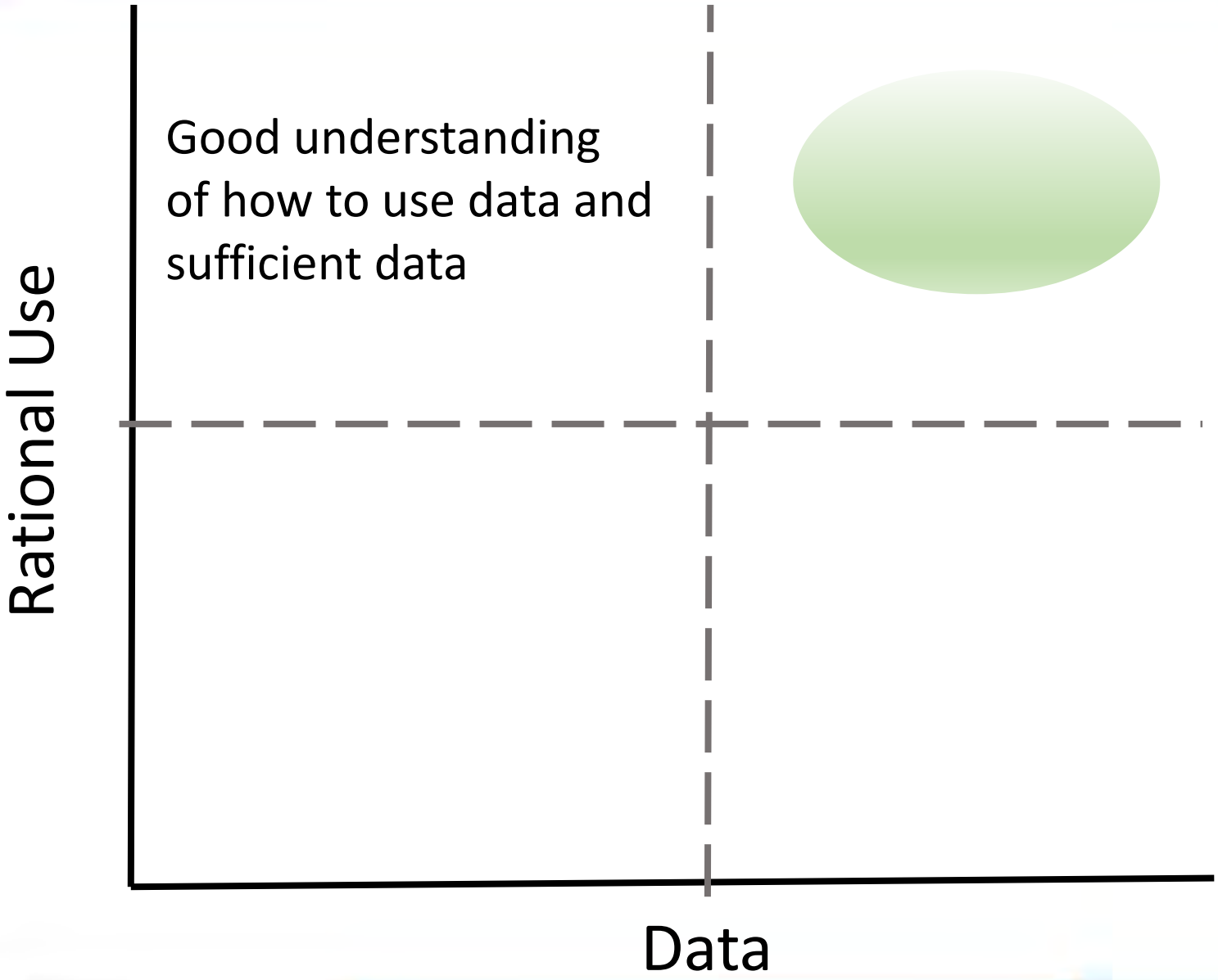
Regulatory Readiness



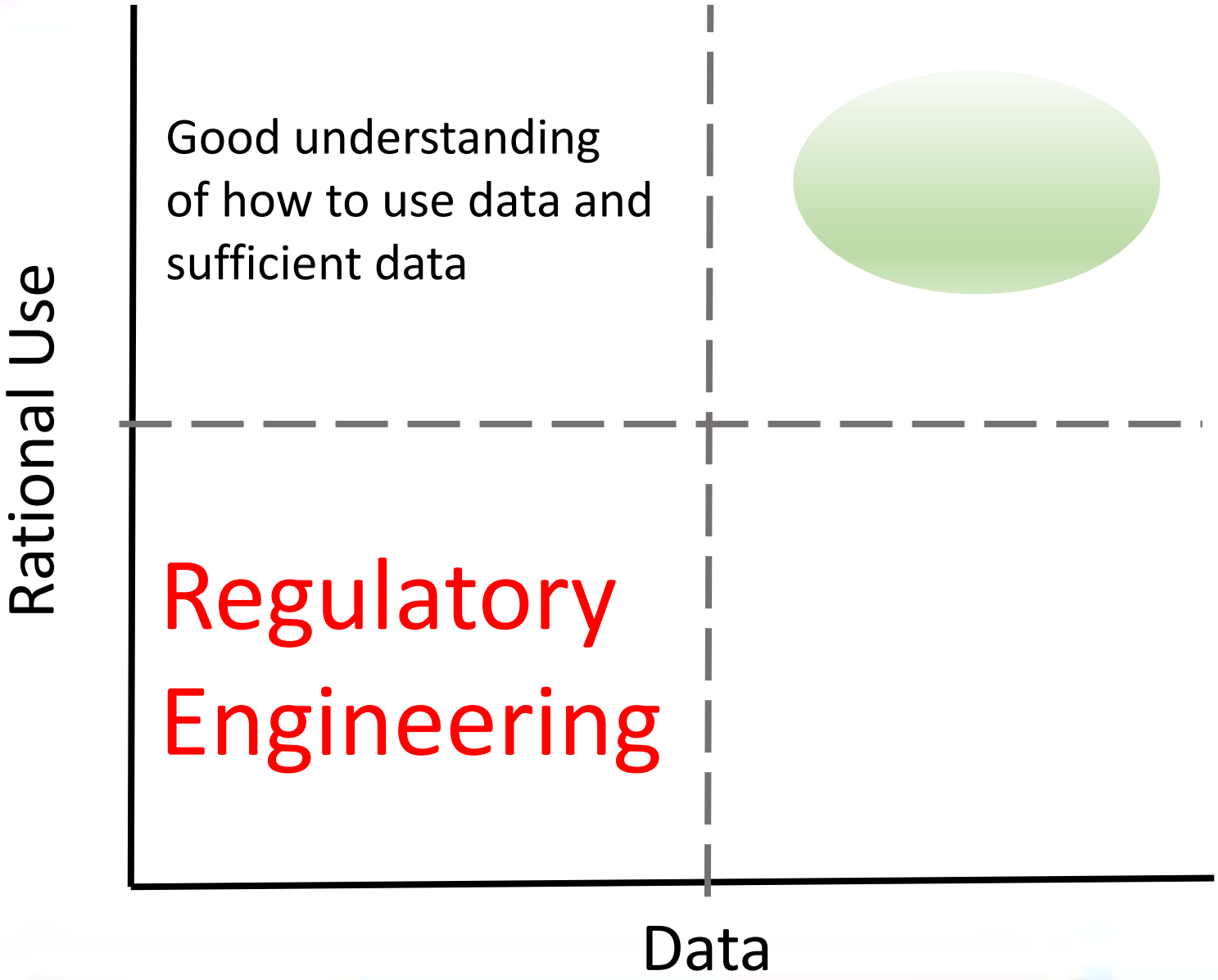
Regulatory Readiness: Case 1



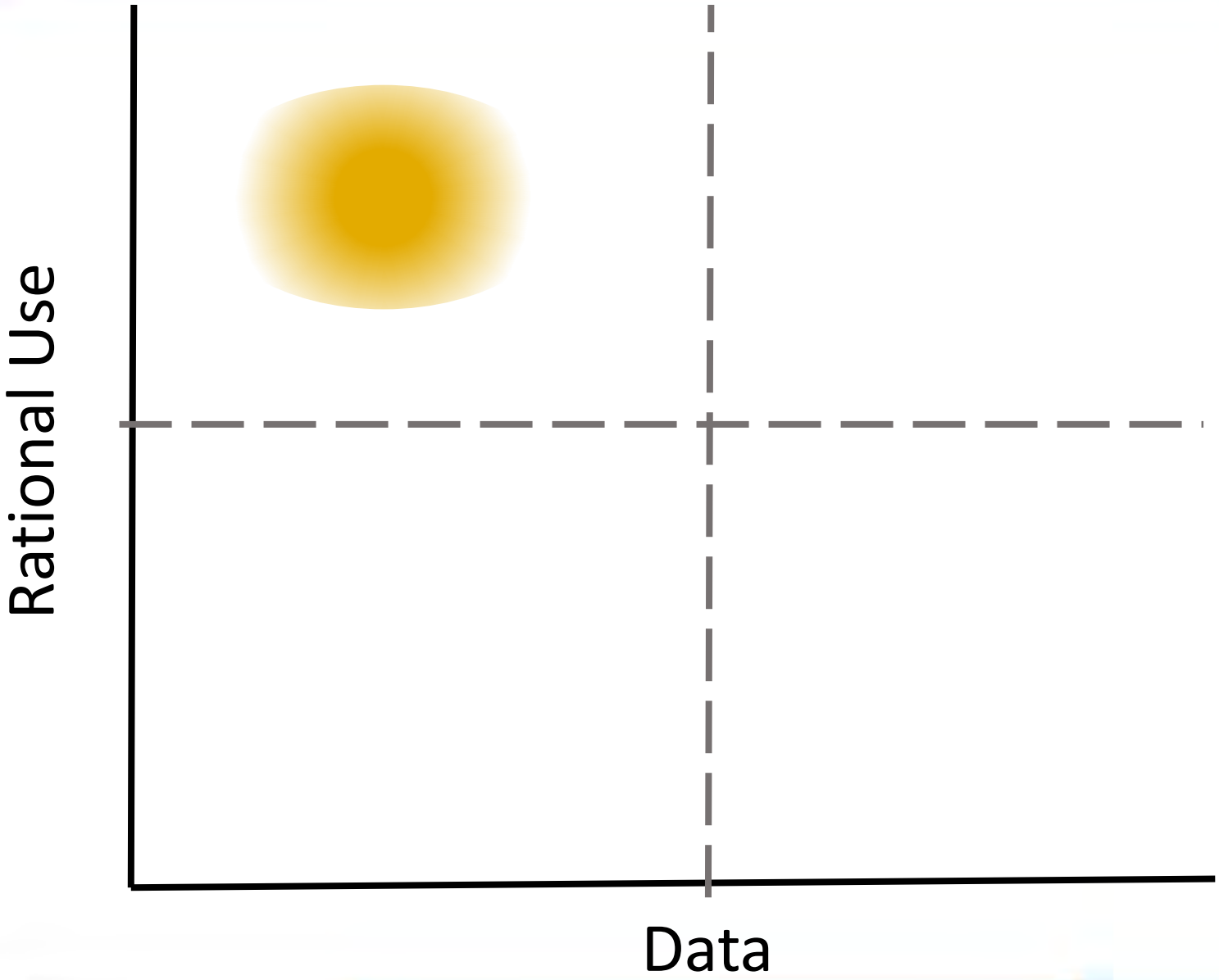
Regulatory Readiness: Case 1



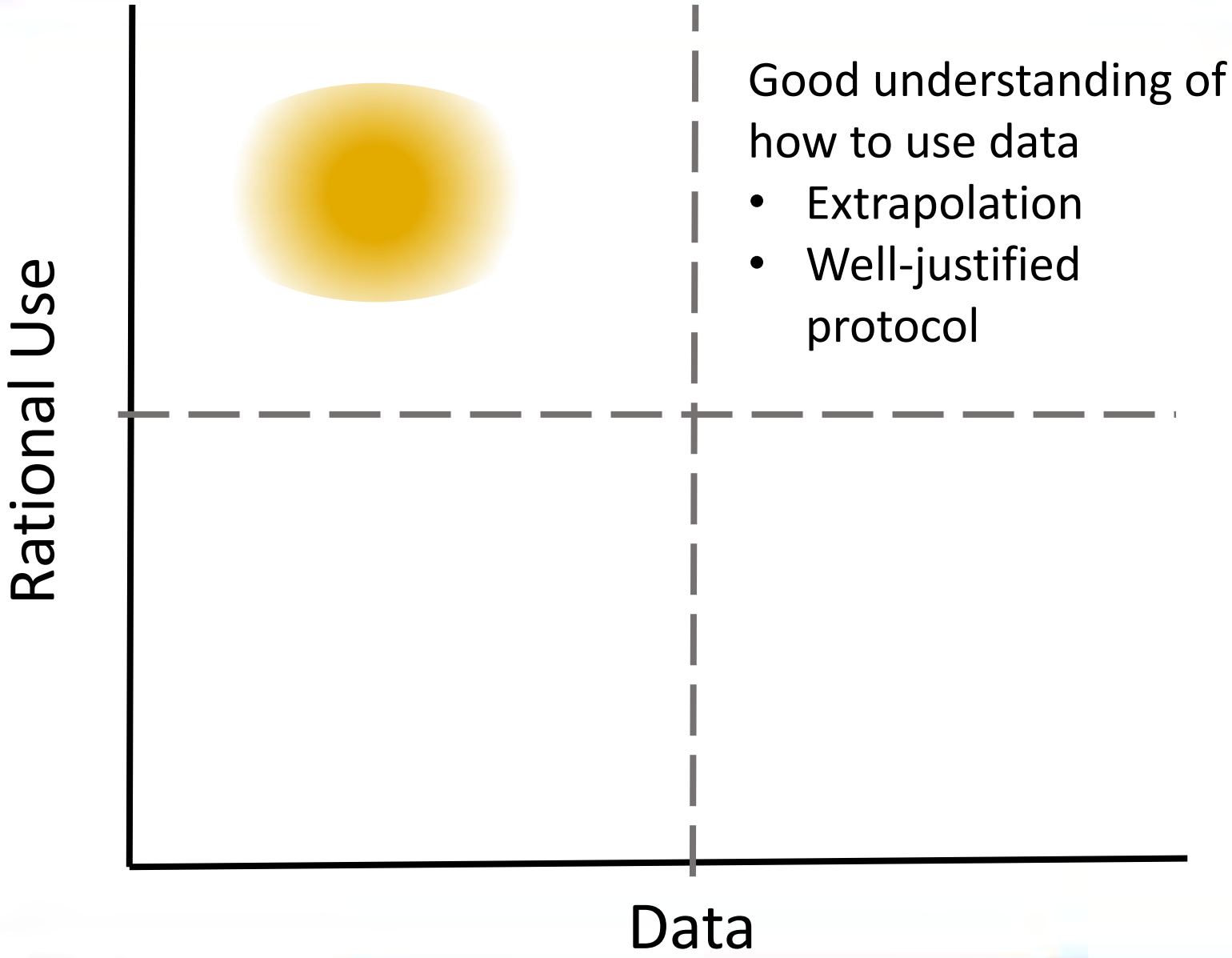
Regulatory Readiness: Case 1



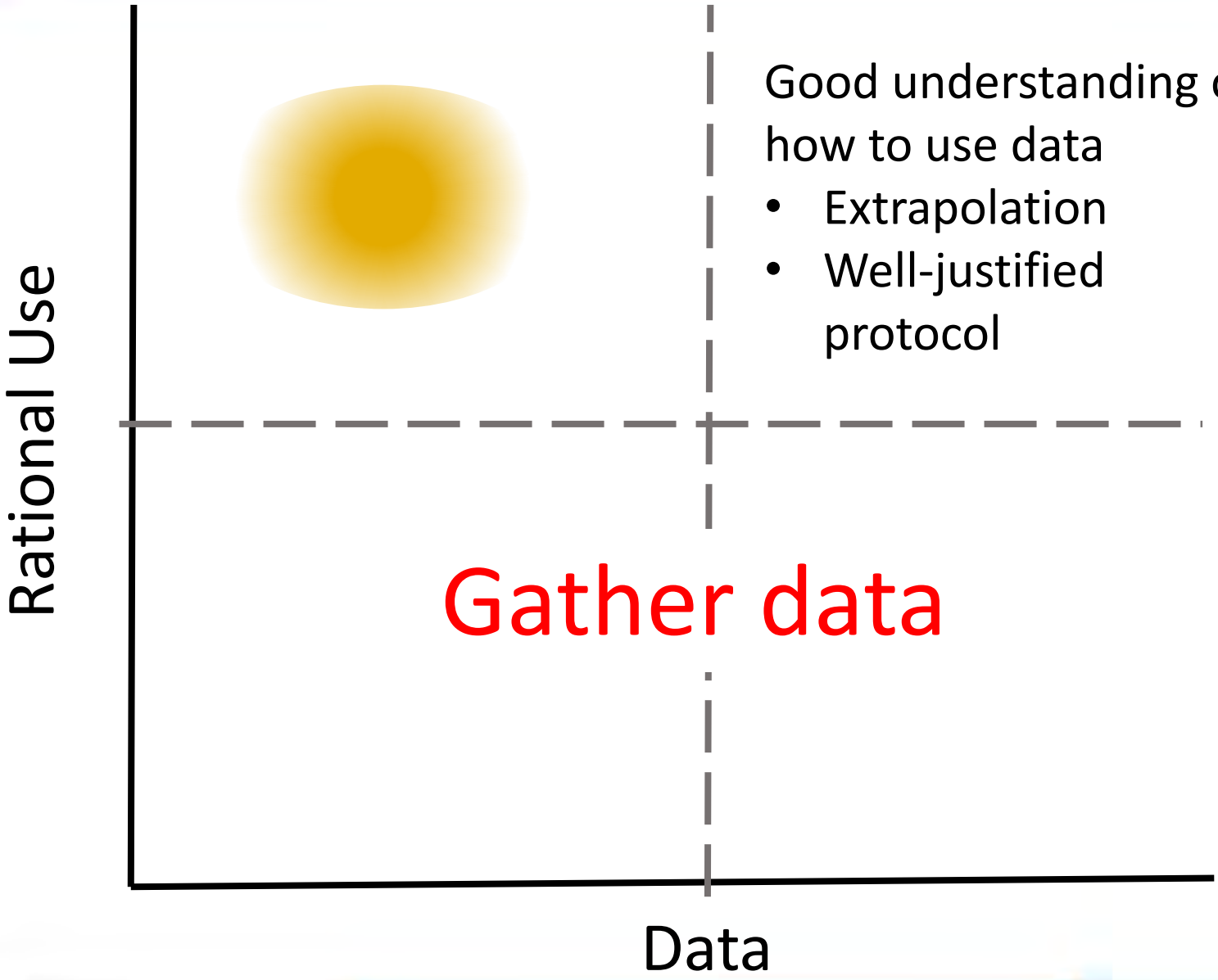
Regulatory Readiness: Case 2



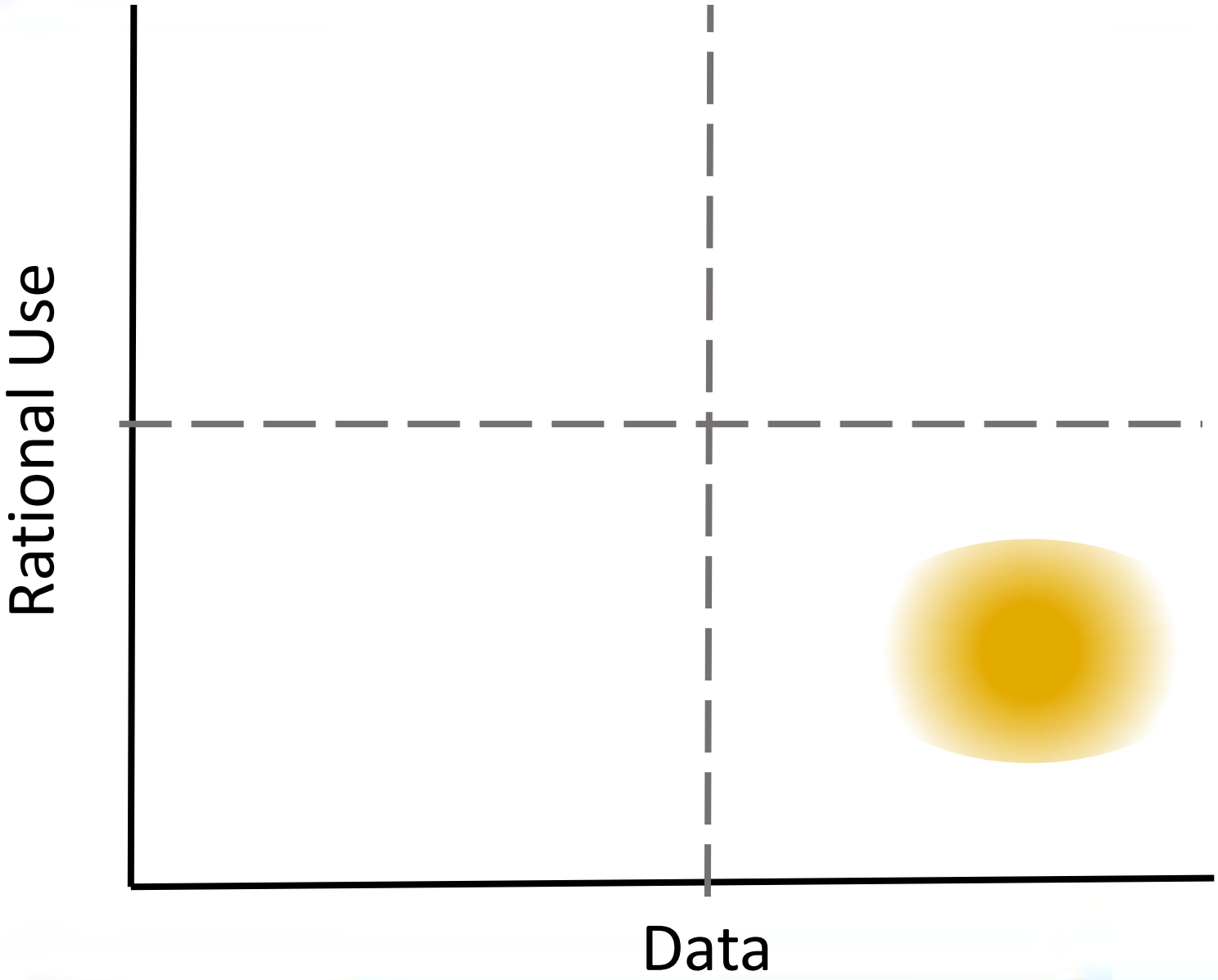
Regulatory Readiness: Case 2



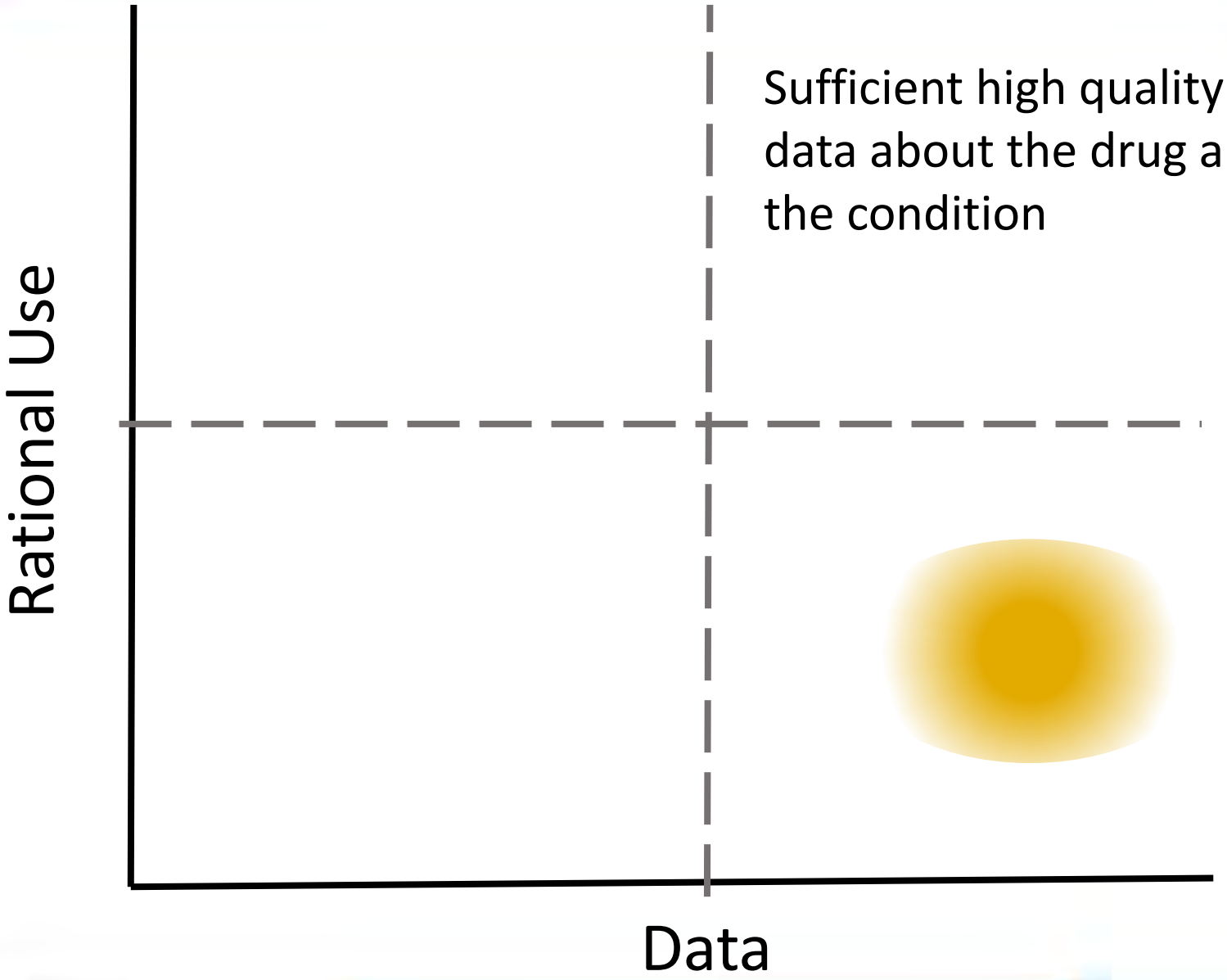
Regulatory Readiness: Case 2



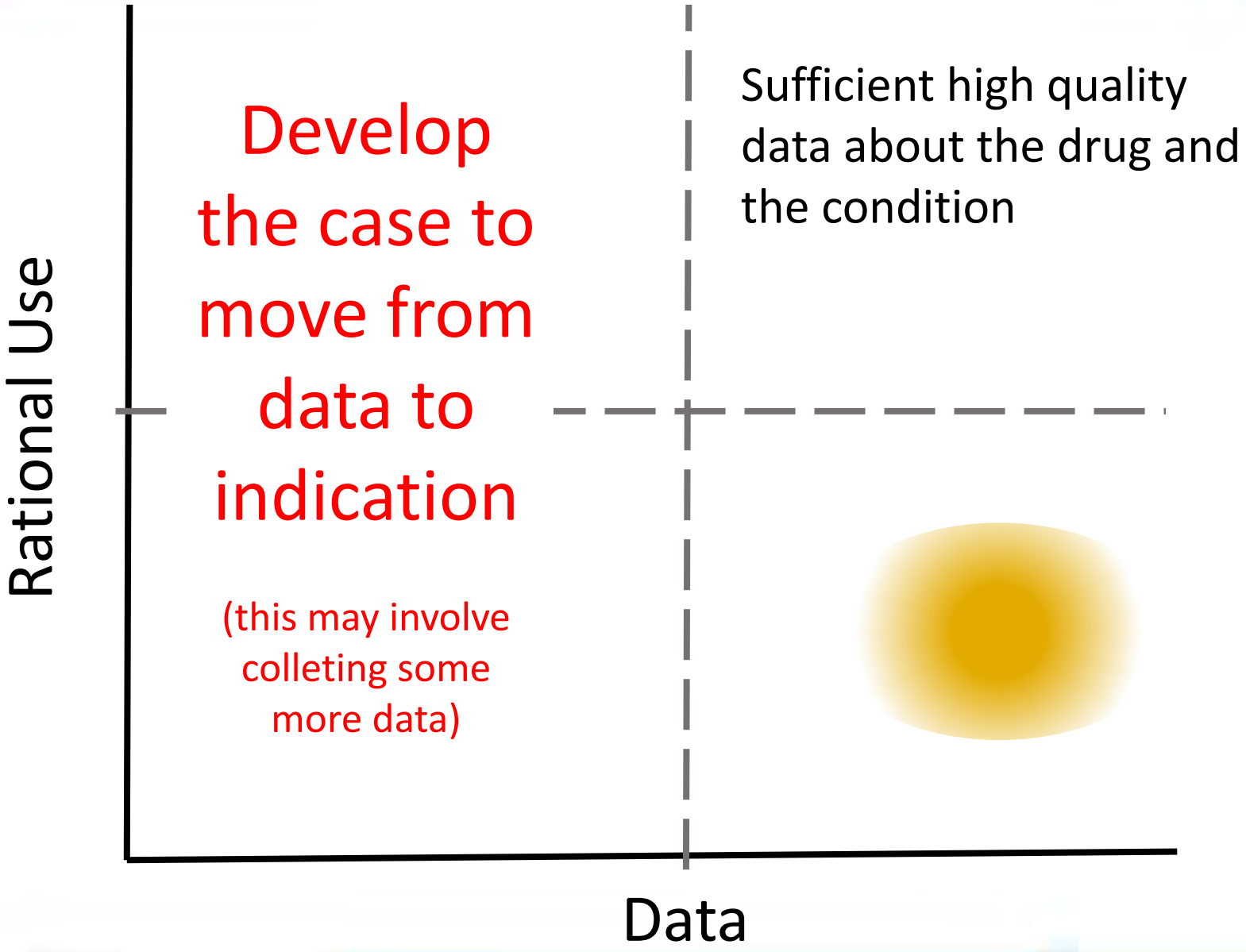
Regulatory Readiness: Case 3



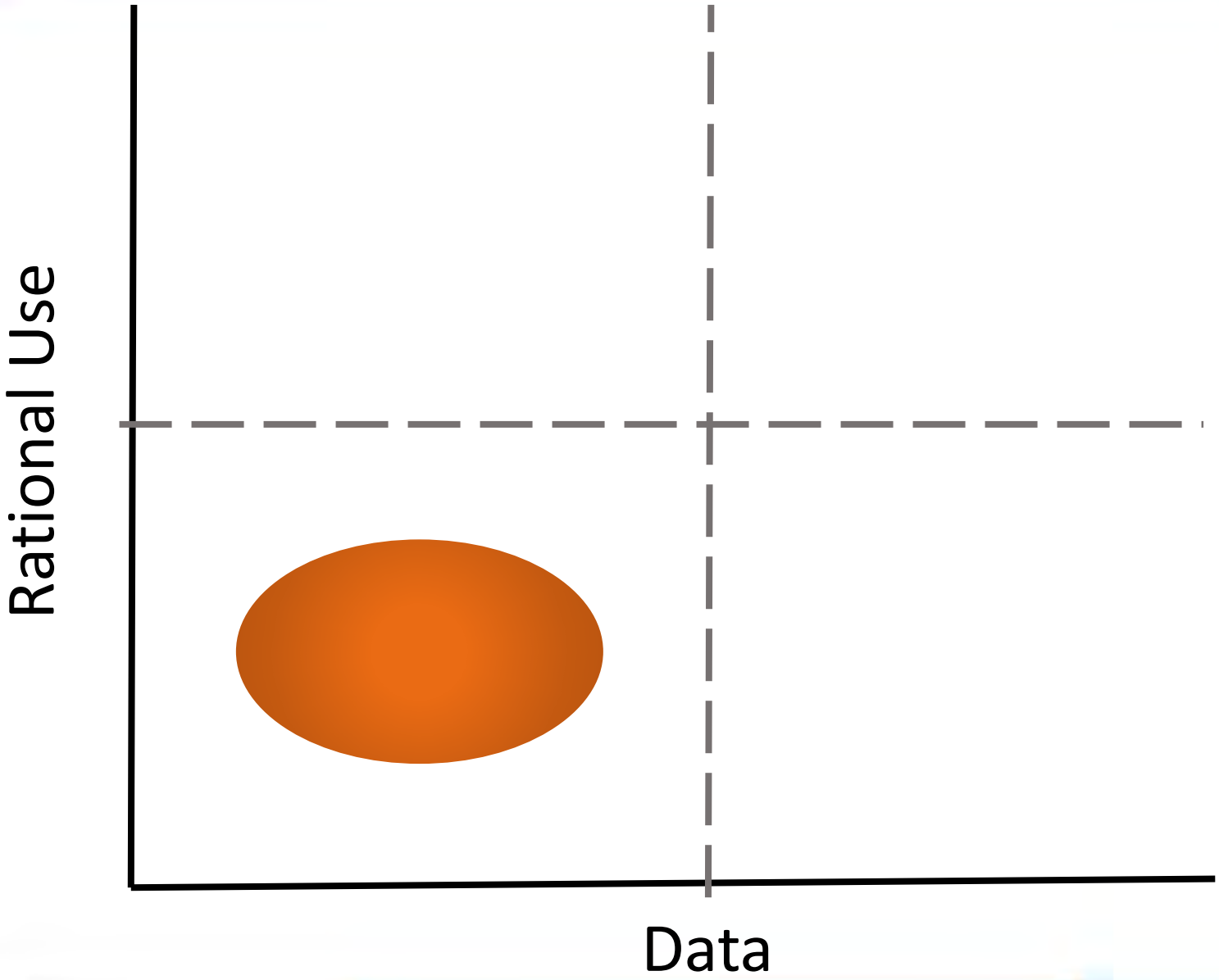
Regulatory Readiness: Case 3



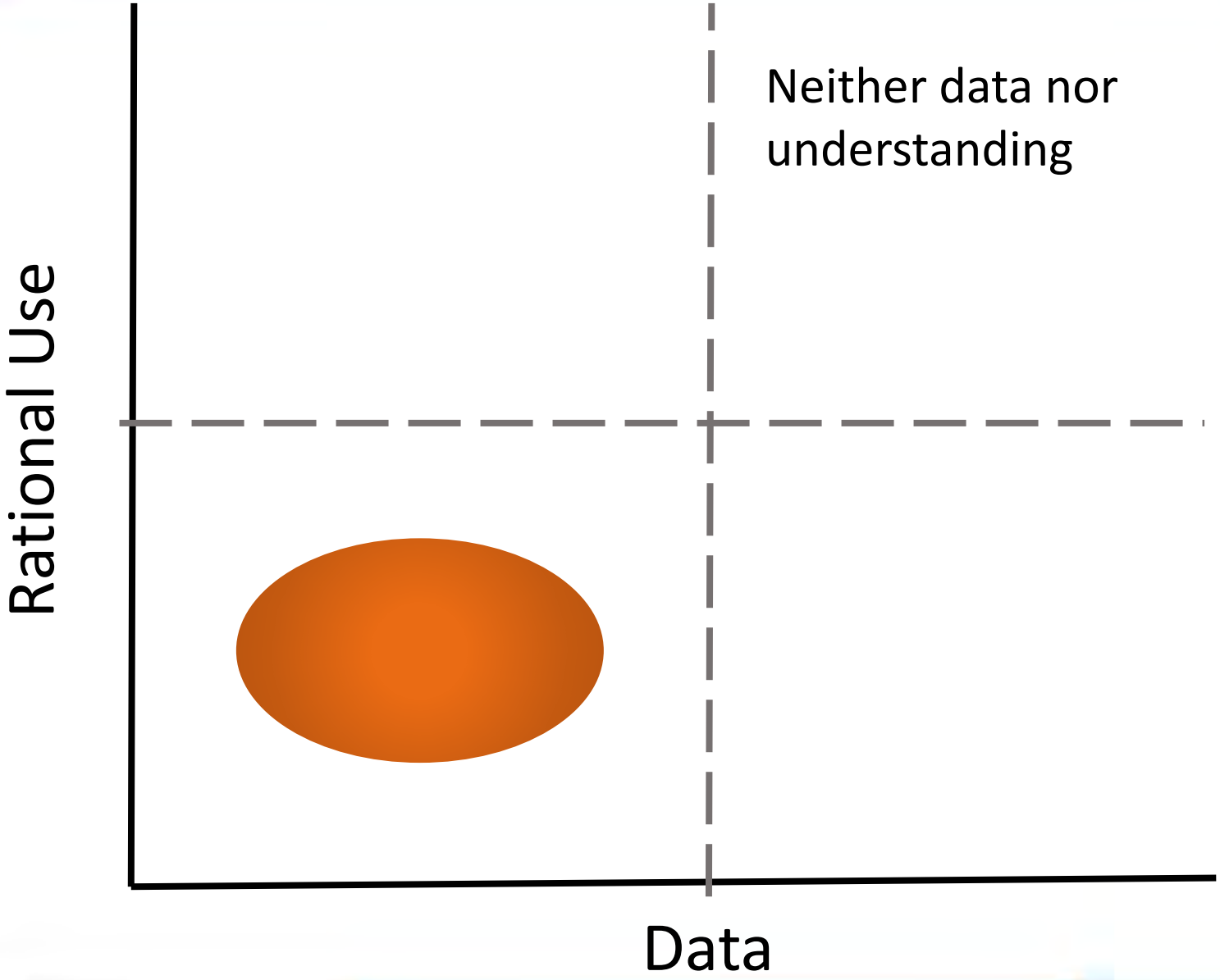
Regulatory Readiness: Case 3



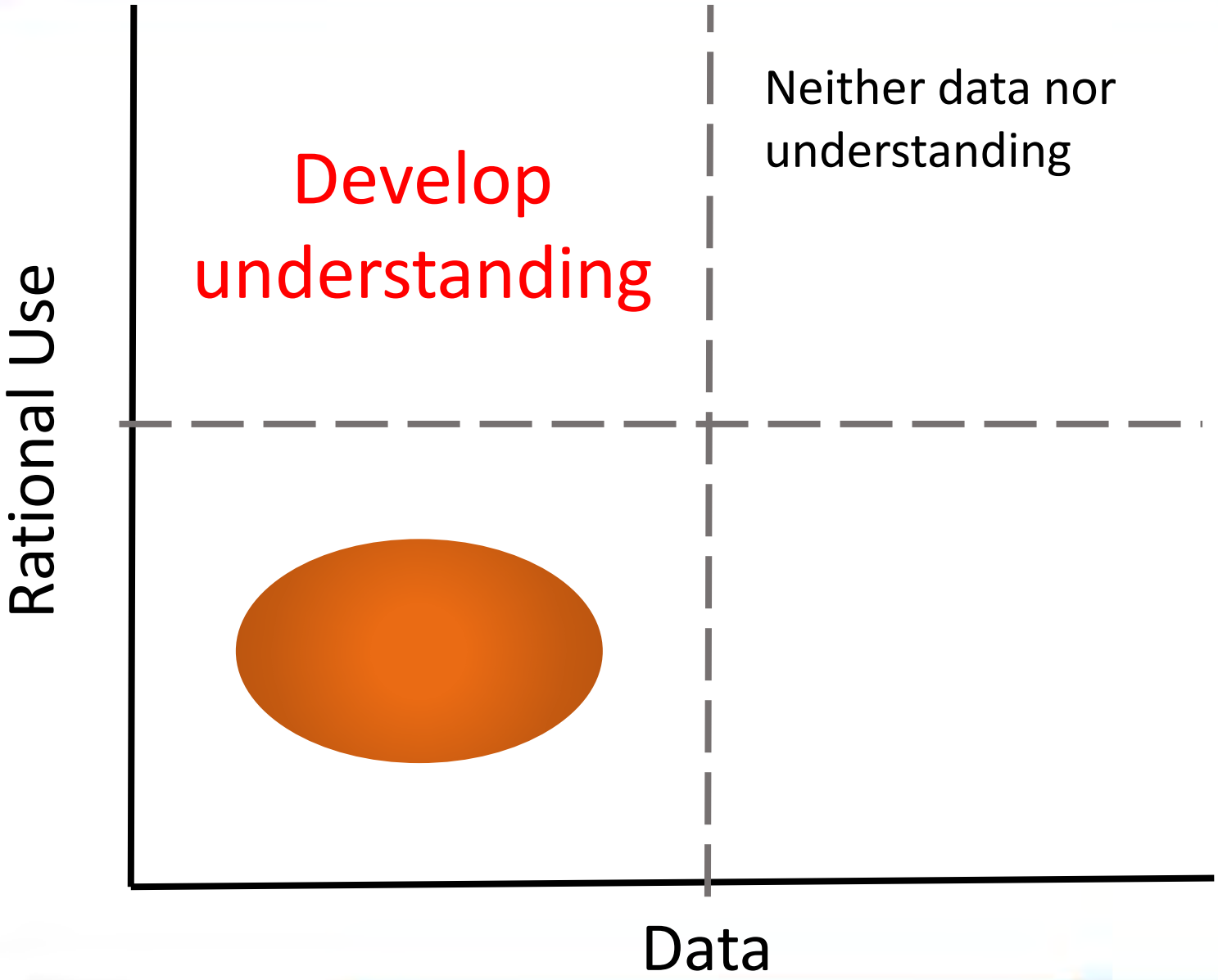
Regulatory Readiness: Case 4



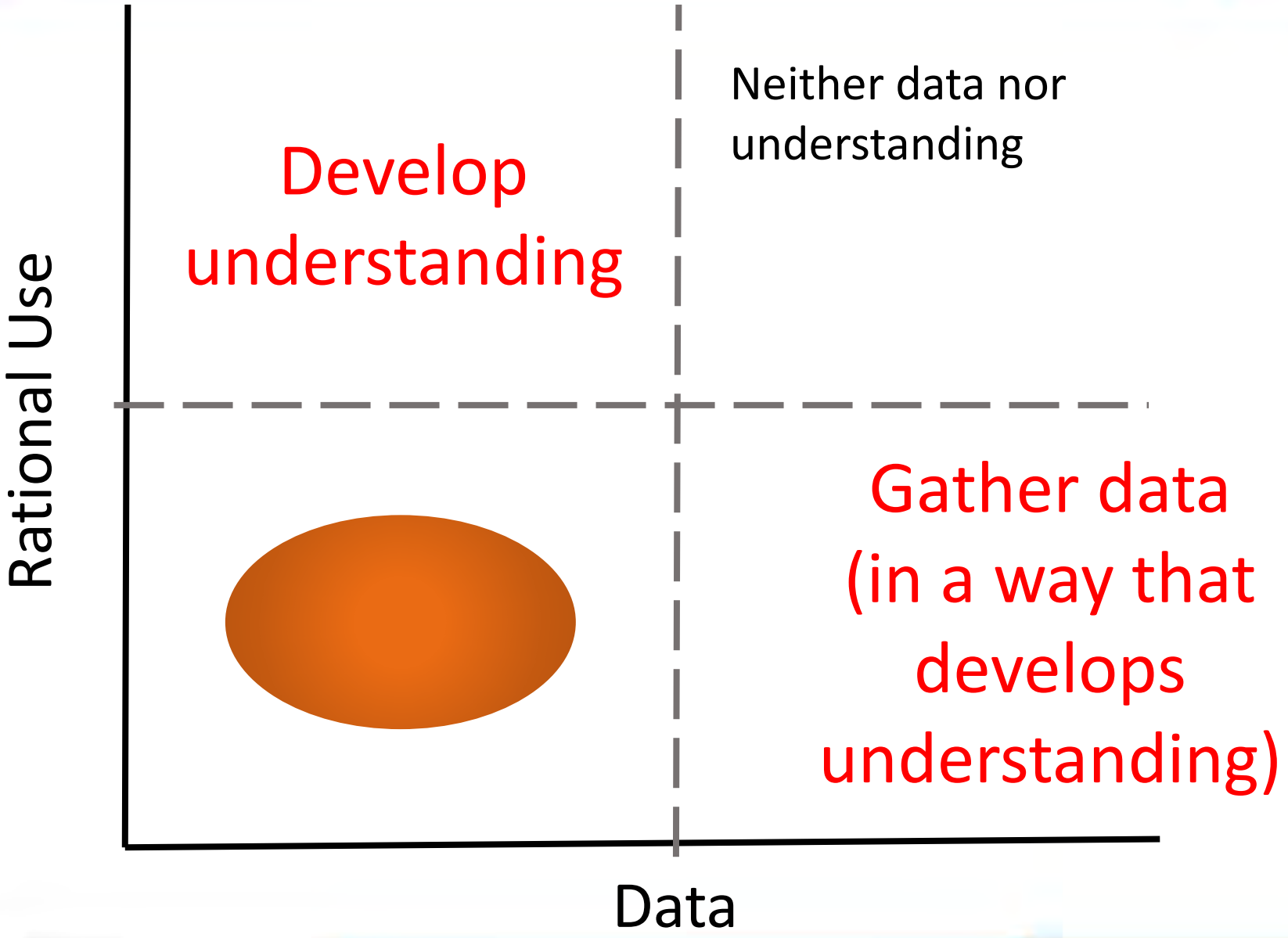
Regulatory Readiness: Case 4



Regulatory Readiness: Case 4



Regulatory Readiness: Case 4



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

CHU Sainte-Justine
Le centre hospitalier universitaire mère-enfant

Pour l'amour des enfants

Université de Montréal

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

	Total n	No Treatment n=249	Any Treatment *n* = 1138	Vasopressor Treatment *n* = 470
Gestnl age, wk		Proportion of Infants, %	*P* = .001	*P* .0005
23	85	7	93	52
24	246	10	90	47
25	289	16	84	34
26	338	18	82	32
27	429	27	73	25

Variability in « any » Rx

Center	% Treated	Lowest MAP d1	OR	(95% CI)	Adjusted OR	(95% CI)
A	29	28	1		1c	
B	46	27	2	(1–4)	3	(1–6)
C	61	20	4	(2–7)	5	(2–10)
D	69	24	5	(3–9)	9	(5–18)
E	80	25	9	(5–20)	33	(14–80)
F	85	24	13	(6–27)	25	(11–56)
G	91	23	24	(11–50)	44	(19–102)
H	92	23	26	(13–52)	54	(25–118)
I	93	23	32	(7–145)	84	(17–404)
J	93	25	34	(15–78)	80	(32–

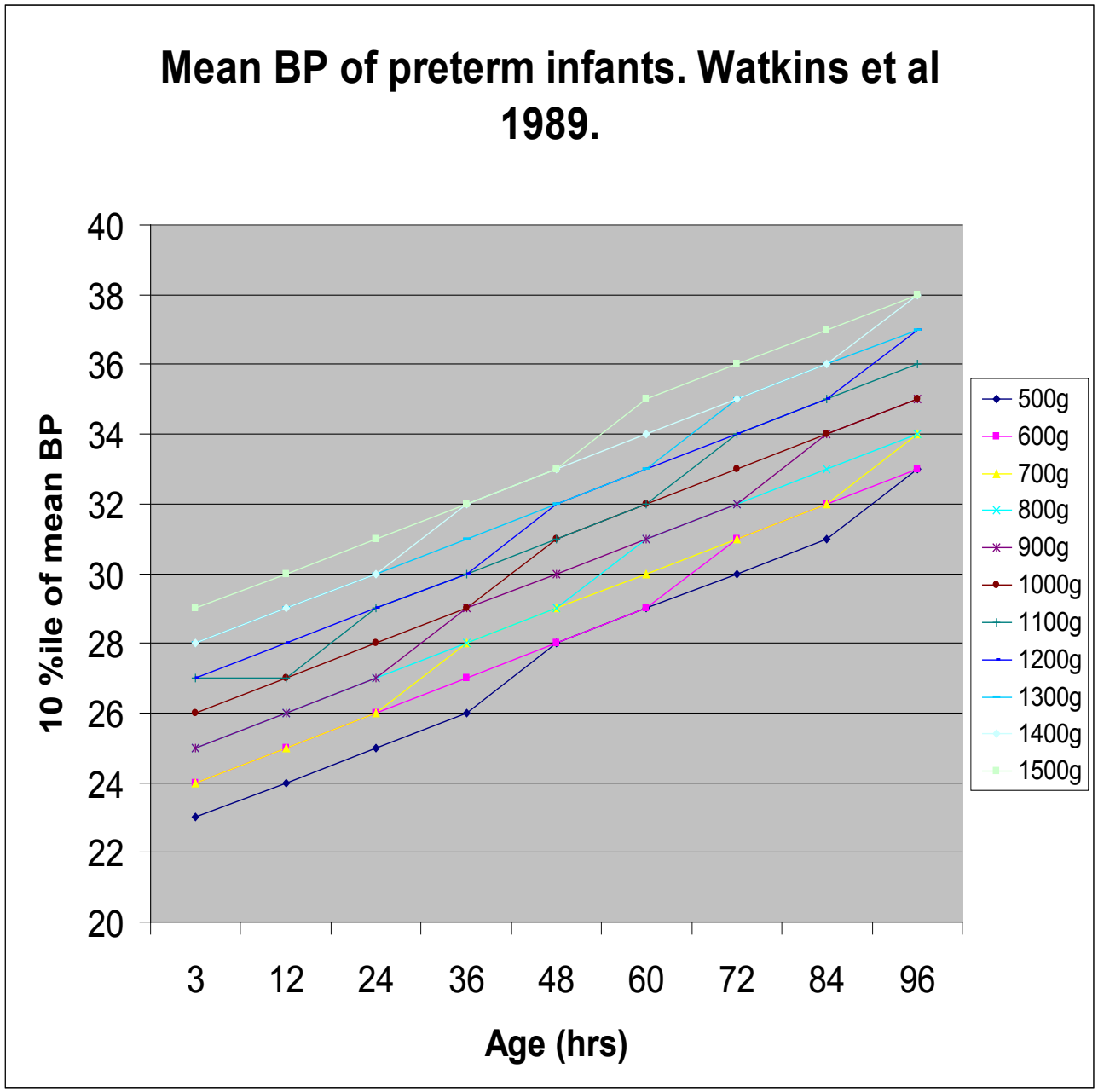
Variability in inotrope Rx

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

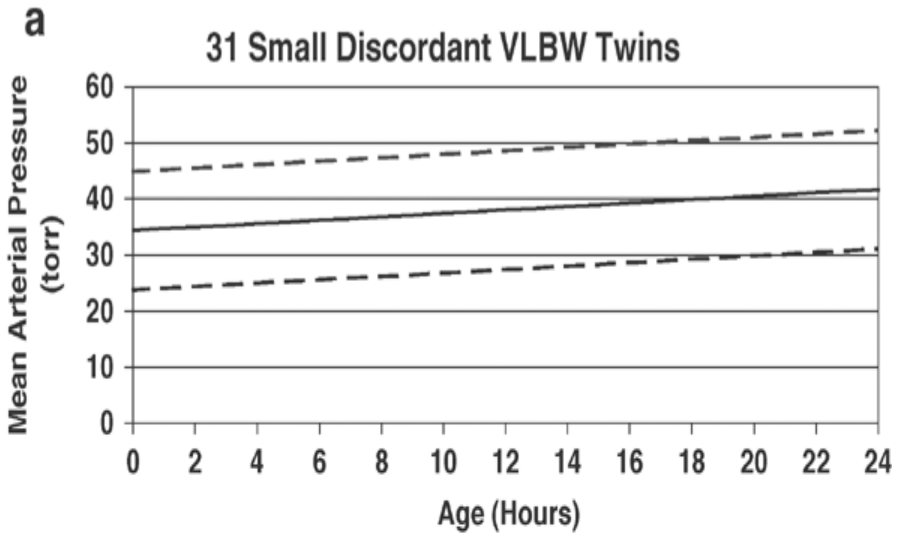
What normally happens?

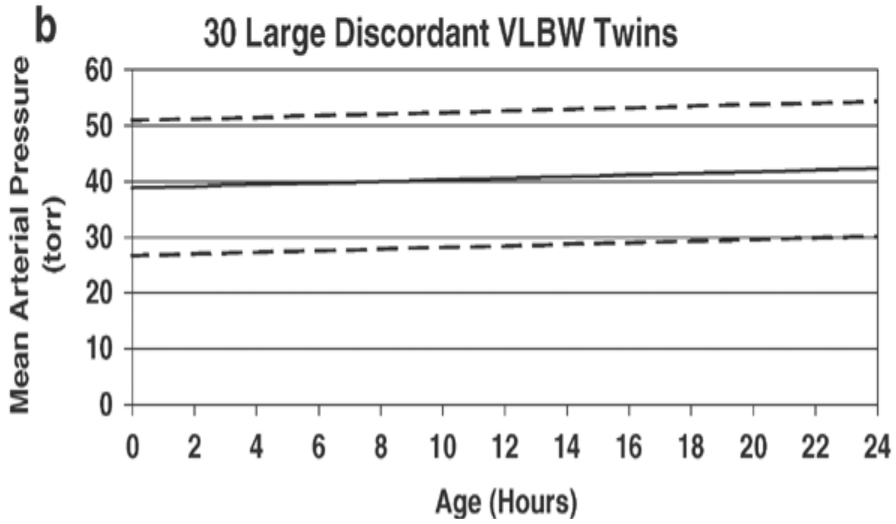
- Numerically low blood pressures are frequent in the first 3 days of life
- No clear correlation between “hypotension” and systemic perfusion
- Most “hypotension” due to low vascular resistance

- Spontaneous elevation of BP


Mean BP of preterm infants. Watkins et al 1989.
10 %ile of mean BP
40
38
36
34
32
30
28
26
24
22
20
3
12
24
36
48
60
72
84
96
Age (hrs)
500g
600g
700g
800g
900g
1000g
1100g
1200g
1300g
1400g
1500g

Both body weight and gestational age are important in determining BP after birth





Cordero L, et al. Mean Arterial Pressure in Very Low Birth Weight (801 to 1500 g) Concordant and Discordant Twins During the First Day of Life. J Perinatol. 2003;23(7):545-51.

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

Faust K, et al. Short-term outcome of very-low-birthweight infants with arterial hypotension in the first 24 h of life. Arch dis childh: F&N ed. 2015;100(5):F388-92.

Independent variable	Dependent variable		
	IVH	BPD	Death
Gestational age (week)	**0.76 (0.72 to 0.80) <0.001**	**0.71 (0.67 to 0.75) <0.001**	**0.69 (0.62 to 0.77) <0.001**
Female gender	0.86 (0.72 to 1.03) 0.100	**0.61 (0.51 to 0.75) <0.001**	**0.64 (0.44 to 0.94) 0.022**
Multiple birth	**1.28 (1.05 to 1.55) 0.013**	**0.75 (0.60 to 0.93) 0.008**	1.32 (0.88 to 1.97) 0.177
Small for gestational age (<10th percentile)	**0.65 (0.47 to 0.88) 0.006**	**2.59 (2.00 to 3.37) <0.001**	**2.86 (1.80 to 4.55) <0.001**
Maternal steroid treatment	**0.64 (0.47 to 0.87) 0.004**	1.13 (0.80 to 1.60) 0.488	0.68 (0.38 to 1.24) 0.206
Maternal treatment with antibiotics	0.86 (0.69 to 1.06) 0.160	0.88 (0.70 to 1.11) 0.266	1.07 (0.68 to 1.69) 0.779
Maternal treatment with tocolytics	1.14 (0.93 to 1.40) 0.220	0.93 (0.75 to 1.15) 0.498	1.13 (0.73 to 1.75) 0.574
Birth due to amniotic infection	0.90 (0.72 to 1.13) 0.382	**0.71 (0.55 to 0.91) 0.006**	0.70 (0.43 to 1.13) 0.574
Birth due to placental abruption	**1.40 (1.02 to 1.90) 0.036**	1.00 (0.70 to 1.42) 0.987	0.78 (0.38 to 1.59) 0.487
Inborn	1.01 (0.55 to 1.85) 0.982	1.14 (0.56 to 2.31) 0.721	1.03 (0.32 to 3.35) 0.964
Apgar <7 at 5 min of age	**1.54 (1.24 to 1.91) <0.001**	1.08 (0.85 to 1.37) 0.516	**1.63 (1.08 to 2.44) 0.020**
Umbilical artery pH <7.1	1.43 (0.89 to 2.31) 0.140	0.76 (0.43 to 1.33) 0.330	1.12 (1.09 to 5.60) 0.801
Early-onset sepsis	**2.06 (1.16 to 3.67) 0.014**	1.32 (0.71 to 2.45) 0.378	**2.47 (1.09 to 5.60) 0.031**
Treatment with inotropes during the first 24 h of life	**1.86 (1.43 to 2.42) <0.001**	**2.40 (1.82 to 3.16) <0.001**	1.48 (0.92 to 2.38) 0.109
Lowest mean arterial blood pressure during the first 24 h of life (mm Hg)	**0.97 (0.96 to 0.99) 0.003**	**0.96 (0.94 to 0.98) <0.001**	**0.94 (0.90 to 0.98) 0.003**

Logan JW, et al, ELGAN Investigators: ***Early postnatal hypotension and developmental delay at 24 months of age among extremely low gestational age newborns.*** *Archives of Disease in Childhood - Fetal and Neonatal Edition 2011, 96(5):F321-F328.*

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

Exposures and BSID outcomes		Lowest ¼ile MAP§	Vaso-pressor¶	Labile MAP†	BSID < 70		N
					MDI	PDI	
Lowest ¼ile MAP§	Yes		45	42	30	34	206
	No		20	19	25	31	739
Vasopressor ¶	Yes	38		30	31	35	244
	No	16		22	25	31	701
Labile MAP †	Yes	39	32		28	30	225
	No	17	24		26	32	720
BSID MDI < 70	Yes	25	30	26		70	250
	No	21	24	23		20	695
BSID PDI < 70	Yes	24	28	22	58		300
	No	21	25	25	12		645
Maximum number of infants		206	244	225	250	300	945
Row percent		22	26	24	26	32	

§ 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

Dempsey EM, Barrington KJ. Treating hypotension in the preterm infant: when and with what: a critical and systematic review. J Perinatol. 2007;27(8):469-78.

- 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

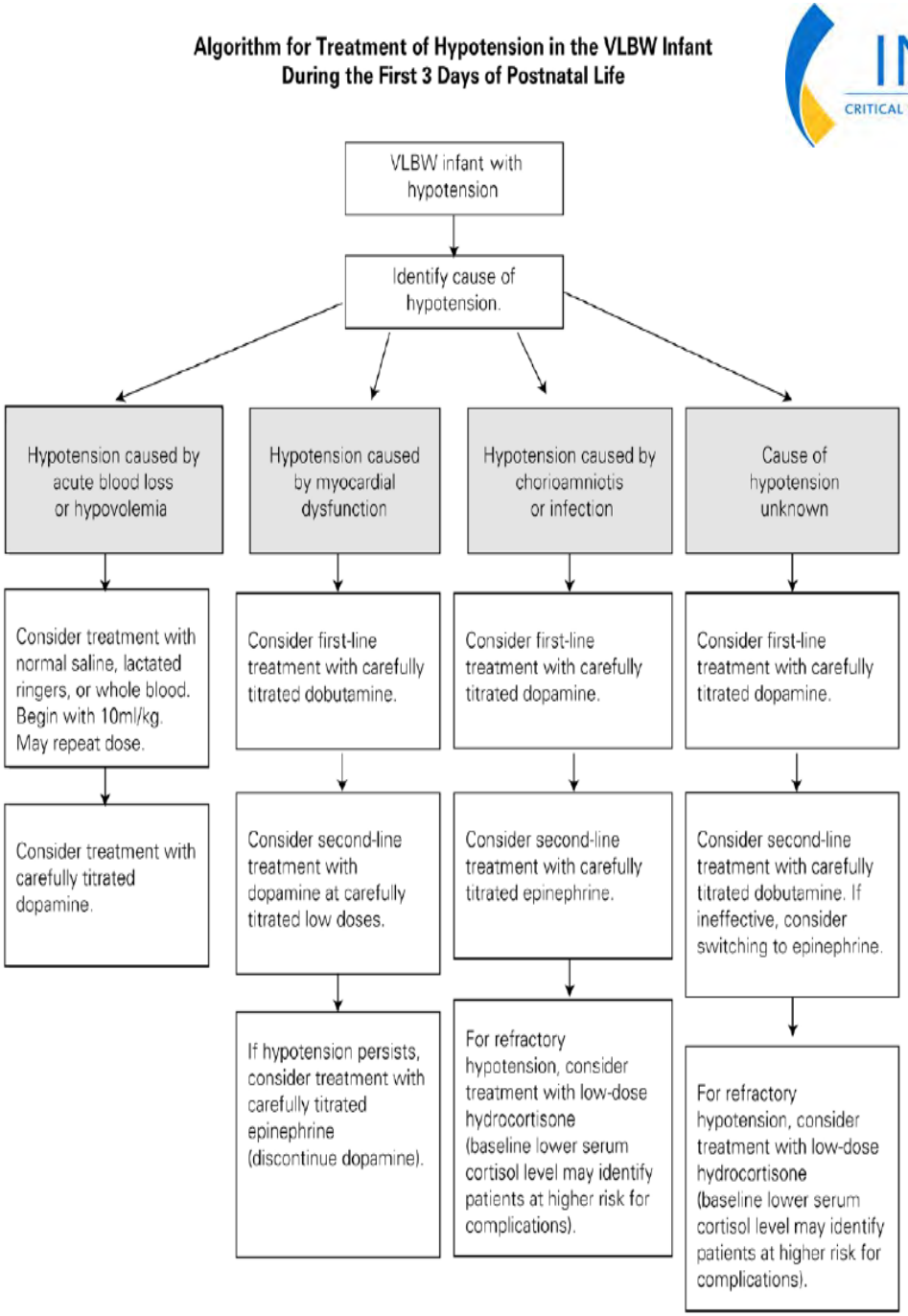
- None of the publications satisfied *a priori* criteria
- 3 studies had good data on the incidence of IVH and frequent evaluation of BP, all limited.

- 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.

First Author	Number of infants	BP measure-ment Method	IVH ascer-tainment	Main findings
Bada HS[114]	VLBW infants, 72 without and 28 with greater than grade 1 IVH.	BPs from UACs recorded every minute (then averaged over 15 minutes),	Head U/S at 6, 12 and 24 hours, then daily for 7 days. Tapes were read blindly.	Norms for groups >1000g and <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.
Miall-Allen VM 1987 [119]	33 infants, 26 to 30 wk gestation; birth wt ranged 700-1700g.	Continuous BP measuremen t from arterial line	Ultrasounds "at least daily" by examiner unaware of BPs.	Albumin given to an unknown number of infants, 7 received dobutamine or dopamine or both. **Sustained mean BP <30mmHg significantly associated with major IVH** or PVL, (n= 9).
Watkins AMC[40]	131 VLBW infants for 4 days. 58 infants with IVH, 22 with ischaemic lesions.	BP from art. lines for first 4 d of life. Data taken retrospective ly from charts.	Daily cranial ultrasounds for 4 days, then weekly. Not blinded.	Developed 10th percentiles for 100 gram birth weight groups at each 12 hours of life **Hypotension <10th percentile for more than 2hours was associated with decreased survival and increased IVH**. Some infants received blood products or dopamine, data not given.

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

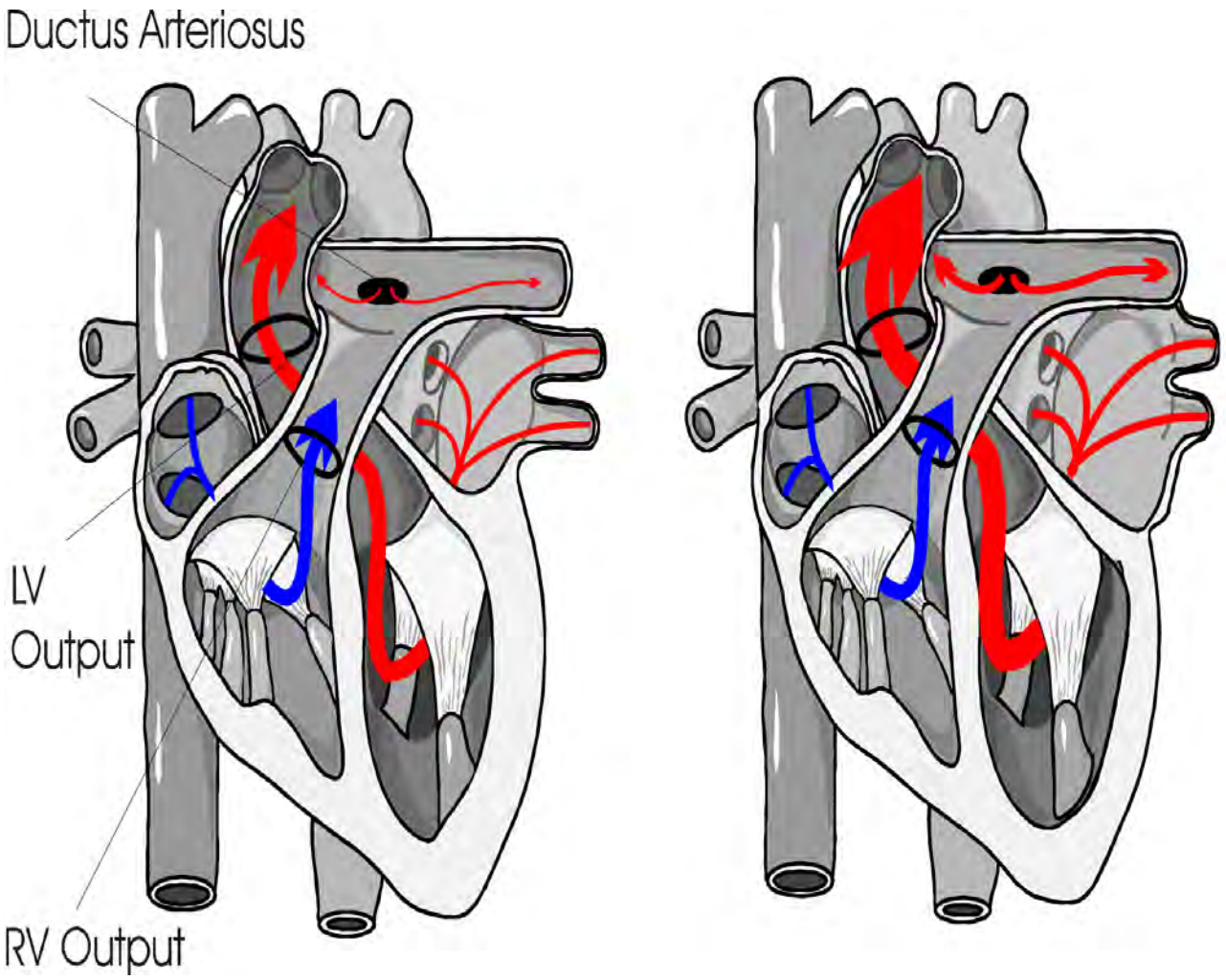
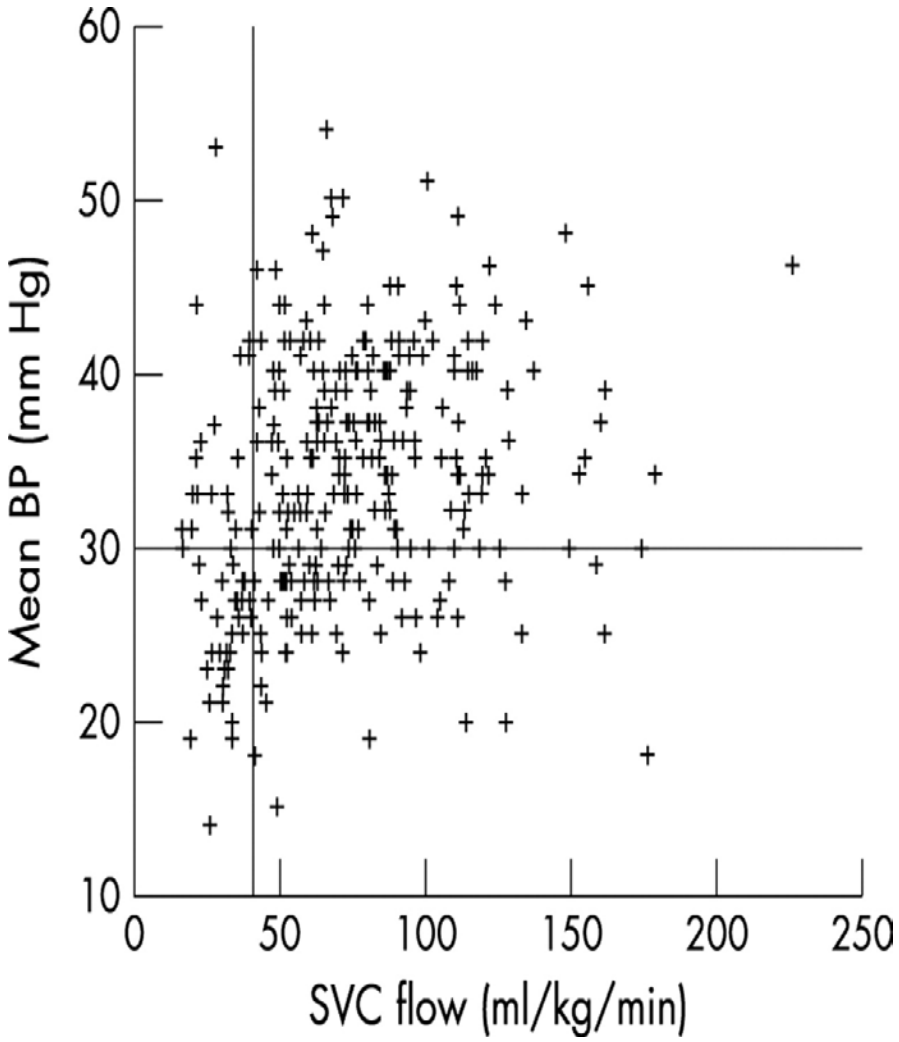


Figure 3 Scatter plot of mean blood pressure (BP) against superior vena cava (SVC) flow for all observations. Reference lines represent SVC flow of 41 ml/kg/min and mean BP of 30 mm Hg.



Osborn, D A et al. Arch. Dis. Child. Fetal Neonatal Ed. 2004;89:F168-F173

Functional Echocardiography

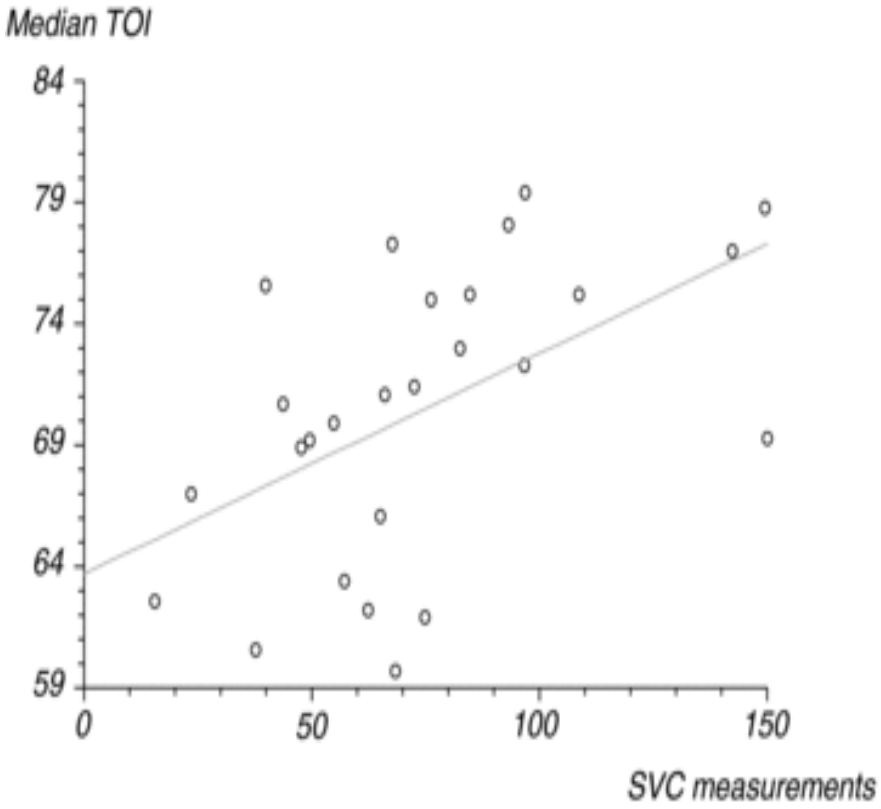
- Threshold of 40 mL/kg/min well-supported but a bit simplistic
  - Ignores HgB, SpO2, VO2
- Not simple to measure SVC flow
- Inter-observer variability
- Intermittent

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



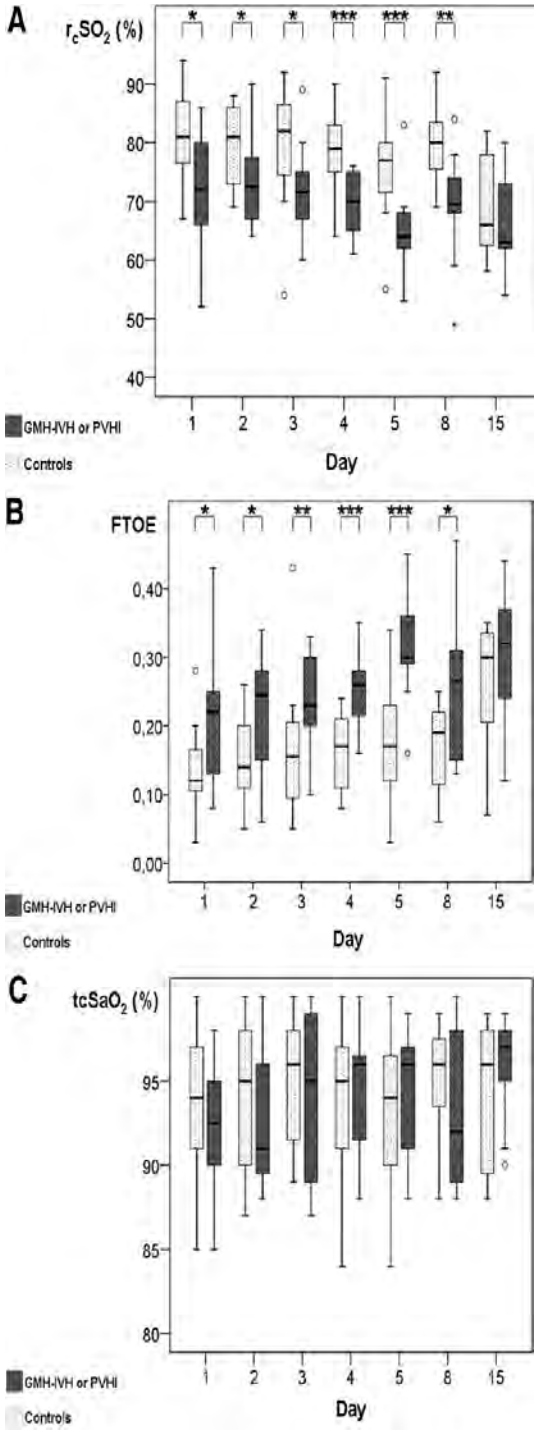


Figure 1. The course of rcSO2 (A), FTOE (B), and tcSaO2 (C) in preterm infants with GMH-IVH or PVHI versus a preterm control group.

Verhagen E A et al. Stroke 2010;41:2901-2907

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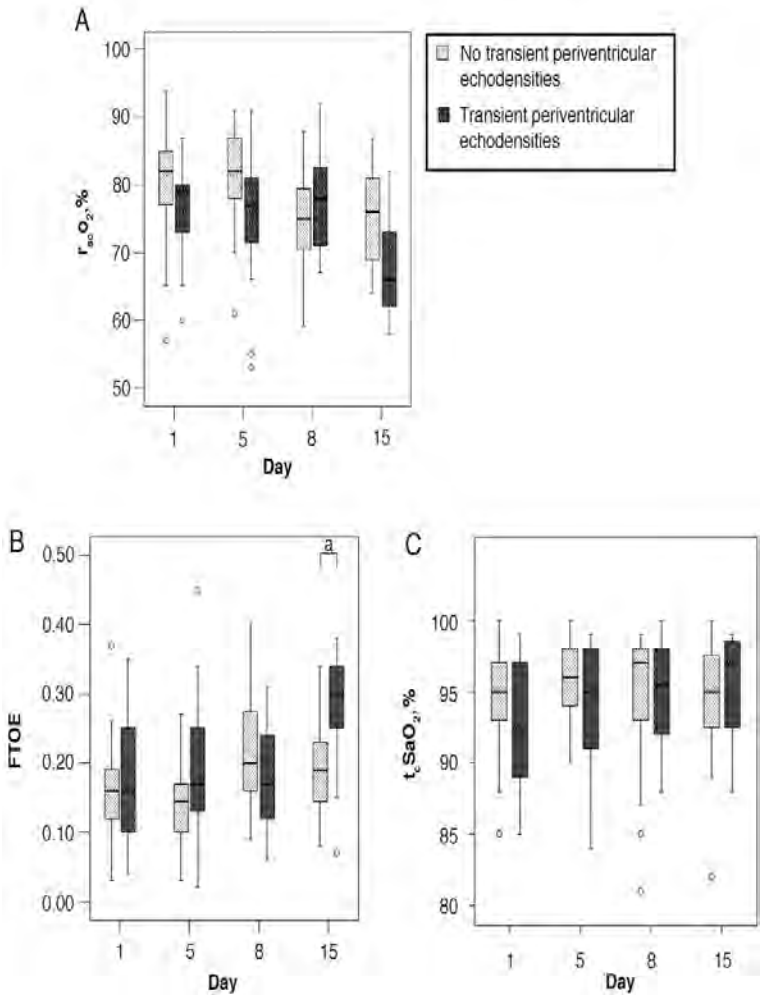
American Heart Association
Learn and Live

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. a Differences between the 2 groups (P < .05, TPE versus no TPE).



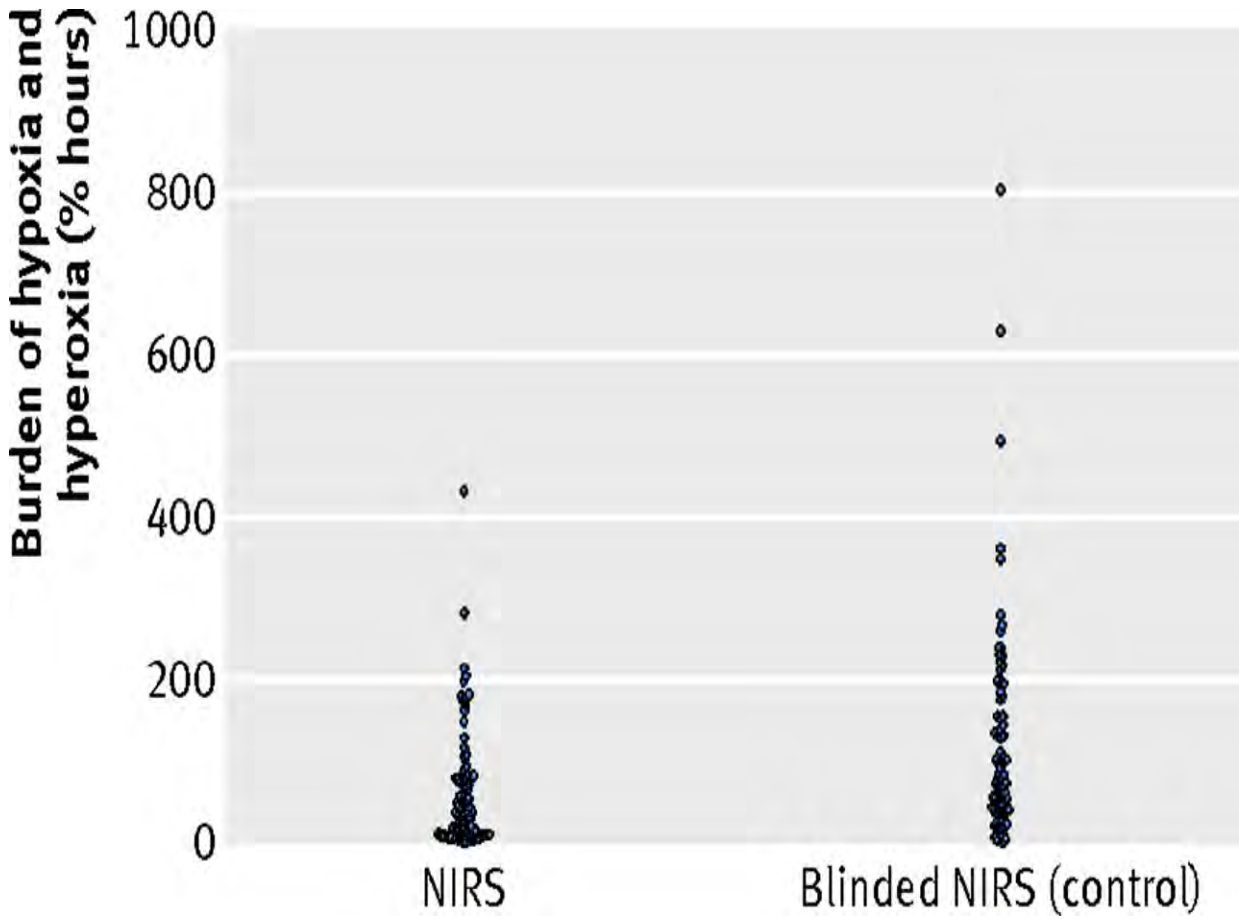
Verhagen E A et al. Pediatrics 2009;124:294-301

Can we affect the cerebral NIRS signal?

- Hyttel-Sorensen S, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. BMJ. 2015;350:g7635.
- 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.



Simon Hyttel-Sorensen et al. BMJ 2015;350:bmj.g7635

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?

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International Neonatal Consortium

Hemodynamic Adaptation: Challenges in Neonatal Drug Studies

Heike Rabe
Brighton & Sussex Medical School
University of Sussex
University of Brighton

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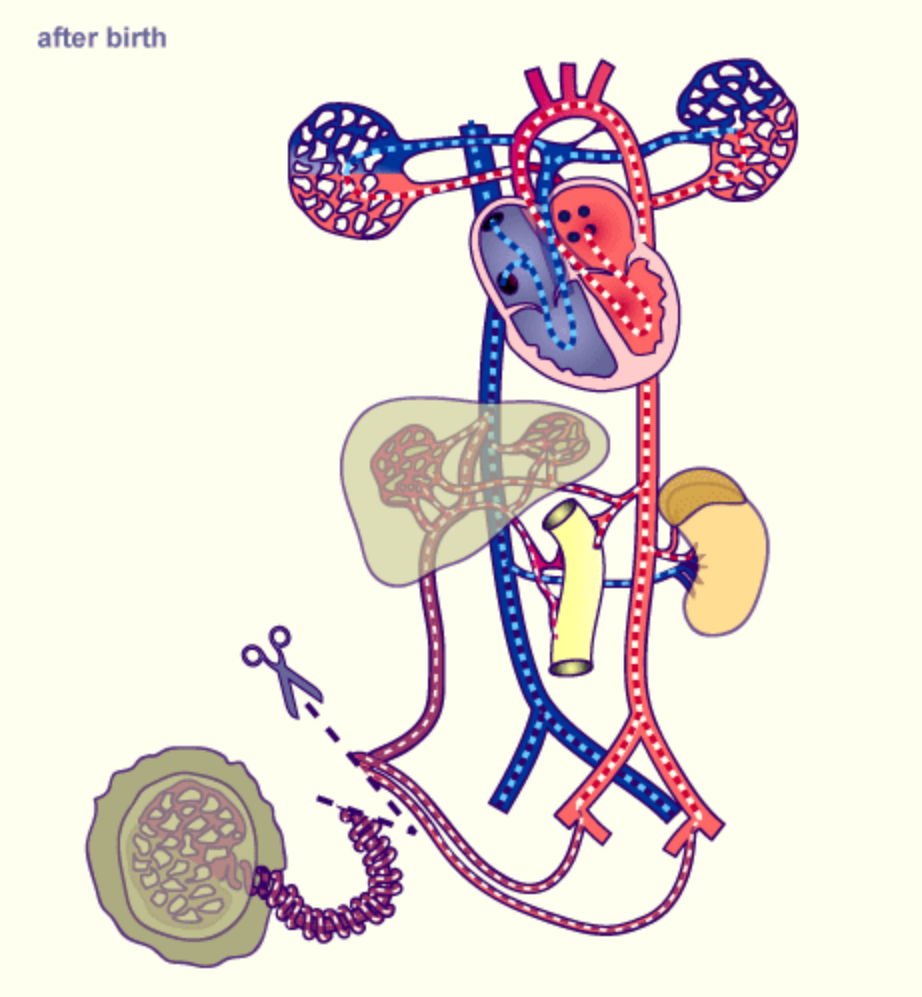
Postnatal Changes in Circulation

- 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

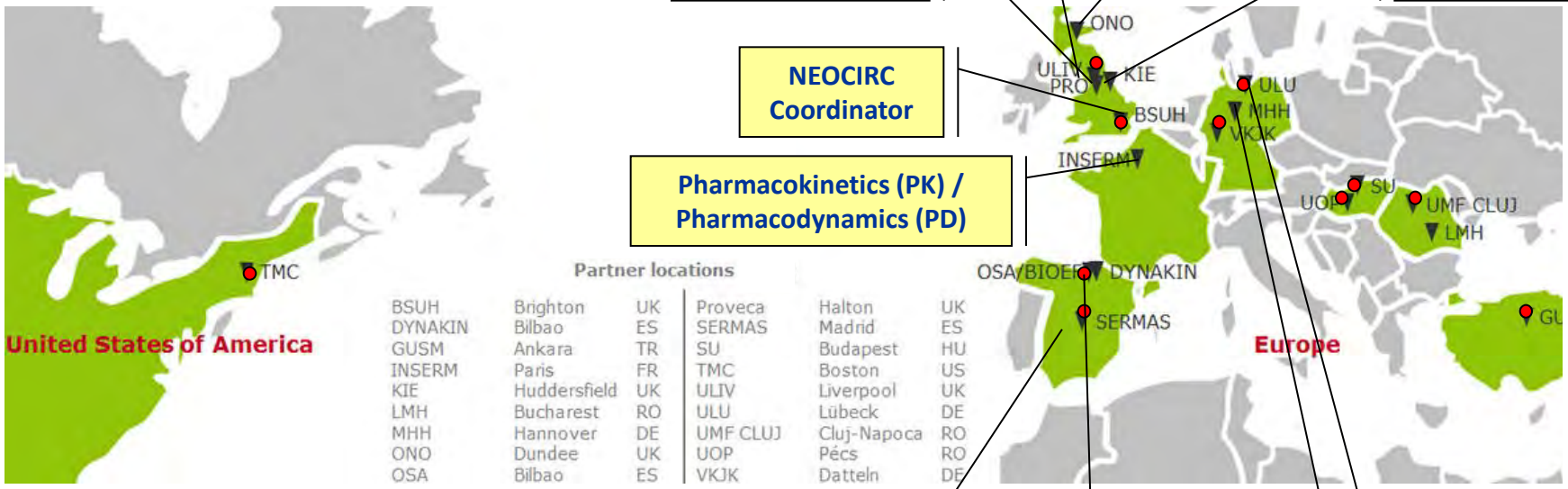
  *Linderkamp 1981

Outcome measure: *Survival without brain damage*

neocirculation
an international research consortium dedicated to exploring and improving the newborn circulation

SEVENTH FRAMEWORK PROGRAMME

- 8 countries
- 18 partners



Partner locations

BSUH	Brighton	UK	Proveca	Halton	UK
DYNAKIN	Bilbao	ES	SERMAS	Madrid	ES
GUSM	Ankara	TR	SU	Budapest	HU
INSERM	Paris	FR	TMC	Boston	US
KIE	Huddersfield	UK	ULIV	Liverpool	UK
LMH	Bucharest	RO	ULU	Lübeck	DE
MHH	Hannover	DE	UMF CLUJ	Cluj-Napoca	RO
ONO	Dundee	UK	UOP	Pécs	RO
OSA	Bilbao	ES	VKJK	Datteln	DE

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

Hemodynamic Adaptation

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

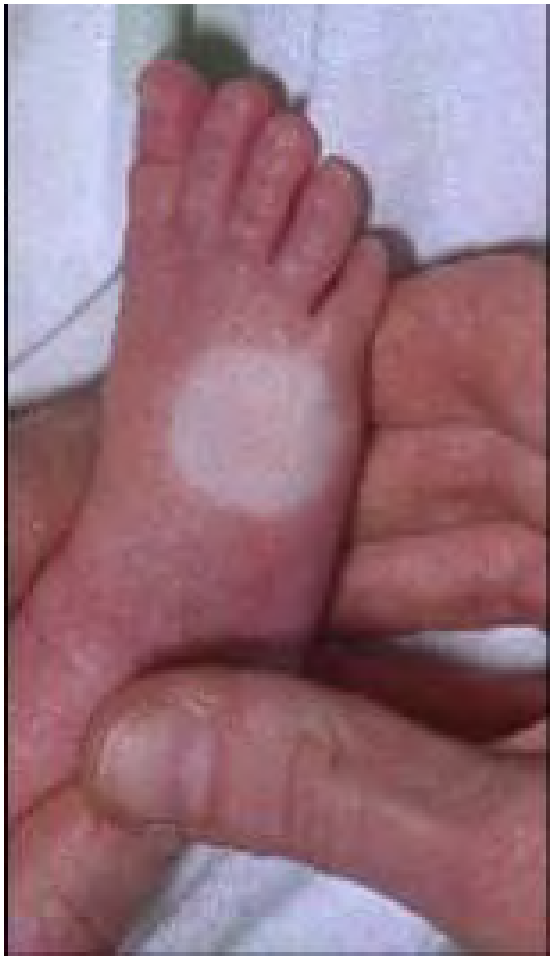
  - Consider whether short term biomarkers change?

Non-invasive Assessments of Neonatal Haemodynamics

- Clinical examination:
  - capillary refilling time
  - skin colour
  - blood pressure
  - urine output
- NIRS:
  - regional oxygenation
- Echocardiography and Doppler:
  - Cardiac output
  - Superior vena cava flow
- Laser Doppler and White light Spectroscopy:
  - peripheral vasomotion
- Pulse Oxymetry:
  - oxygenation and perfusion index
- Biochemical:
  - 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



Hemodynamic Adaptation: Predictive Value of Capillary Refill Time

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

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

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

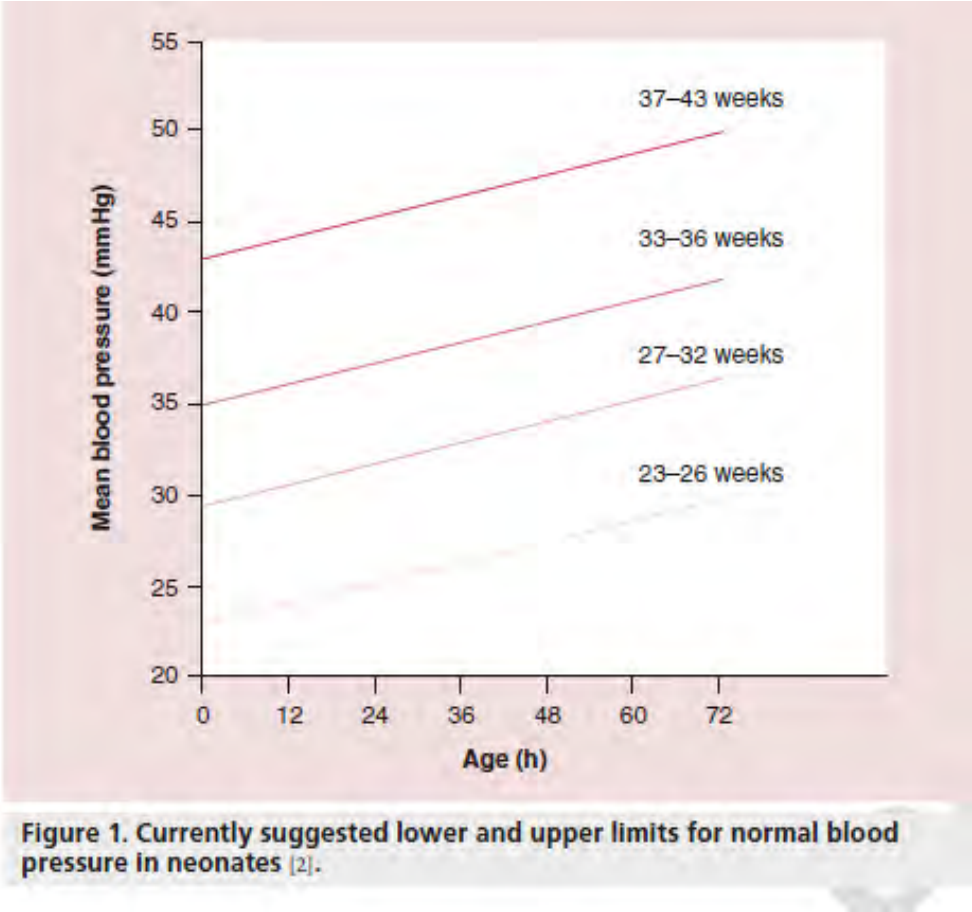


Figure 1. Currently suggested lower and upper limits for normal blood pressure in neonates [2].

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

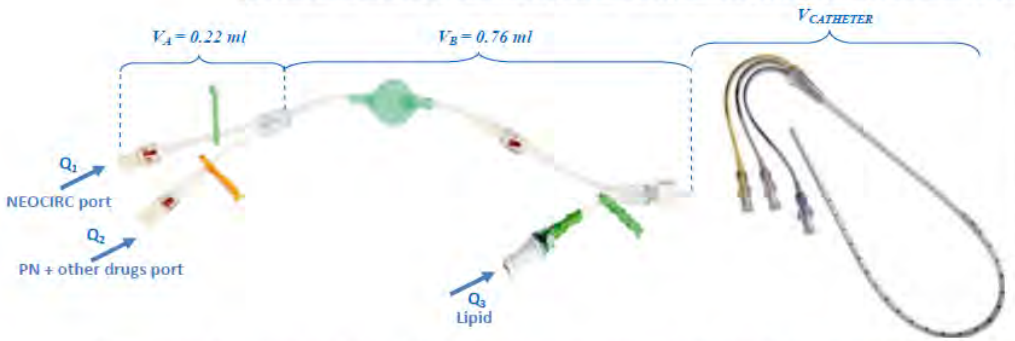
Hemodynamic Adaptation: NEO-CIRC Lessons

- 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)



Catheter TYPE and LUMEN,
e.g. ARGYLE Triple Lumen UVC (5 Fr), Blue :

_____

_____

$V_{CATHETER}$: _____ ml

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):

Port	Drug	Infusion rate (ml/h)
Q_1	NEOCIRC saline flush	Q_1=
Q_2	PN + other drugs	Q_2=
Q_3	Lipid	Q_3=

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

$$Time\_to\_clear\_dead\_space\_[ml] = \left[\left(\frac{V_A}{Q_1}\right) + \left(\frac{V_B}{Q_1+Q_2}\right) + \left(\frac{V_{CATHETER}}{Q_1+Q_2+Q_3}\right)\right] \times 60$$

Where: V_A= 0.22 ml, V_B= 0.76 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 (3+2):

_____

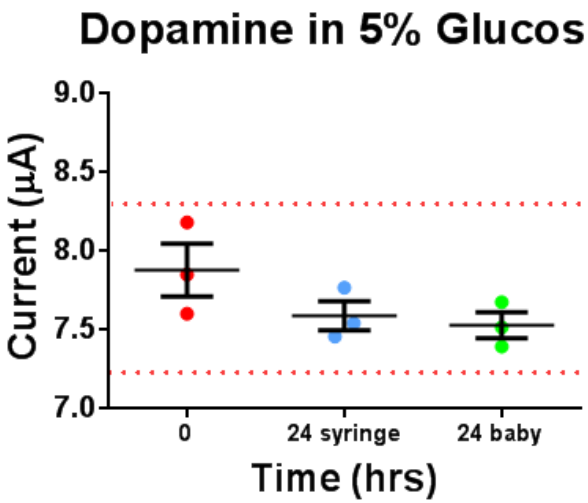
NeoCirc-001 eoi calculations (Ready-set "Unite"), version 1, 14/07/2015

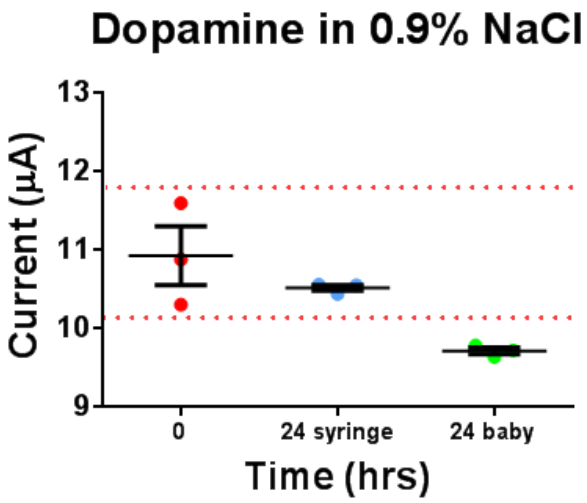
Time to baby: 30 min
End clearance: 74 min

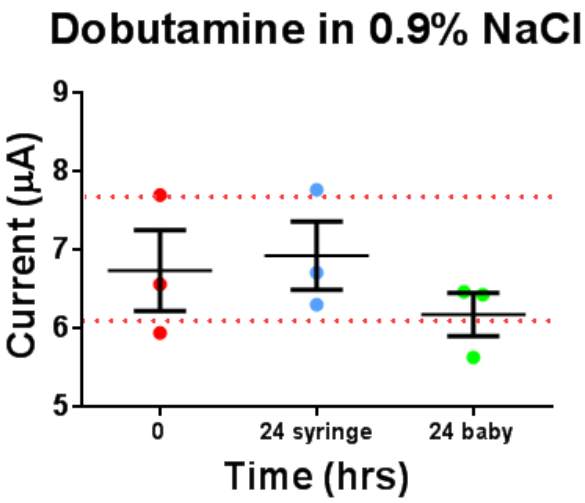
Understanding the changes in inotrope stability using a clinical model of infusion

C Thompson PAS 2016

Understanding the changes in inotrope stability using a clinical model of infusion







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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*

Hemodynamic Adaptation

Dobutamine Half Life	
Adults	2-3 min
NEO-CIRC:Neonatal Piglet (Mielgo unpublished data)	5.6 min (wash out: 28-40 min)
NEO-CIRC 001A: (unpublished data)	Mean 24 min (wash out up to 180 min)

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

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Coffee Break
30 minutes

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Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Gene Dempsey
University College Cork, Ireland

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International Neonatal Consortium

Practical Challenges: Administration

CRITICAL PATH INSTITUTE

Eur J Pediatr (2014) 173:233–235
DOI 10.1007/s00431-013-2096-2

SHORT COMMUNICATION

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

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Practical Challenges: Recent Trials

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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.

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Feasibility Study of Early Blood Pressure Management in Extremely Preterm Infants

Beau J. Batton, MD[1], Lei Li, PhD[2], Nancy S. Newman, RN[1], Abhik Das, PhD[3], Kristi L. Watterberg, MD[4], Bradley A. Yoder, MD[5], Roger G. Faix, MD[5], Matthew M. Laughon, MD, MPH[6], Krisa P. Van Meurs, MD[7], Waldemar A. Carlo, MD[8], Rosemary D. Higgins, MD[9], and Michele C. Walsh, MD, MS[1], for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network*

Early Blood Pressure Management in Extremely Premature Infants (ELGAN BP)

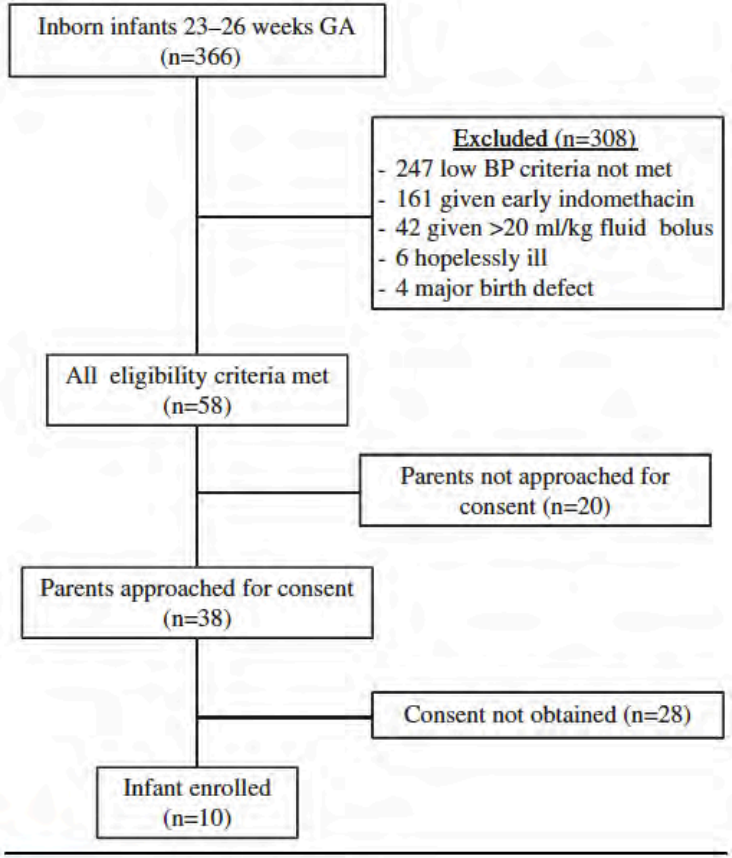
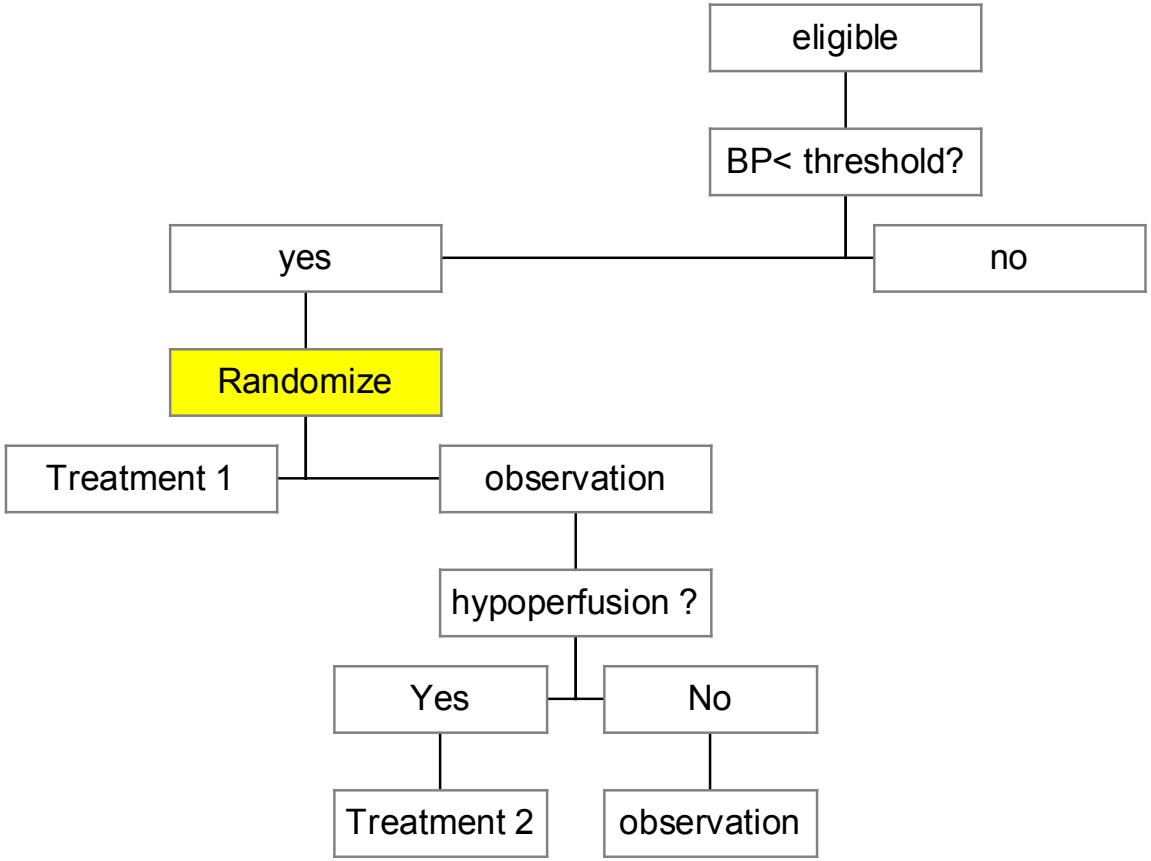


Figure. Flow diagram of infants.

HIPHOP Trial

23-30 weeks gestation



TOHOP

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

- Preterm Infants 23-30 weeks

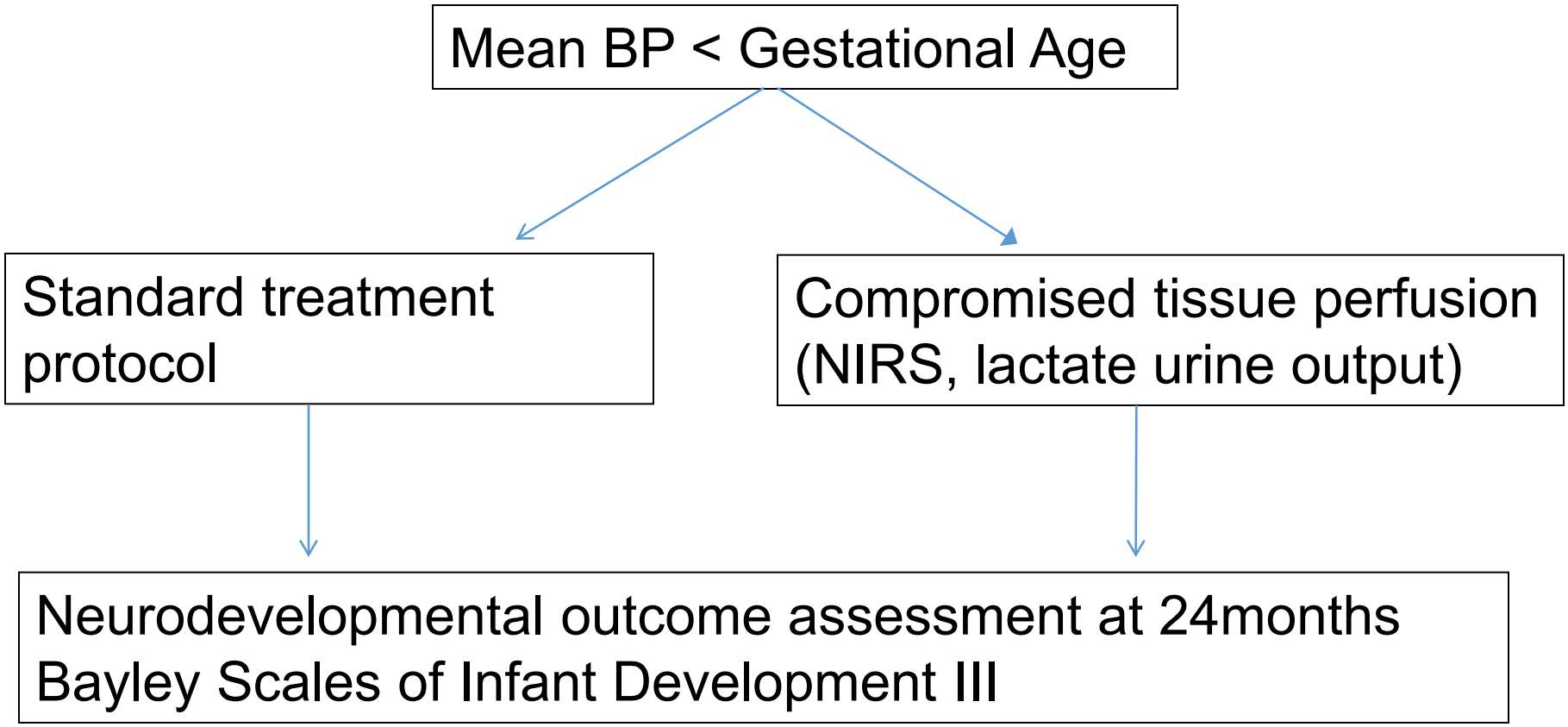
Inclusion Criteria:

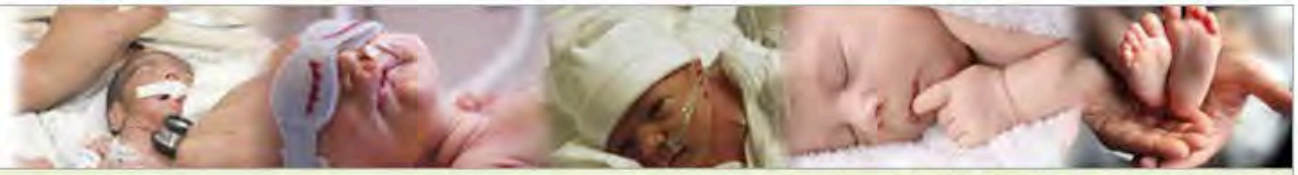
- Idiopathic arterial hypotension as defined by a mean BP in mmHg less than the GA in weeks at birth.
- Written parental consent

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

TOHOP


Mean BP < Gestational Age
Standard treatment protocol
Compromised tissue perfusion (NIRS, lactate urine output)
Neurodevelopmental outcome assessment at 24months
Bayley Scales of Infant Development III



HIP Home Service

Home Search in HIP Contact Sitemap Login Imprint

HIP Home

search GO

Navigation

- About the HIP Trial
- The group
- The project
- Ethics
- Dissemination and news
- Links
- Contact
- Login

SEVENTH FRAMEWORK PROGRAMME

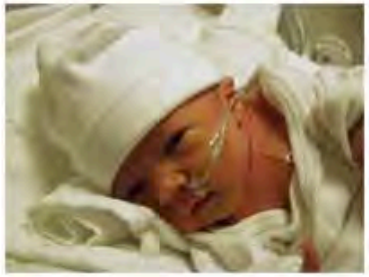
The HIP Trial - The work leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 260777.

The HIP Trial

HIP stands for: Management of **H**ypotension **I**n the **P**reterm 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.



Consortium

Consortium

Quicklinks

- Project Office
- News
- Educational tools for parents

neocirculation

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:
(i) Mean blood pressure (MBP) < gestational age (GA)-1 mmHg (invasive/non-invasive, two readings 15 min apart);
(ii) SVC flow < 51 ml/kg/min;
(iii) CRT > 4 sec;
(iv) Lactate > 4 mmol/l
(v) Base excess <-9 mmol/l

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Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Jeffrey Jacobs
John Hopkins Hospital

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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

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Method of BP Measurement

Direct

- Intra-arterial (Umbilical, Radial, Others)

Indirect

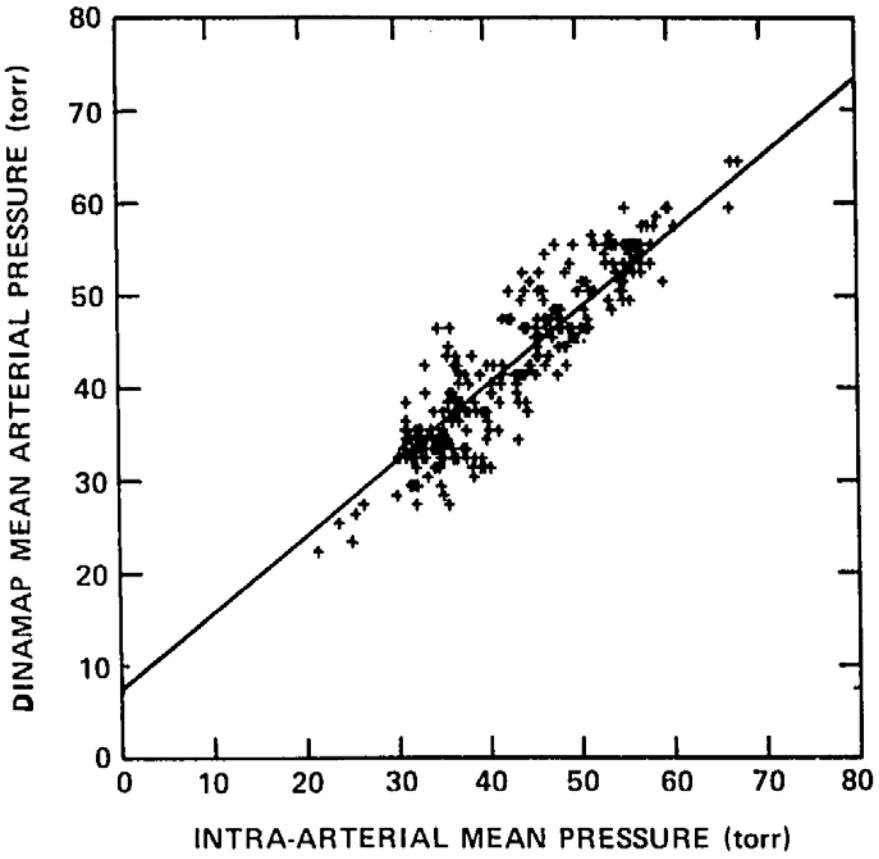
Sphygmomanometer (~~Mercury or~~ Aneroid)

- ø Palpation
- ø Auscultation
- Ultrasonic Doppler

Oscillometric Device

- Measures MAP, calculates SBP & DBP
- Each manufacturer uses different algorithms to determine BP values

Correlation between Oscillometric and Umbilical Artery Mean Blood Pressure



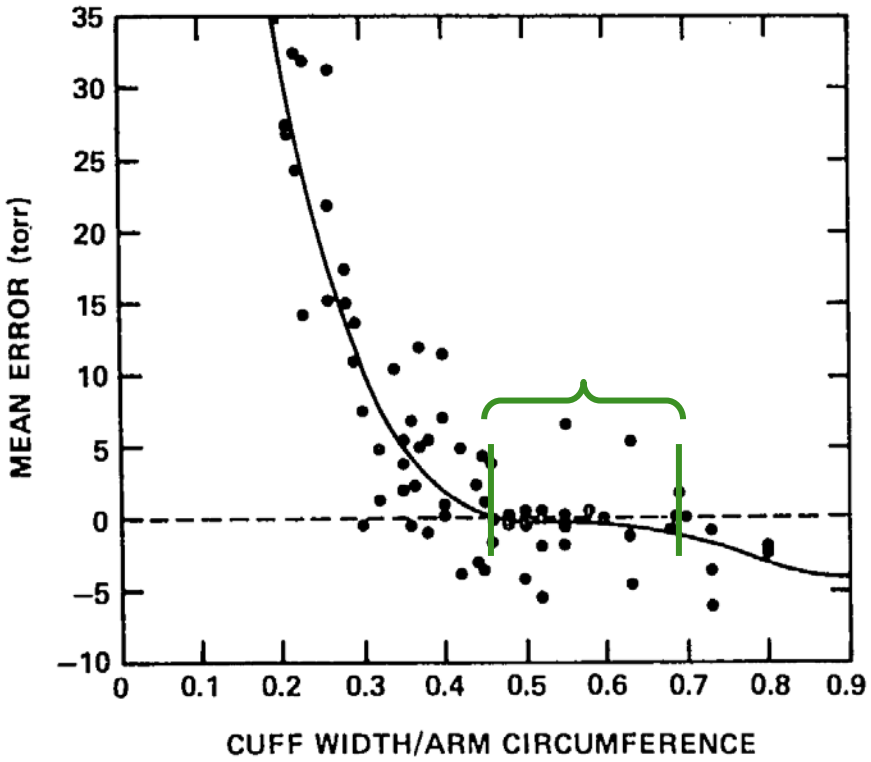
Kimble et al. (1981) Anesthes 54:423-425

- 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



Kimble et al. (1981) Anesthes 54:423-425

🔑 Optimal cuff width to arm circumference ratio is 0.45 to 0.70

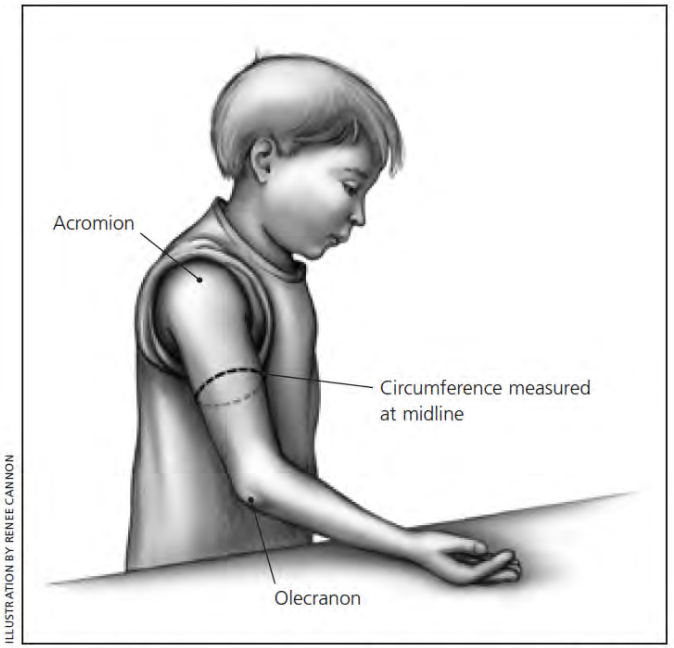


Figure 1. Arm circumference should be measured midway between the olecranon and acromial process.

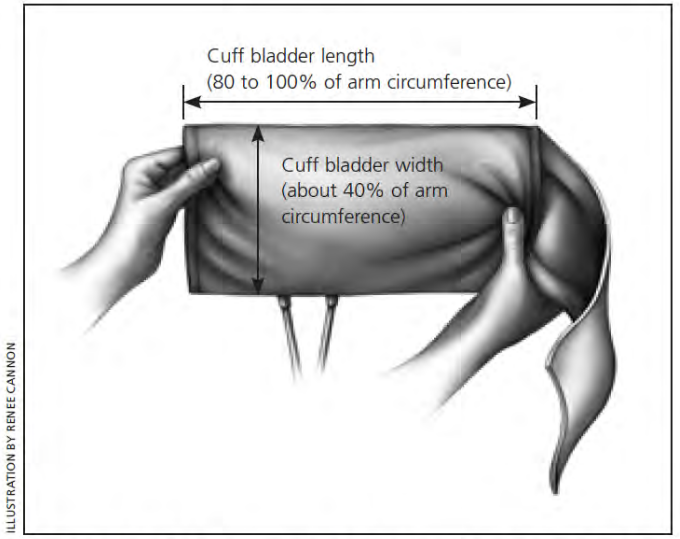


Figure 2. Blood pressure cuff showing size estimation based on arm circumference.

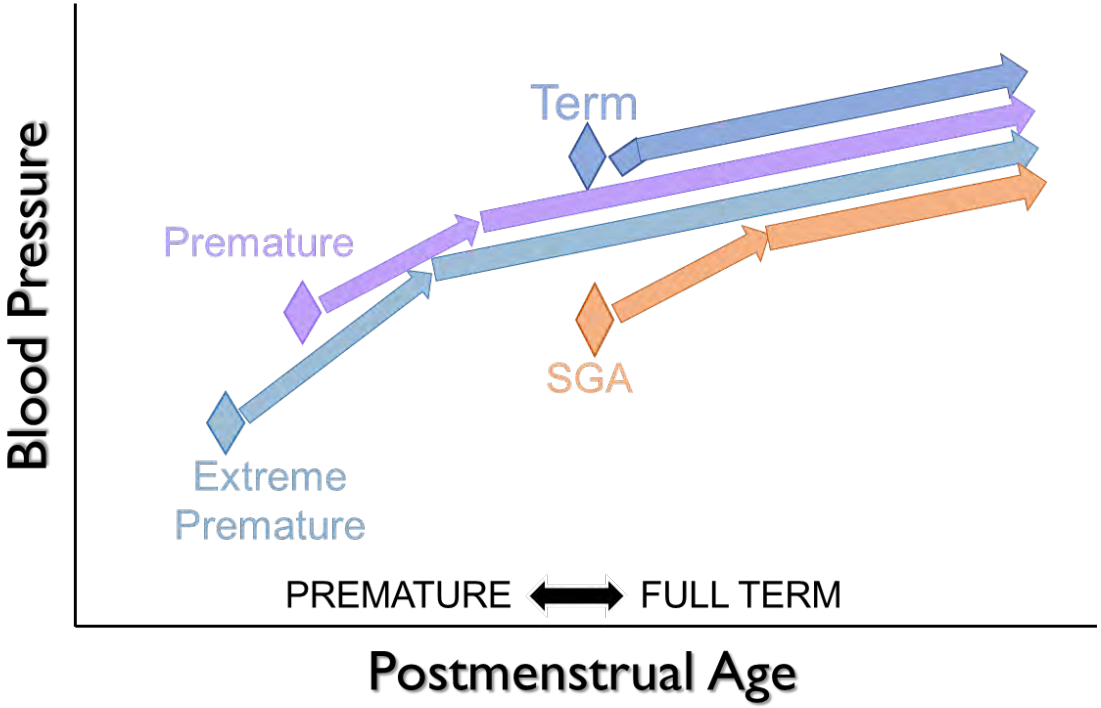
Luma G et al. *Am Fam Physician* 2006;73:1158

A Standard Protocol for Blood Pressure Measurement in the Newborn

Nwankwo et al. (1997) Pediatrics 99:E10

- 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)

Summary



- 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

Dionne JM. Neonatal and Infant Hypertension. In: Flynn J, Ingelfinger J, Portman R, editors. Pediatric Hypertension. 3rd ed. New York, NY. Springer; 2013:395-420.

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%ile 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

	Sahu 2013	Blowey 2011	Seliem 2007
Vasodilators	53%	64%	50%
Calcium Channel Blockers	62%	24%	
ACE Inhibitors	36%	51%	43%
Alpha & Beta Blockers	15%	18%	43%
Diuretics		17%	
None		26%	18%
Multiple agents	51%	45%	32%

Sahu R et al. 2013 J Pediatr 163:84-88
Blowey D et al. 2011 J Am Soc Hypertens 5:478-483
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 → hypertension and chronic kidney disease
- IUGR → 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?

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Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Neil Marlow
University College London

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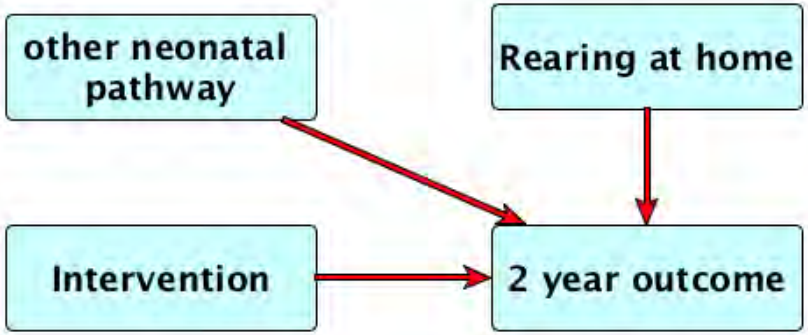
Hypotension – research and safety outcomes – use of 2 year outcomes

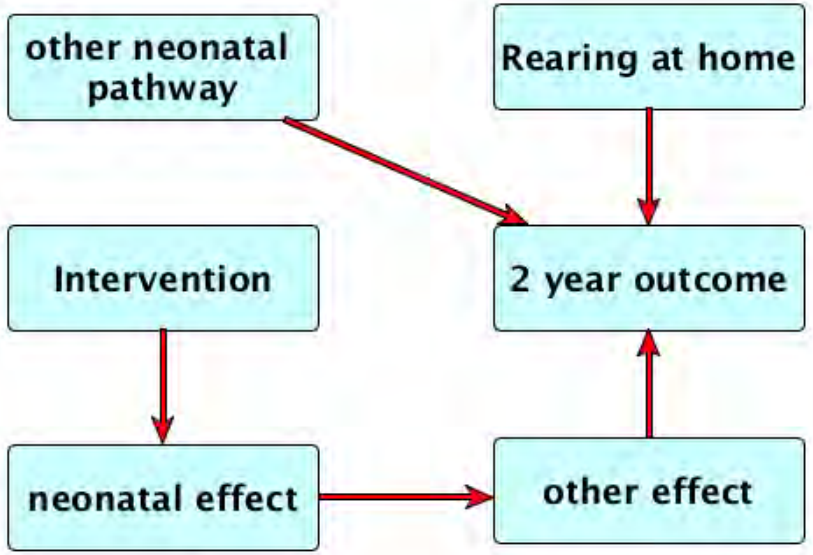
Direct causal pathway



e.g.

$MgSO_4$
Melatonin
Developmental intervention

Indirect causal pathway



e.g.

Indometacin – via PDA, IVH, other?
Caffeine – via reduced BPD, diuretic effect
Respiratory intervention – reduced BPD

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Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Tonse Raju

National Institute of Child Health and Human Development

CRITICAL PATH INSTITUTE

Second Annual Neonatal Scientific Workshop at the FDA: March 7-9, 2016

Hemodynamics Subgroup

Tonse 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**

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

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 $23^{0/7}$ –$26^{6/7}$ weeks of GA infants from this study—secondary analyses paper

The Journal of Pediatrics

Volume 161, Issue 1, July 2012, Pages 65–69.e1

Original Article

Feasibility Study of Early Blood Pressure Management in Extremely Preterm Infants

Beau J. Batton, MD[1], Lei Li, PhD[2], Nancy S. Newman, RN[1], Abhik Das, PhD[3], Kristi L. Watterberg, MD[4], Bradley A. Yoder, MD[5], Roger G. Faix, MD[5], Matthew M. Laughon, MD, MPH[6], Krisa P. Van Meurs, MD[7], Waldemar A. Carlo, MD[8], Rosemary D. Higgins, MD[9], Michele C. Walsh, MD, MS[1], Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network*

Show more

doi:10.1016/j.jpeds.2012.01.014

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Referred to by Nestor Eduardo Vain, Keith J. Barrington

Feasibility of Evaluating Treatment of Early Hypotension in Extremely Low Birth Weight Infants

The Journal of Pediatrics, Volume 161, Issue 1, July 2012, Pages 4-7

PDF (82 K)

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 a 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

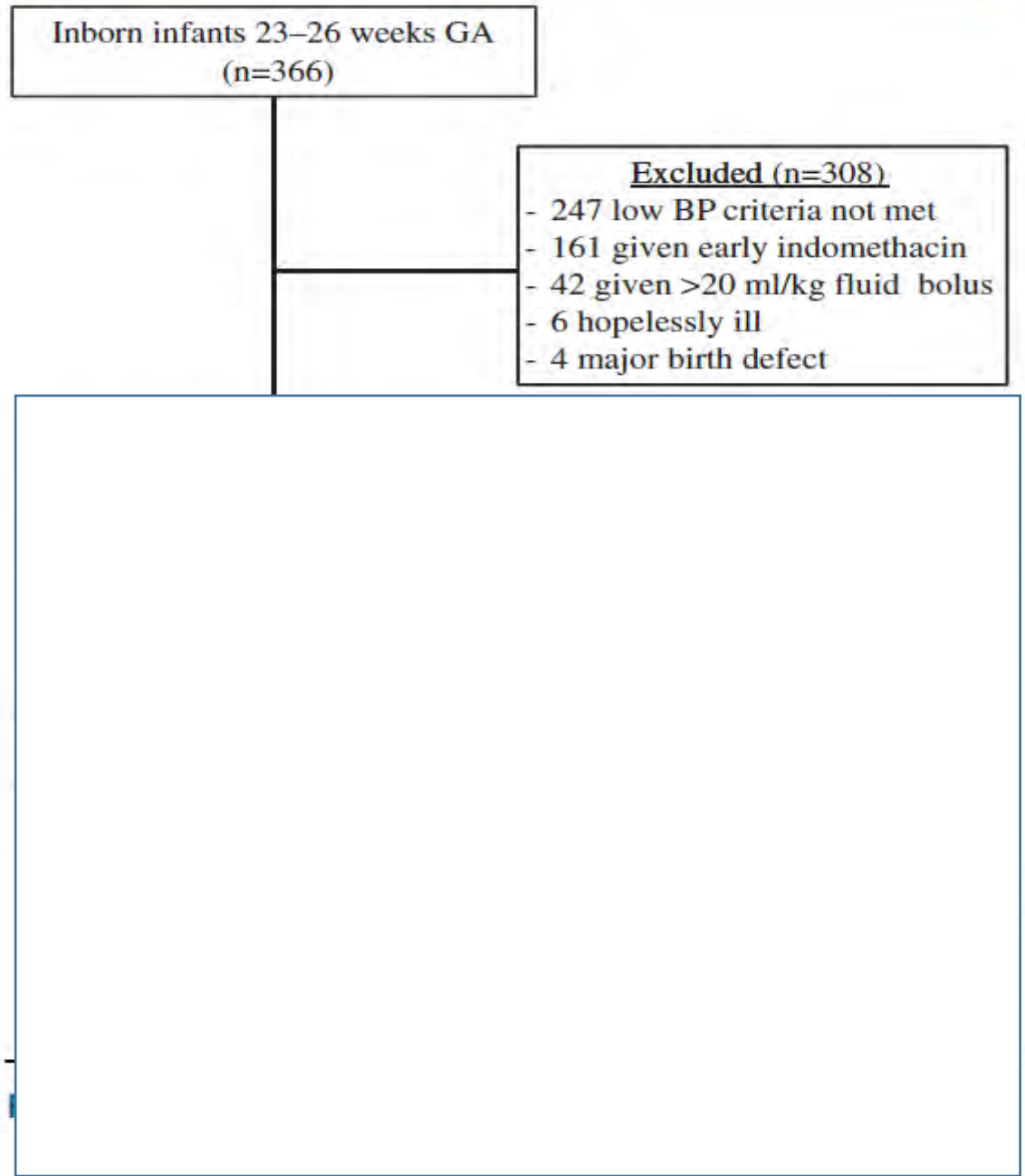
Table I. Threshold for low BP

Postnatal hour	1-6	7-12	13-18	19-24
MAP, mm Hg	24	25	26	27

MAP, mean arterial blood pressure.

Flow Diagram

- December 3, 2009
- December 3, 2010
- Study endpoint:
- Successful enrollment of 60 infants in one year, with a protocol deviation $\leq$ 20%



Flow Diagram

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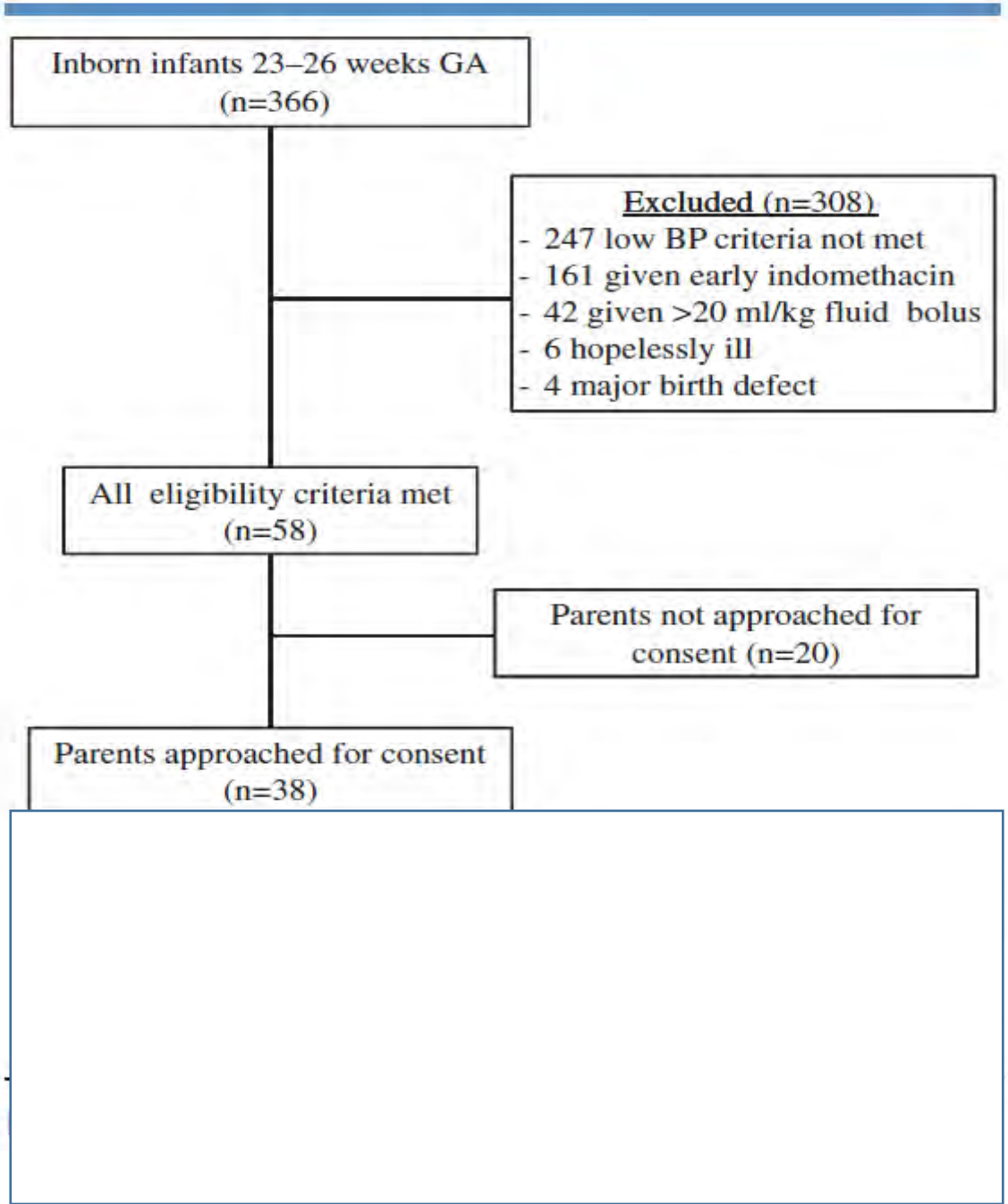

Flow Diagram

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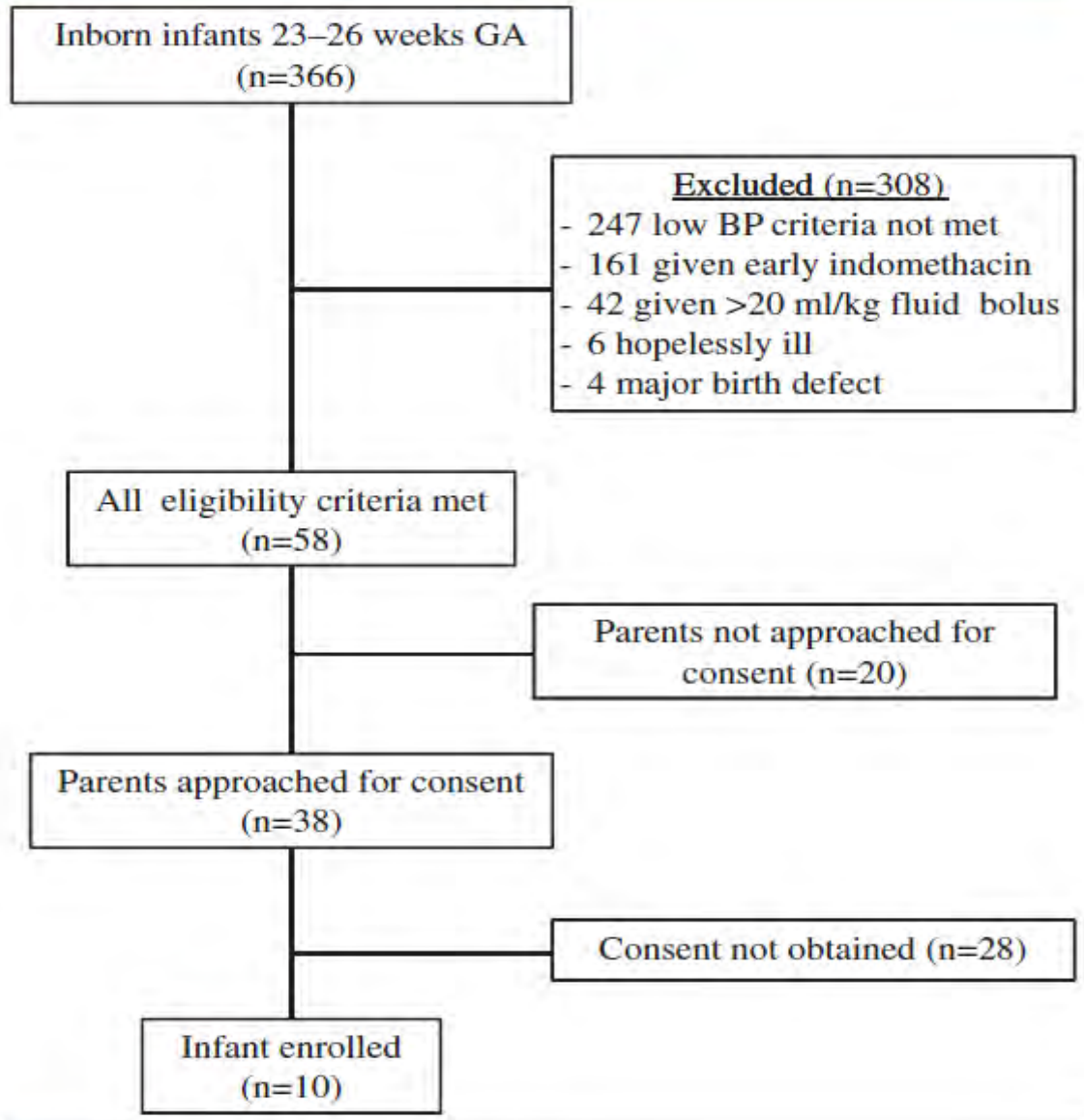


Figure. Flow diagram of infants.

Outcomes for the 10 infants enrolled in the pilot study

Table II. Outcomes for the 10 infants enrolled in the pilot study

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

- 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

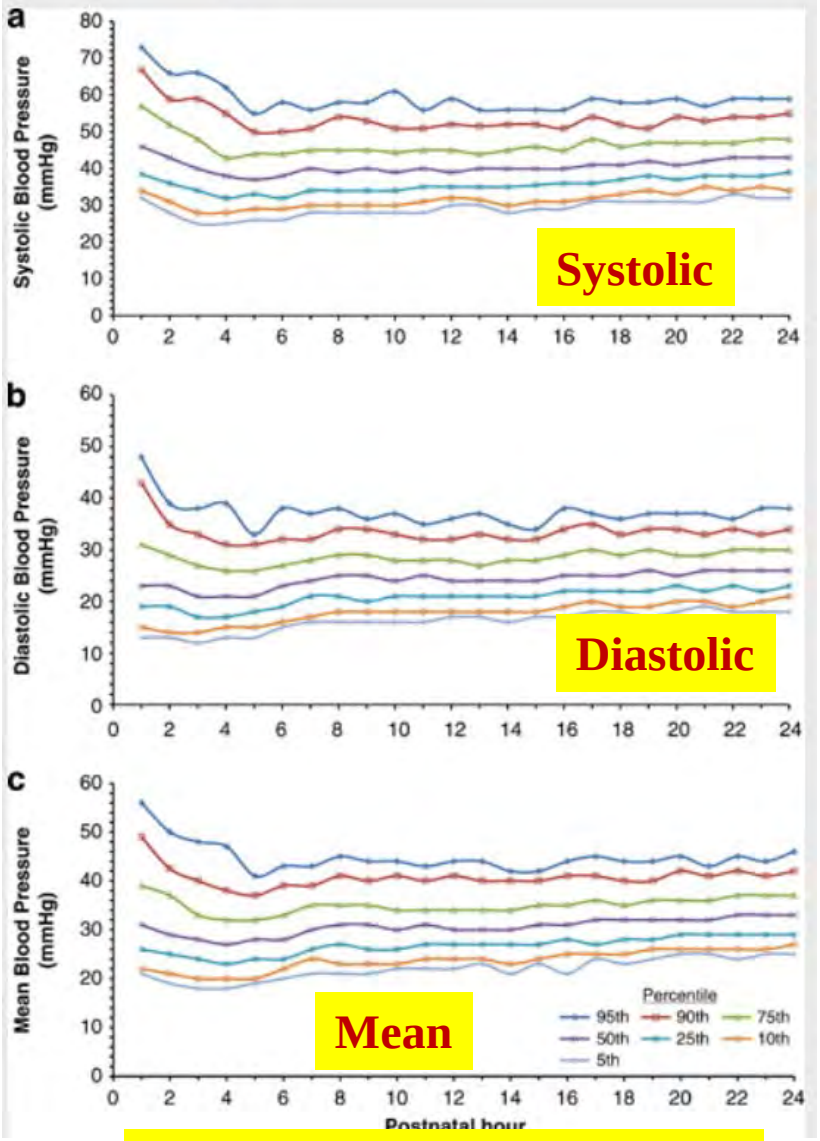
- Low percentage met all eligibility criteria
  - Only 1/3 had protocol-defined low BP; perhaps because 93% women received antenatal glucocorticoids
- Earlier administration of indomethacin (44% of screened infants); often "prophylactic" for IVH
- Difficulty in consenting process: Only 17% success; nearly 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

J Perinatol. 2014 Apr;34(4):301-5. doi: 10.1038/jp.2014.6. Epub 2014 Feb 6.

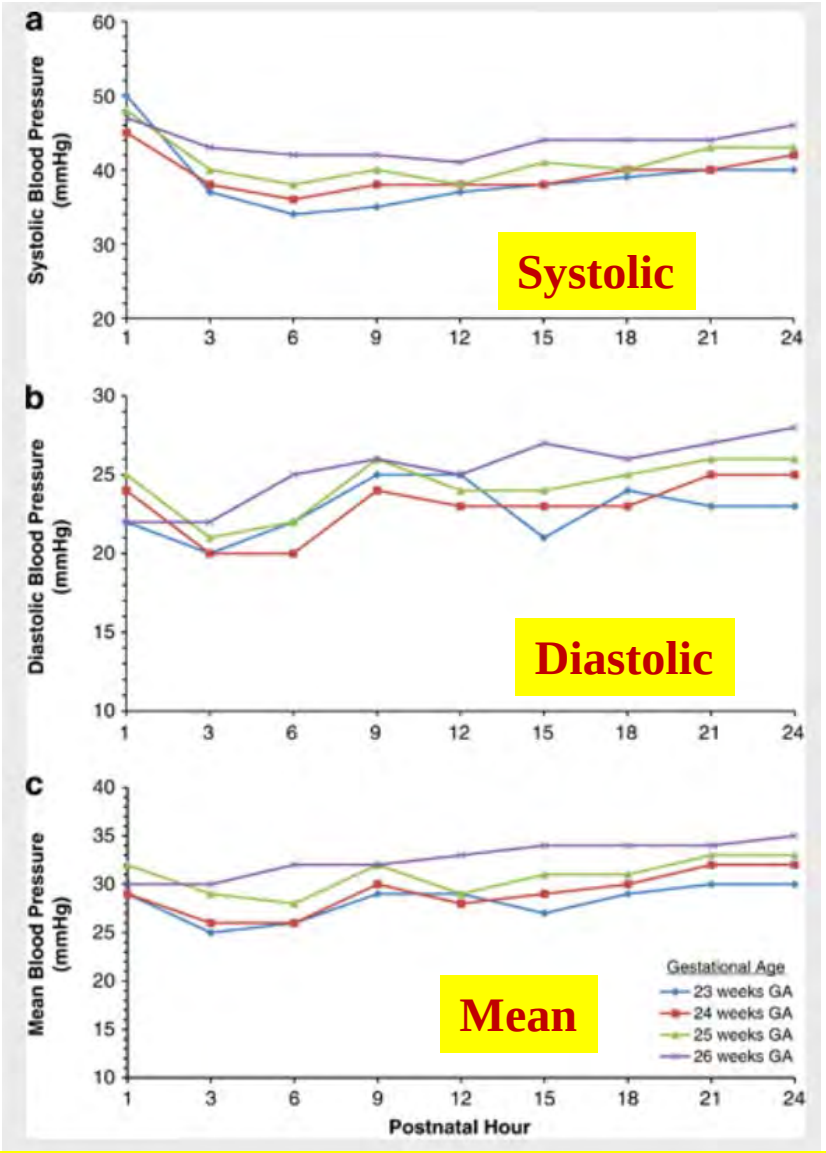
Secondary analyses
367 infants, 18, 709 measurements

Evolving blood pressure dynamics for extremely preterm infants.

Batton B[1], Li L[2], Newman NS[3], Das A[4], Watterberg KL[5], Yoder BA[6], Faix RG[6], Laughon MM[7], Stoll BJ[8], Higgins RD[9], Walsh MC[3]; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network.



BP Changes during the first 24 h



GA Specific BP changes during the first 24 h

The Journal of Pediatrics

Volume 161, Issue 1, July 2012, Pages 65–69.e1

Original Article

Feasibility Study of Early Blood Pressure Management in Extremely Preterm Infants

Beau J. Batton, MD[1], Lei Li, PhD[2], Nancy S. Newman, RN[1], Abhik Das, PhD[3], Kristi L. Watterberg, MD[4], Bradley A. Yoder, MD[5], Roger G. Faix, MD[5], Matthew M. Laughon, MD, MPH[6], Krisa P. Van Meurs, MD[7], Waldemar A. Carlo, MD[8], Rosemary D. Higgins, MD[9], Michele C. Walsh, MD, MS[1], Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network*

Show more

doi:10.1016/j.jpeds.2012.01.014

Referred to by Nestor Eduardo Vain, Keith J. Barrington

Feasibility of Evaluating Treatment of Early Hypotension in Extremely Low Birth Weight Infants

The Journal of Pediatrics, Volume 161, Issue 1, July 2012, Pages 4-7

PDF (82 K)

Thank you….

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Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Shari Targum

US Food and Drug Administration

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Hemodynamic Adaptation: Strategies to Overcome Challenges in Neonatal Drug Studies

Ralph Bax

European Medicines Agency

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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:

Hemodynamic Voting Slide 1

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

Hemodynamic Voting Slide 2

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

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Lunch
1 Hour

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Backup Slides

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Second Annual Neonatal Scientific Workshop

March 8th, Afternoon

FDA

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"Progress of the International Neonatal Consortium – Workgroup Updates"

Ron Portman, INC Co-Director
Novartis, Chair

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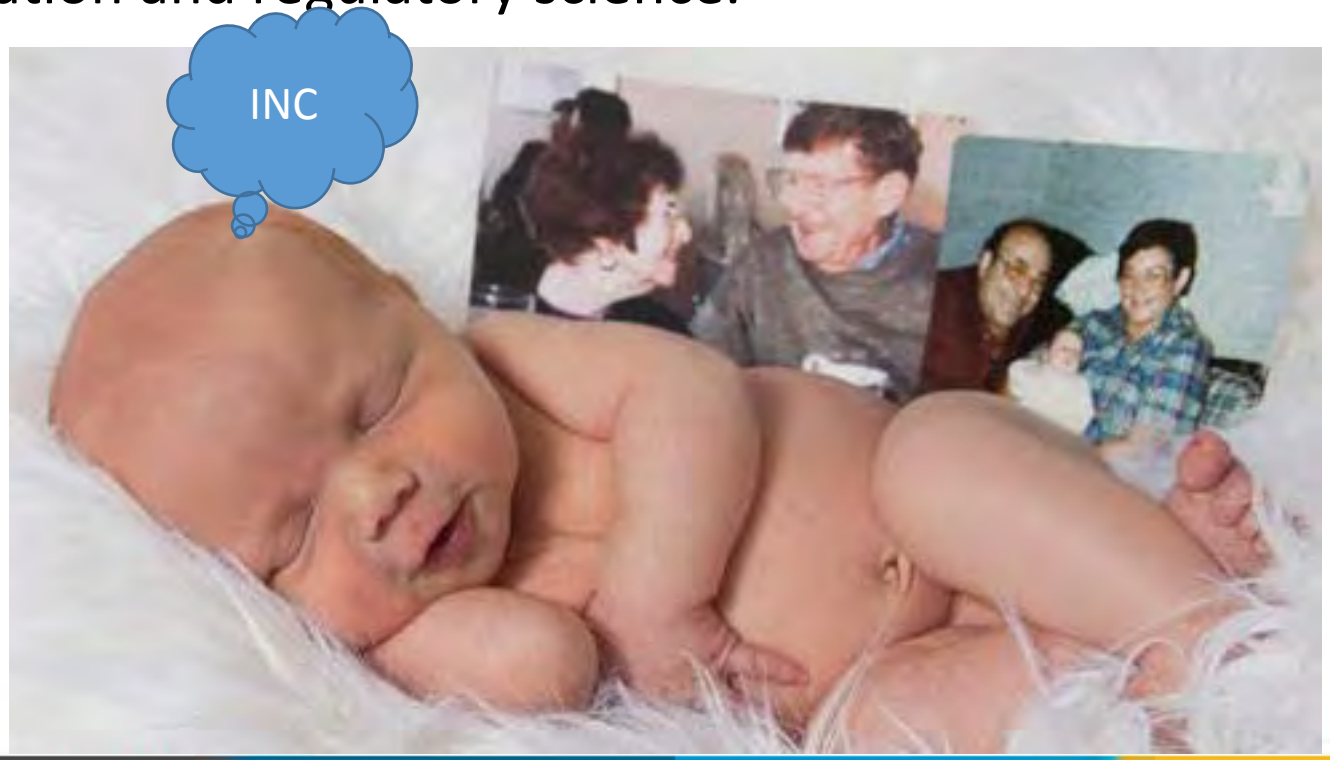
Agenda – Workgroup Updates

1:30 pm	**Clinical Pharmacology Workgroup** Bob Ward (University of Utah) Karel Allagaert (University of Leuven) Jeff Barrett (Sanofi)
2:00 pm	**Seizures Workgroup** Janet Soul (Harvard University) Ronit Pressler (Great Ormond Street Hospital)
2:30 pm	**COFFEE BREAK**
3:00 pm	**Bronchopulmonary Dysplasia (BPD) Workgroup** Robin Steinhorn (Children's National Hospital) Wolfgang Göpel (University Lübeck/VOC)
3:45 pm	**Data Workgroup** Tom Diacovo (Columbia University) Kate Costeloe (Queen Mary University of London)
4:30 pm	**Concluding Remarks** Jon Davis, INC Co-director (Tufts Medical Center)

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)

- McCune, S.K., Mulugeta, Y.A. "Regulatory science needs for neonates: a call for neonatal community collaboration and innovation." *Front Pediatr*. 2: 135-137 (2014).
- Davis, J.M., Turner, M.A. "Global Collaboration to Develop New and Existing Drugs for Neonates", *JAMA Pediatrics*, published online August 10 (2015).
- Offringa, M., Davis, J.M., Turner, M., Ward, R., Bax, R., Maldonado, S., Sinha, V., McCune, S., Zajicek, A., Benjamin, D., Bucci-Rechtweg, C., Nelson, R. "Applying Regulatory Science to Develop Safe and Effective Medicines for Neonates." *Therapeutic Innovation & Regulatory Science journal*. DOI: 10.1177/2168479015597730 (2015).
- 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.
- Hudson, L., **"**Collaborating to Accelerate the Development of Safe and Effective Therapies for Neonates." *Infant* 11 (4)(2015).
- Turner, M.A. et al., "The International Neonatal Consortium: Collaborating to Advance Regulatory Science for Neonates." Pediatrics Research, in review.

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.

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

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.

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Clinical Pharmacology

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

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Clinical Pharmacology – First Project

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.

Clinical Pharmacology

Bob Ward, Karel Allegaert, Jeff Barrett

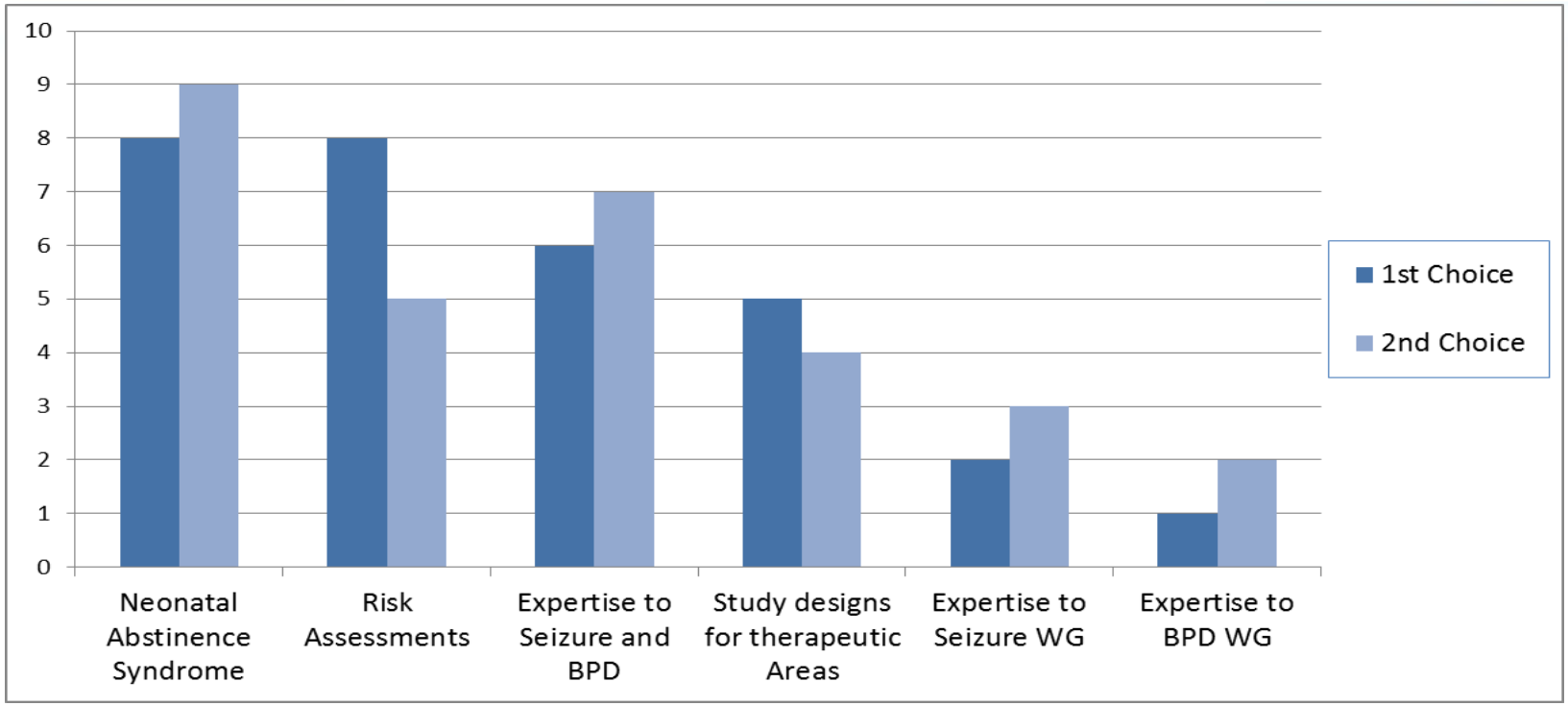
- Clinical pharmacology encompasses a broad range of knowledge of medications as well as pathophysiology of diseases that can inform clinical trials and their results
  - Study design
  - Regulatory requirements
  - Pharmacometrics
  - Pharmacogenetics
  - Pharmacodynamic measures/surrogate markers

- 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

Clinical Pharmacology

- 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.

Clinical Pharmacology – Next Project



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**
- **Bob Ward - University of Utah, Co-chair**
- **Jeff Barrett - Sanofi, Co-chair**
- Dina Apele-Freimane - Riga Stradins University Hospital, Latvia
- Jack Aranda - University Hospital of Brooklyn
- Raafat Bishai - AstraZeneca
- Danny Benjamin - Duke University (DCRI)
- Edmund Capparelli – UC San Diego
- Edress Darsey – Pfizer
- Walter Kraft – Thomas Jefferson University
- Irja Lutsar – University of Tartu, Estonia & PDCO
- Jeff Ming – Sanofi
- Min Soo Park – Yonsei University, Seoul, South Korea
- Randy Prescilla – Lilly/Boston's Children Hospital
- Catherine Sherwin - University of Utah
- 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

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Seizures Workgroup

Janet Soul, Harvard University
Ronit Pressler, Great Ormond Street Hospital

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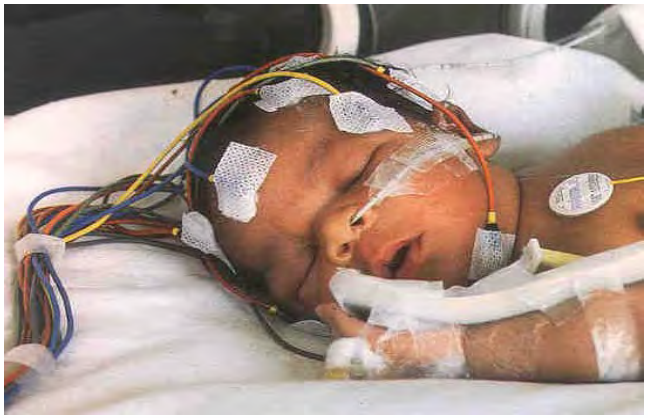
Why treat neonatal seizures?

- 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



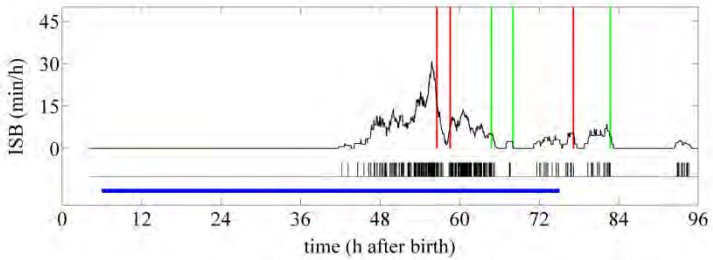
Challenges of drug development

- 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

Seizure burden analysis



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)
5. PK/PD analysis approach
6. Drug specific safety measures, incl biomarkers
7. 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

- **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

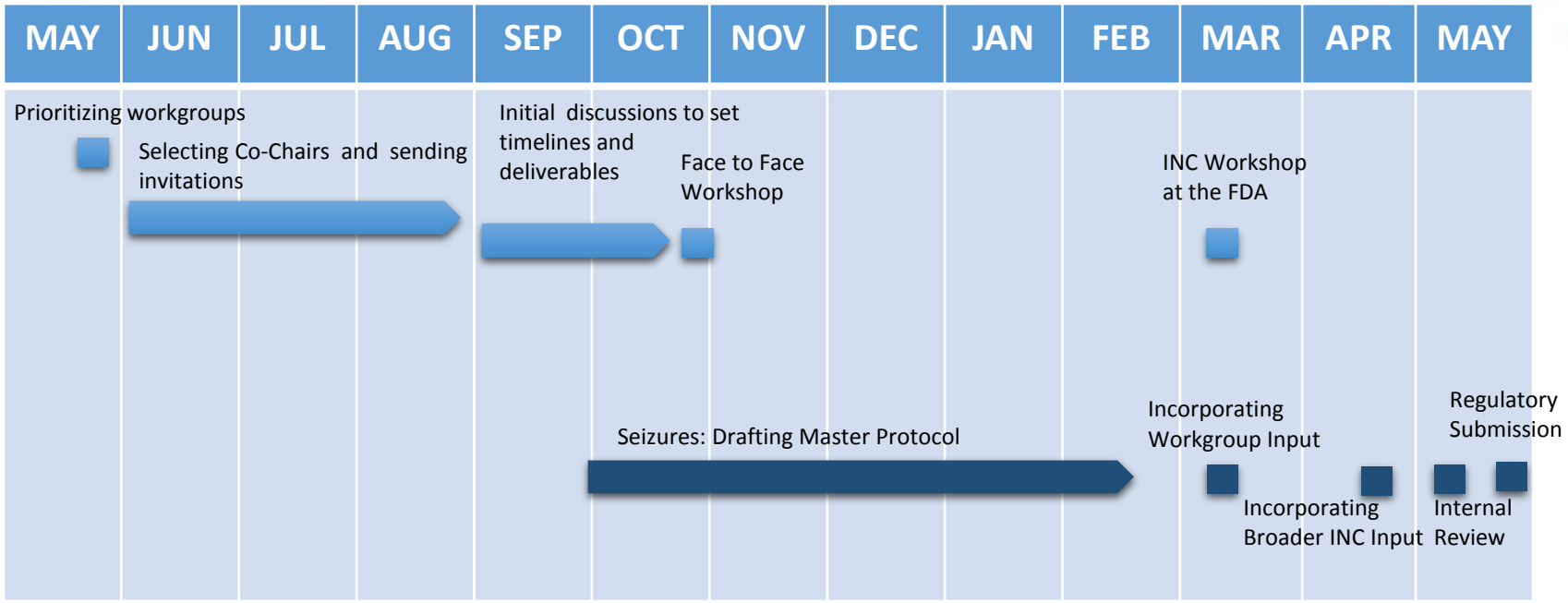
Ethics subgroup – results & discussion points

- 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



- 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

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Thank You

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

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Coffee Break
30 minutes

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BPD Workgroup

Robin Steinhorn, Children's National Hospital
Wolfgang Göpel, University of Lübeck

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BPD Workgroup Members

- **Robin Steinhorn – Children's National Hospital, Co-chair**
- **Wolfgang Göpel – U-Lübeck/ VOC, Co-chair**
- Steve Abman – University of Colorado
- Ron Ariagno - Stanford
- 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

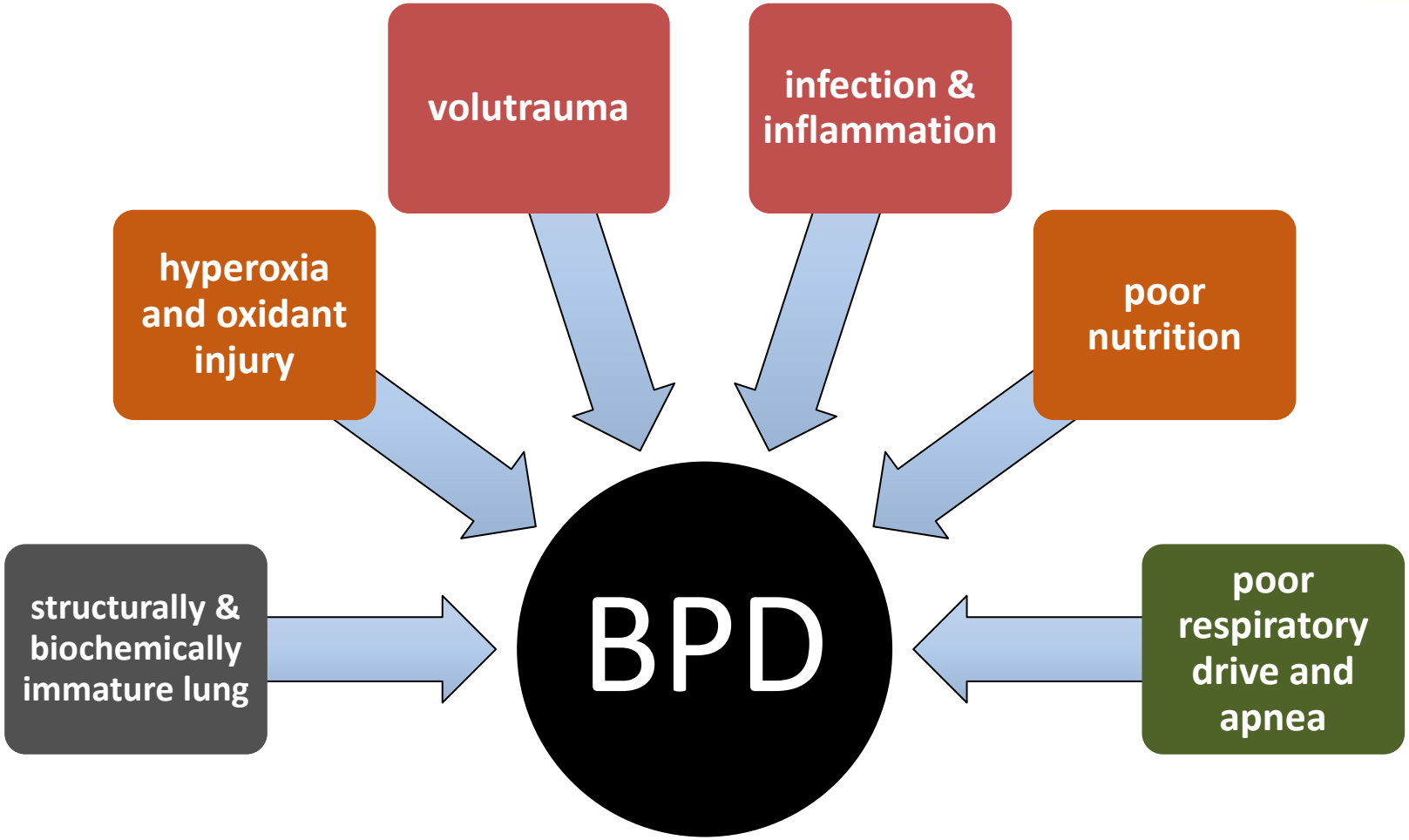
BPD in Preterm Infants

- 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

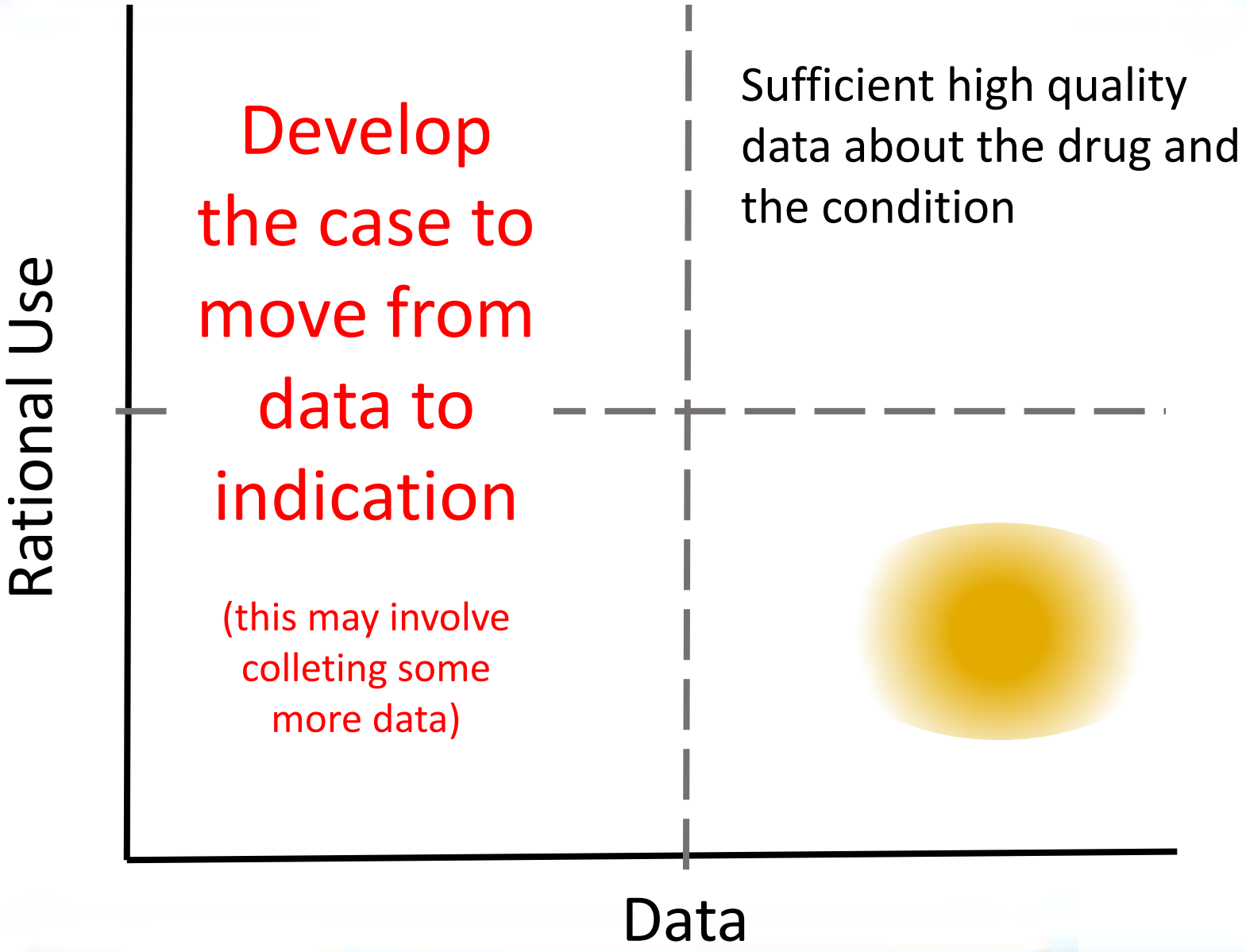
- BPD – complex phenotypes (BPD in a 25 week infant is probably a different disease than that in a 29 week infant)
- Multi-institutional collaborations essential, but introduce tremendous variability in practice and outcomes
- Current challenges in balancing risks and benefits of preventive strategies
  - 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



Responses of individual patients modulated by genetic, epigenetic and antenatal factors

Regulatory Readiness: Case 3



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

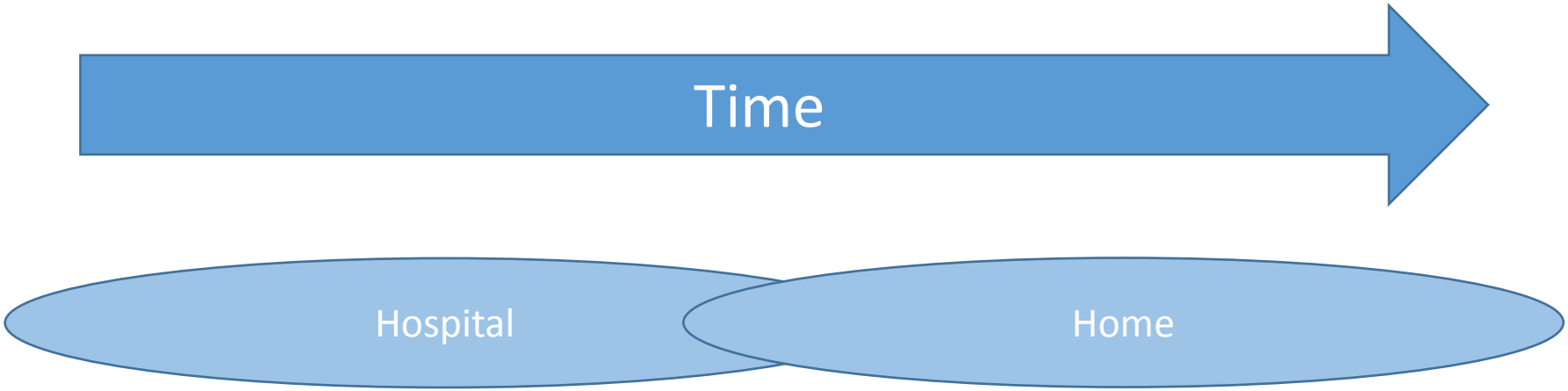
Name	Year	Definition	Comments
Northway	1979	Oxygen use at 28 days of life	
Shennan	1988	Oxygen use at 36 weeks PMA	A child on 4 LPM HFNC support and 21% O_2 at 36 weeks would not have BPD
Modified Shennan		Assigns infants discharged in room air before 36 weeks PMA as no BPD	
NIH Consensus	2001	• None (<28 days of oxygen support) • Mild (oxygen or respiratory support at >28 days but on room air at 36 weeks PMA) • Moderate (<30% oxygen at 36 weeks) • Severe (>30% oxygen or positive pressure at 36 weeks PMA)	A child placed on HFNC support for 2-3 days for worsening apnea would have BPD
Walsh "Physiologic"	2003	SpO2 <88% after 60 minute room air challenge at 36 weeks PMA	

Six questions concerning BPD Definition

- Q1: Transient respiratory insufficiency of prematurity (TRIP)
- Q3: Predictive models, biomarkers
- Q4: Subtypes

Q2: BPD-Definition

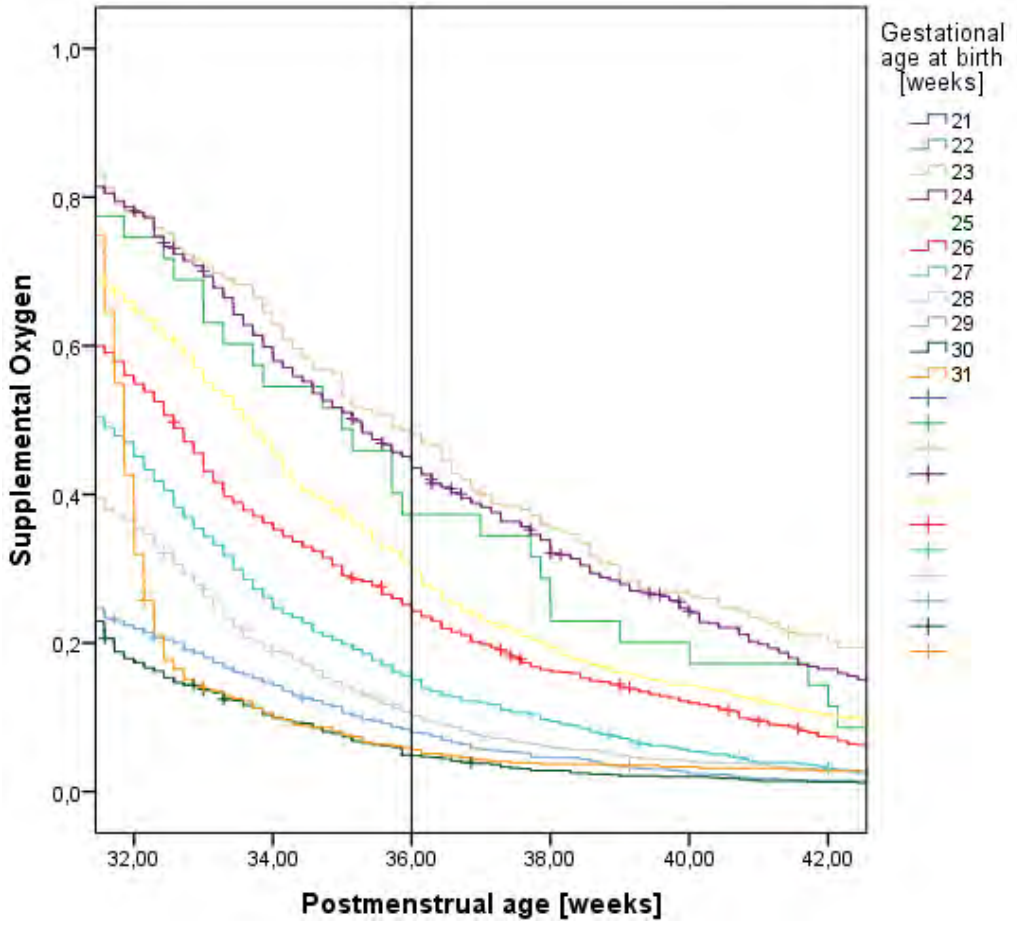
- Q5: Ongoing morbidity
- Q6: Important outcomes for families



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

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

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



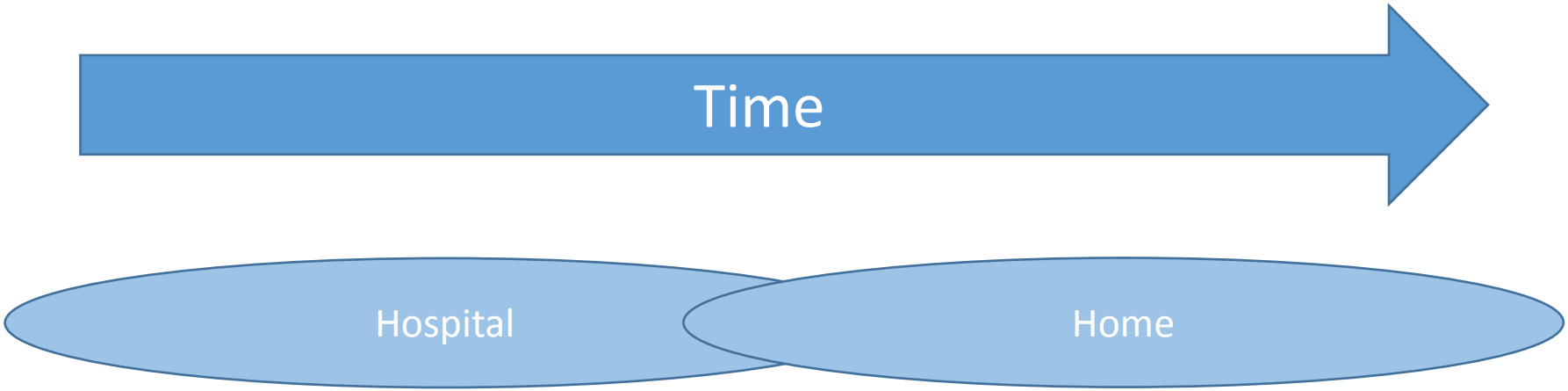
- Oxygenation is the most secure and pragmatic indicator of lung function.
- Pulse oximetry is the only practical way to measure systemic oxygen levels. The threshold should be 90%.
- The optimal time point for BPD assessment is under discussion (graph).

Six questions concerning BPD Definition

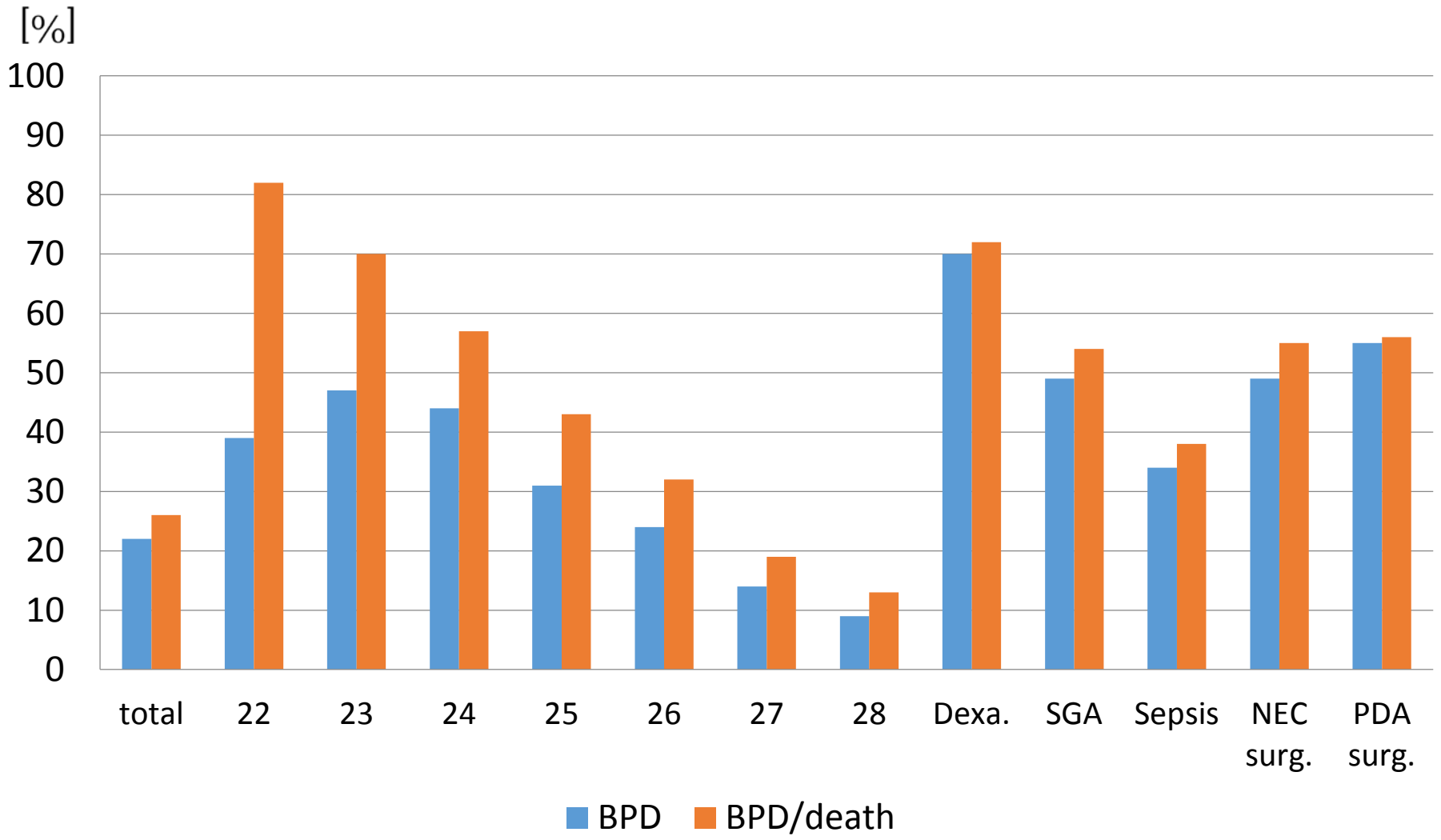
- Q1: Transient respiratory insufficiency of prematurity (TRIP)
- Q2: BPD-Definition
- Q3: Predictive models, biomarkers

Q4: BPD-Subtypes

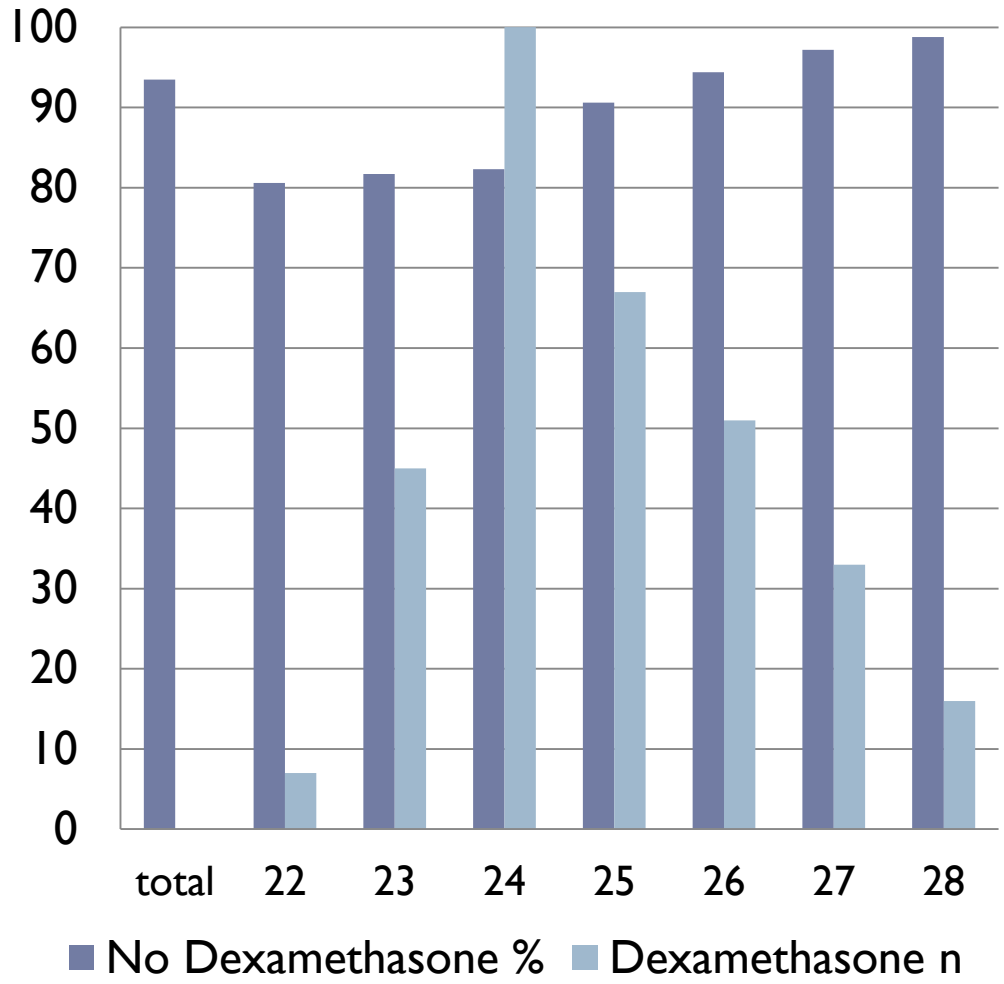
- Q5: Ongoing morbidity
- Q6: Important outcomes for families



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

iNO in ELBW infants at risk for BPD

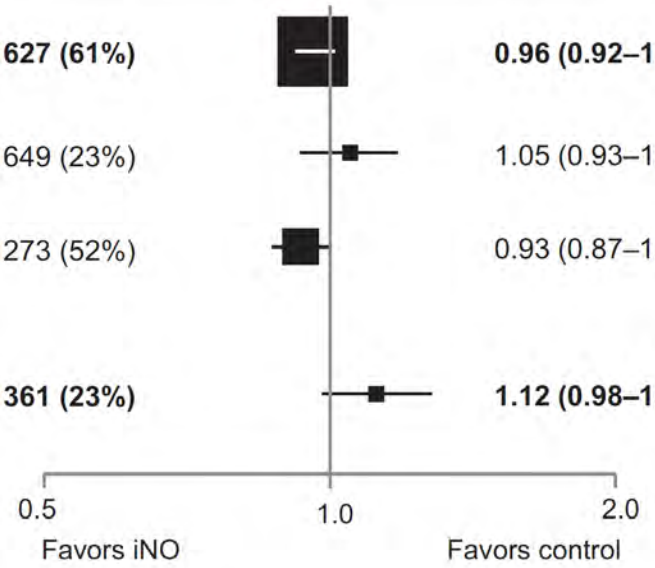
PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Inhaled Nitric Oxide in Preterm Infants: An Individual-Patient Data Meta-analysis of Randomized Trials

Lisa M. Askie, Roberta A. Ballard, Gary R. Cutter, Carlo Dani, Diana Elbourne, David Field, Jean-Michel Hascoet, Anna Maria Hibbs, John P. Kinsella, Jean-Christophe Mercier, Wade Rich, Michael D. Schreiber, Pimol (Srisuparp) Wongsiridej, Nim V. Subhedar, Krisa P. Van Meurs, Merryn Voysey, Keith Barrington, Richard A. Ehrenkranz, Neil N. Finer and on behalf of the Meta-analysis of Preterm Patients on Inhaled Nitric Oxide (MAPPiNO) Collaboration

Pediatrics 2011;128;729; originally published online September 19, 2011; DOI: 10.1542/peds.2010-2725

Outcome	No. of Trials	iNO	Control	RR (95% CI)	*P*
Death or CLD	**10**	**956/1629 (59%)**	**993/1627 (61%)**	**0.96 (0.92–1.01)**	**.108**
Death	11	386/1649 (23%)	374/1649 (23%)	1.05 (0.93–1.18)	.441
CLD in survivors	9	616/1261 (49%)	660/1273 (52%)	0.93 (0.87–1.00)	.060
Severe neurologic event after randomization	**10**	**337/1355 (25%)**	**312/1361 (23%)**	**1.12 (0.98–1.28)**	**.092**



iNO in a High Risk Subgroup

THE JOURNAL OF PEDIATRICS • www.jpeds.com MEDICAL PROGRESS

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]

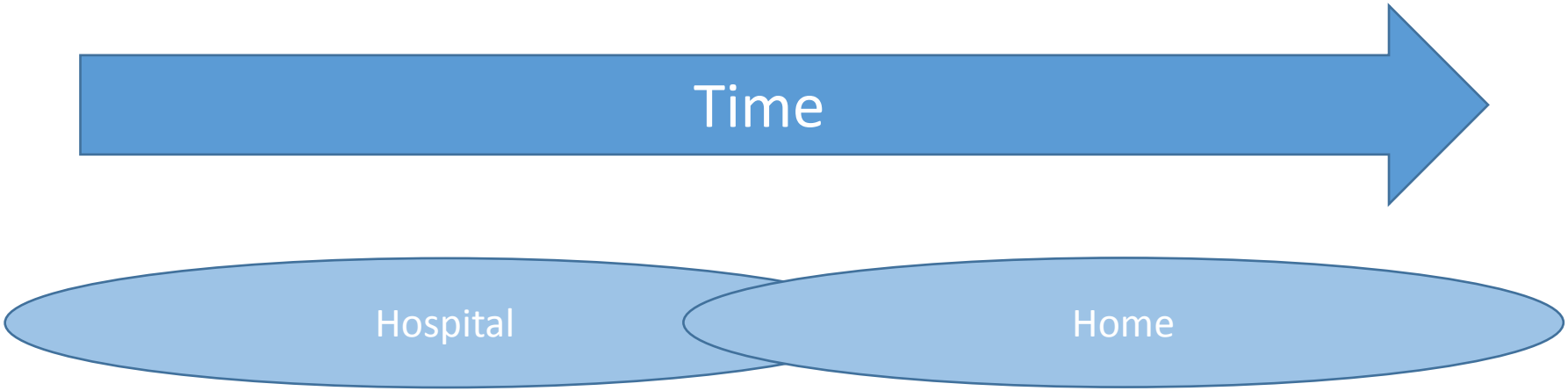
of trials in which iNO was started early in preterm infants after PPROM in th

Design	Treated with iNO	GA, wk	Ultrasound diagnosis of PH	Pre-iNO MAP, cmH_2O	Pre-iNO oxygenation index	Age at start iNO, h
ıse series	8	24-31	5/8	12-22	25-76	2-11
ıse series	5	24-34	Some	n/a	n/a	n/a
ıse report	2	29-31	1/2	n/a	n/a	10-24
ıse series	8	24-30	7/8	12.6 +/− 2.8	28.8 +/− 18.3	11.5 +/− 11.6
;T	6	24-31	2/6	n/a	11-64	12 +/− 8
ıse series	9	25-31	4/9	15-19	25-80	0.5-12
ıse series	6	26-31	6/6	13-18	23-35	6-24
ıse series	7	28-33	Some	n/a	n/a	0.2-15
)hort	17	27 +/− 2	17/17	n/a	20-70	1.5-16.5

ıirway pressure; *n/a*, not available; *PH*, pulmonary hypertension; *RCT*, randomized controlled trial.
ı +/− 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**



Prediction of Late Death or Disability at Age 5 Years

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

	Death or disability at 5 y		
Neonatal morbidities	**No./total no.**	**% (95% CI)**	**OR (95% CI)**
None	85/759	11.2 (9.0-13.7)	1.0
Any single morbidity	135/590	22.9 (19.6-26.5)	2.4 (1.7-3.2)
BPD	112/494	22.7	
Brain injury	20/84	23.8	
Severe ROP	3/12	25.0	
Any 2 morbidities	61/139	43.9 (35.5-52.6)	6.2 (4.1-9.3)
BPD + brain injury	37/84	44.0	
BPD + Severe ROP	22/53	41.5	
Brain injury + severe ROP	2/2	100.0	
All 3 Morbidities	16/26	61.5 (40.6-79.8)	12.7 (5.6-28.9)

Schmidt B, J Pediatr 2015; 167:982-6

BPD – First Project

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?

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"Progress of the International Neonatal Consortium – Workgroup Updates"

The Data Workgroup

Tom Diacovo and Kate Costeloe

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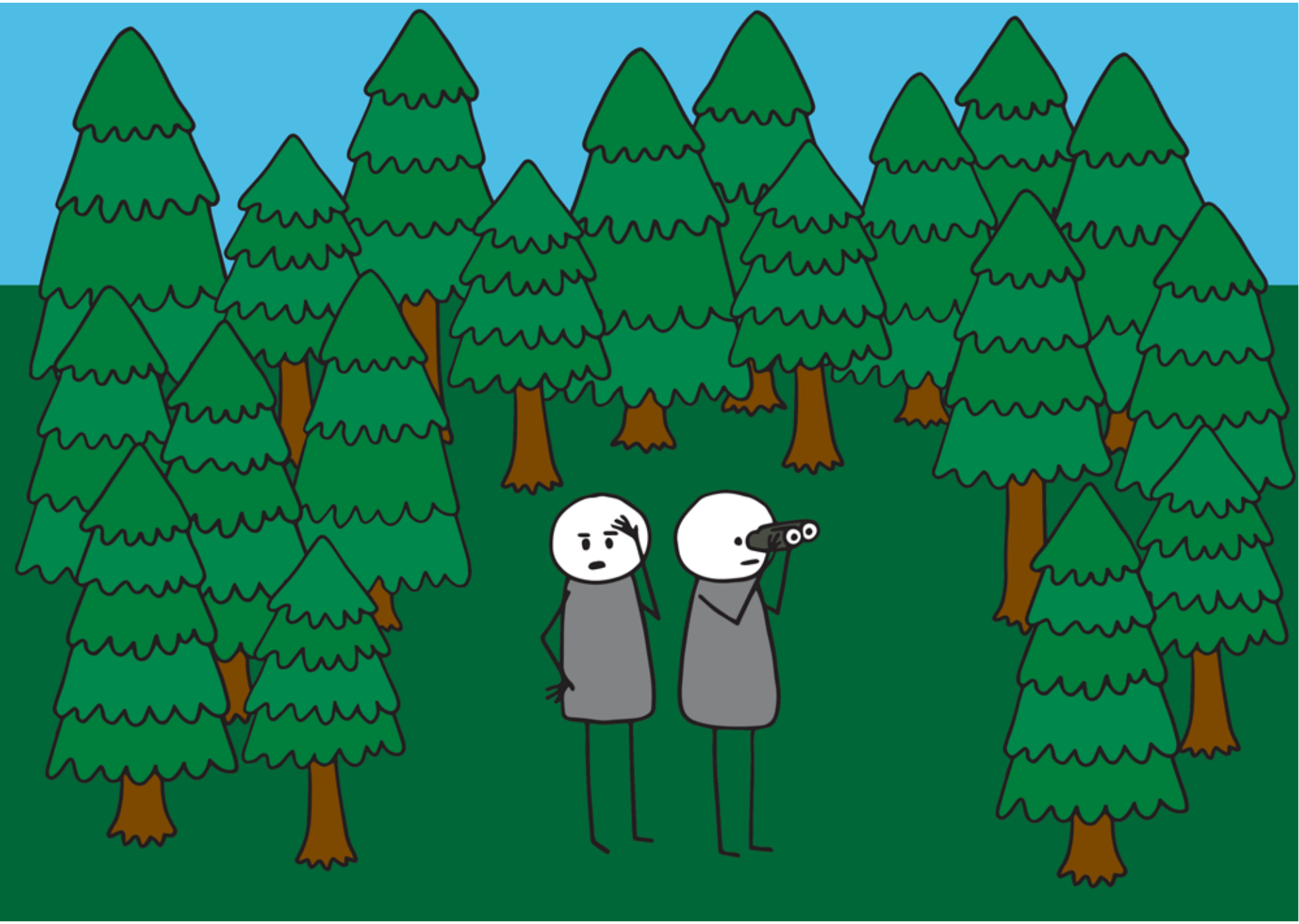
First Call : Sept 2015:
Potential Deliverables for the Data Workgroup

- **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

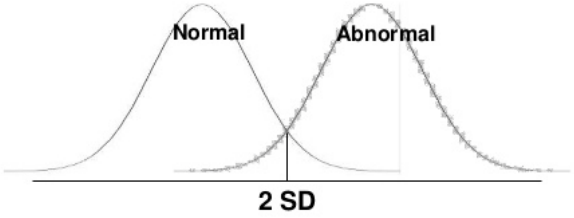
Issues to address by stakeholders

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

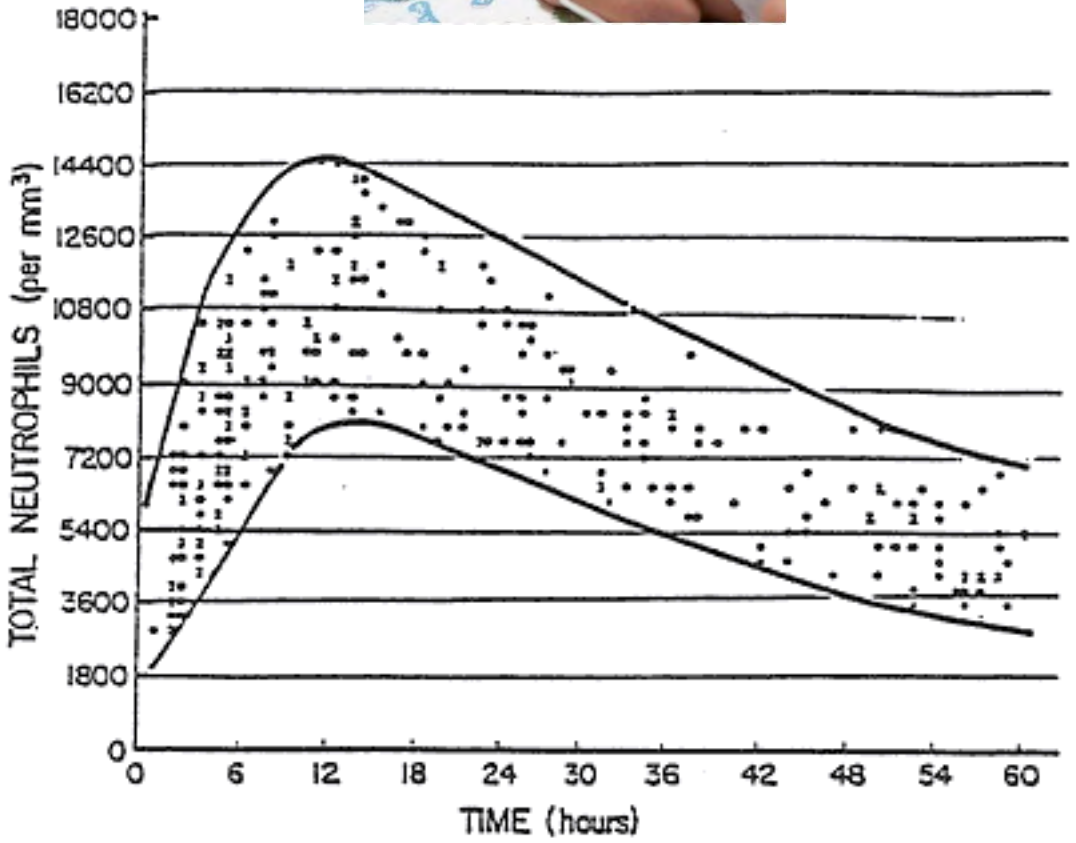
Normal vs Abnormal



- 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."

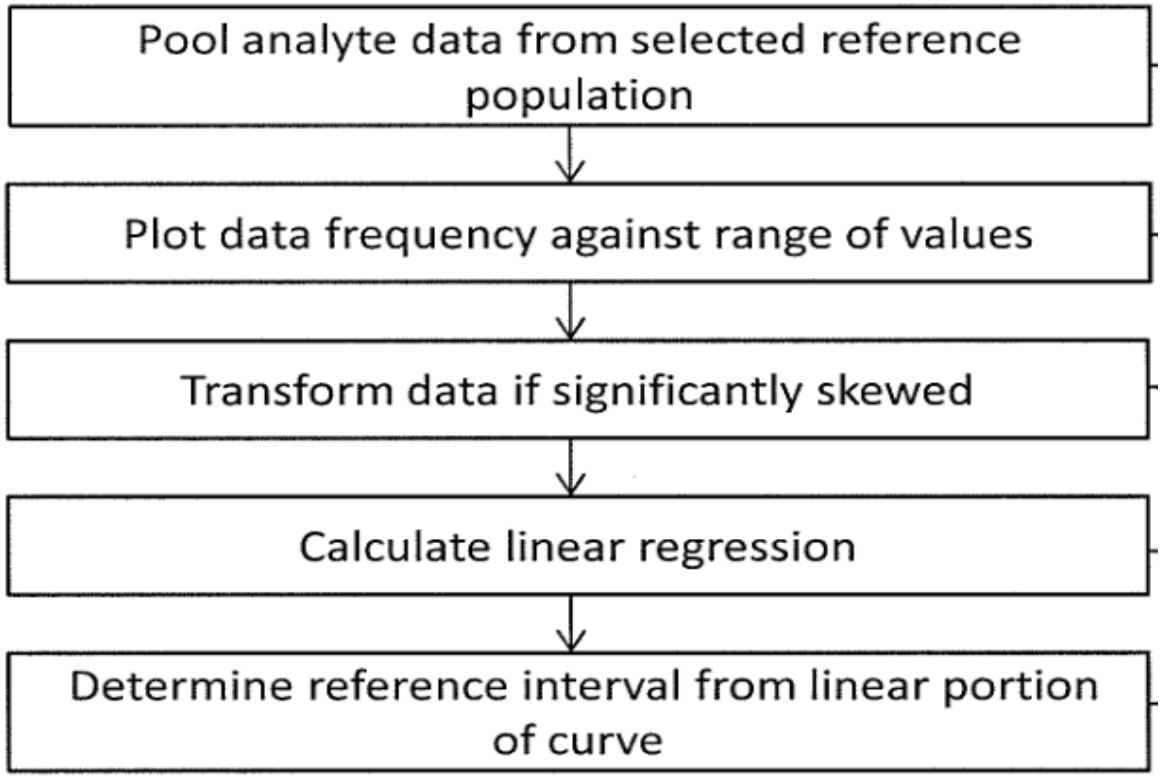
Plasma creatinine (μmol/l)

0 1 2 3

Postnatal age (weeks)

Can one establish reference ranges from databases with large collections of clinical laboratory data?

Computerized Hoffman Method for indirect determination of reference ranges (Katayev et al. Am J Clin Pathol. 2010)



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

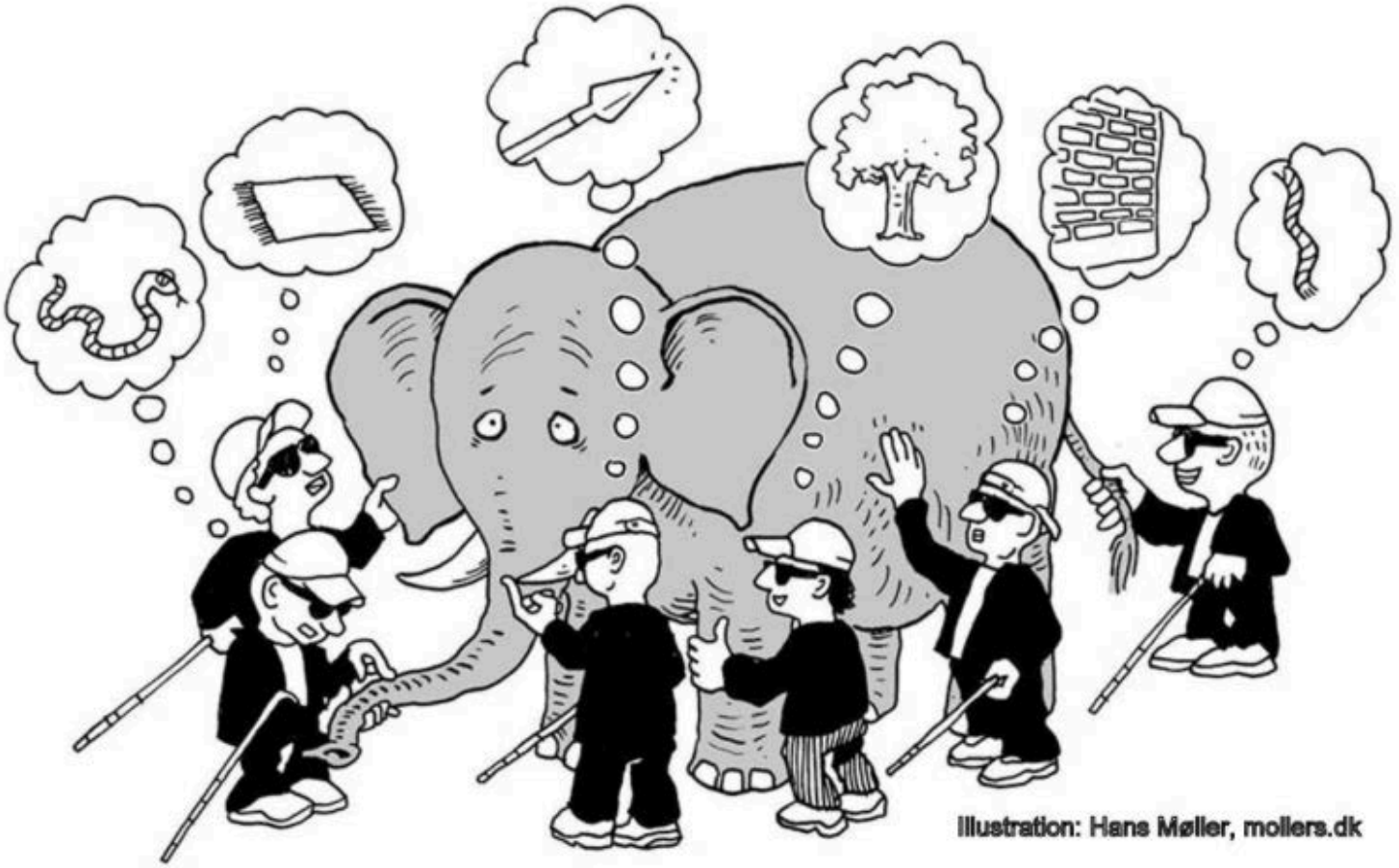


Illustration: Hans Møller, mollers.dk

0800 - 0820	Introduction: what the stakeholders expect from the data group	Mark Turner
0820 - 0830	Plan for the day	TD / KC
0830 - 0915	Multi-institutional databases – The How	Jeff Jacobs
0930 - 0945	*Surveying the literature: biomarker outcomes in neonatal trials"*	Lauren Kelly
1000 - 1145	Topic: Defining an abnormal lab event 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)**	TD to lead & KC to make notes 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 NNRD, NRND (Japan), ANZNN
- Agreed the key items we are interested to map
- Checking how much has already been done by other groups

Definitions 1

- *'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

1230 - 1520	Topic: Standardising datasets and definitions of trial outcomes	KC to lead & TD to make notes
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.

INC
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Concluding Remarks

Jon Davis, INC Co-Director
Tufts Medical Center

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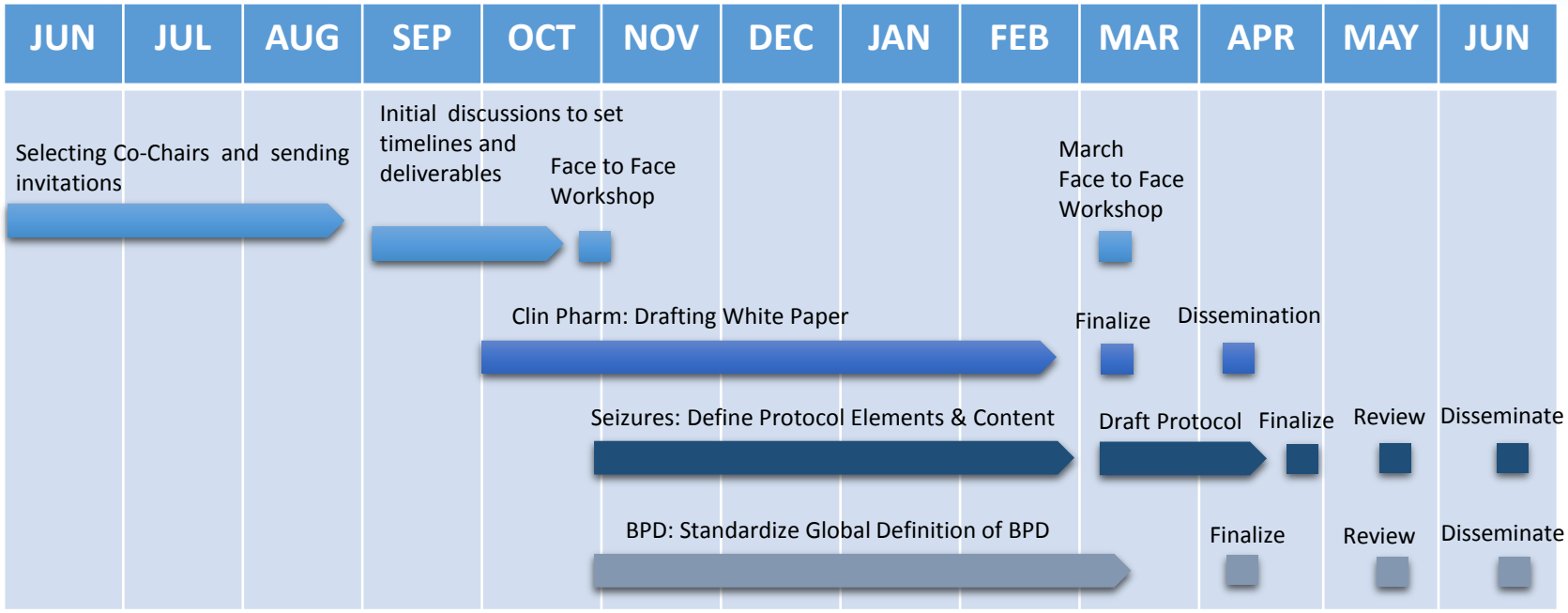
Workgroup Timelines and Deliverables



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

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

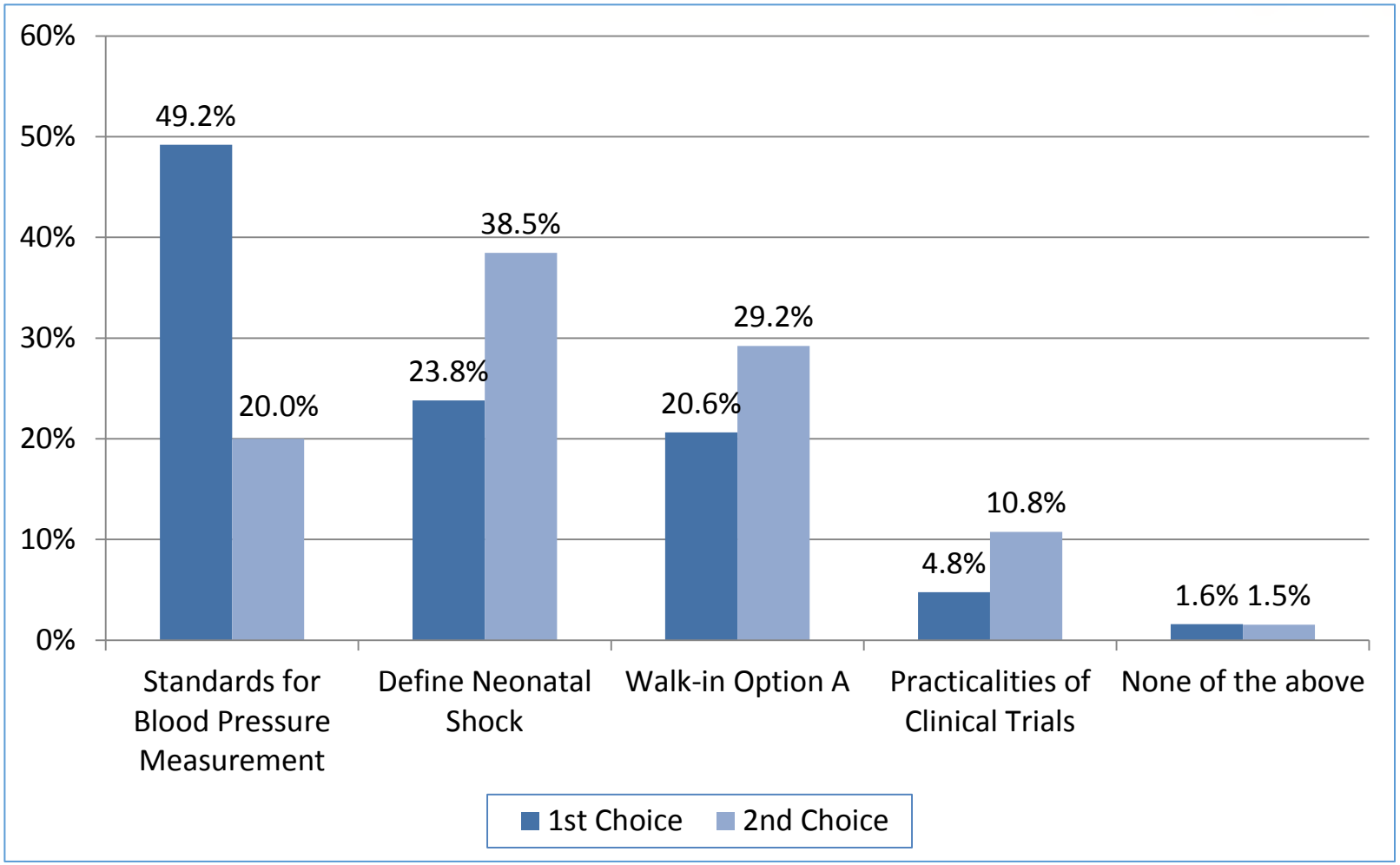
N=64	First	Second
A. Make the most of existing data	19%	22%
B. Standard protocol for new studies	44%	29%
C. How to assess efficacy in the CNS	36%	48%

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



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Thank You