Agenda – September 13th

8:00 a.m.	**Welcome to Day 2** RALPH BAX (EMA)
8:15 a.m.	**Session IV:** *Precision Medicine for Neonates: Horizon Scanning* MARK TURNER (UNIVERSITY OF LIVERPOOL), CHAIR
10:00 – 10:30 a.m.	COFFEE BREAK
10:30 – 12:00 p.m.	**Session V:** *Long-term Outcomes* LEX DOYLE (UNIVERSITY OF MELBOURNE) & NEIL MARLOW (UNIVERSITY COLLEGE LONDON), CO-CHAIRS
12:00 – 1:00 p.m.	LUNCH
1:00 - 3:00 p.m.	**Session VI**: *Necrotizing Enterocolitis* RON PORTMAN (NOVARTIS), CHAIR
3:00 – 3:15 p.m.	*Concluding Remarks*, MARK TURNER, INC CO-DIRECTOR
3:15 p.m.	WORKSHOP ADJOURNED

Agenda – Long-term Outcomes

10:30 a.m.

Session V: *Long-term Outcomes*

LEX DOYLE (UNIVERSITY OF MELBOURNE) & NEIL MARLOW (UNIVERSITY COLLEGE LONDON), CO-CHAIRS

Long-term outcomes from clinical trials – why, what, when and how?
LEX DOYLE (UNIVERSITY OF MELBOURNE)

Should Long-term Outcomes be the Standard for Neonatal Trials?
NEIL MARLOW (UNIVERSITY COLLEGE LONDON)

Session V Panel:

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PETER ANDERSON (UNIVERSITY OF MELBOURNE)
DINA APELE-FREIMANE (PDCO)
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GIANCARLO NATALUCCI (UNIVERSITY OF ZURICH)
A.G. VAN WASSENAER-LEEDMHUIS (AMC)
SUSAN McCUNE (CDER/FDA) *by Webex*

Agenda – Long-term Outcomes

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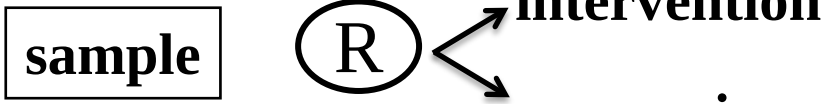
Long-term outcomes from clinical trials - Why, what, when and how?

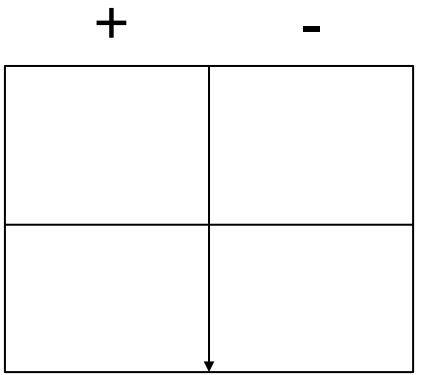
Lex W Doyle
The Royal Women's Hospital
University of Melbourne
Murdoch Children's Research Institute

Outline

1. **Why?**
2. **What?**
3. **When?**
4. **How?**
5. **Follow-up rates?**
6. **When to stop?**

Initial state → Manouvre → Final state



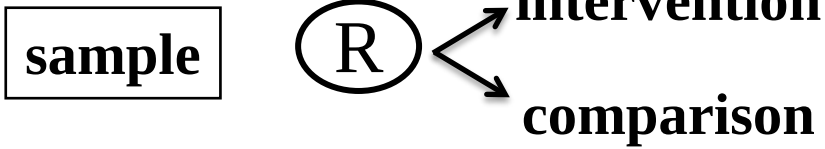


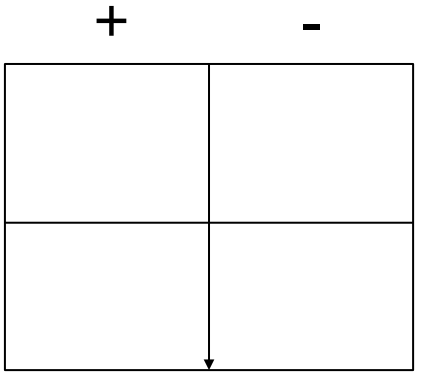
Participants

Intervention
Comparison

Outcome
Time

Initial state → Manouvre → Final state





Scientific	equal risk	equal care	equal look
Clinical	recognisable	feasible	important

Why follow-up?

Participants	**Among infants <1251 g**
Intervention	**how does caffeine**
Comparison	**compared with no caffeine (placebo)**
Outcome	**affect neurodevelopmental outcome**
Time	**at a) 18 mths, b) 5 yrs, c) 11 yrs?**

What Outcomes?

1. Child
2. Family

Long term follow up of high risk children: who, why and how?
BMC Paediatrics 2014; 14:279

Child Outcomes

- **Physical health**
- **Learning and cognition**
- **Mental health**
- **Quality of life**

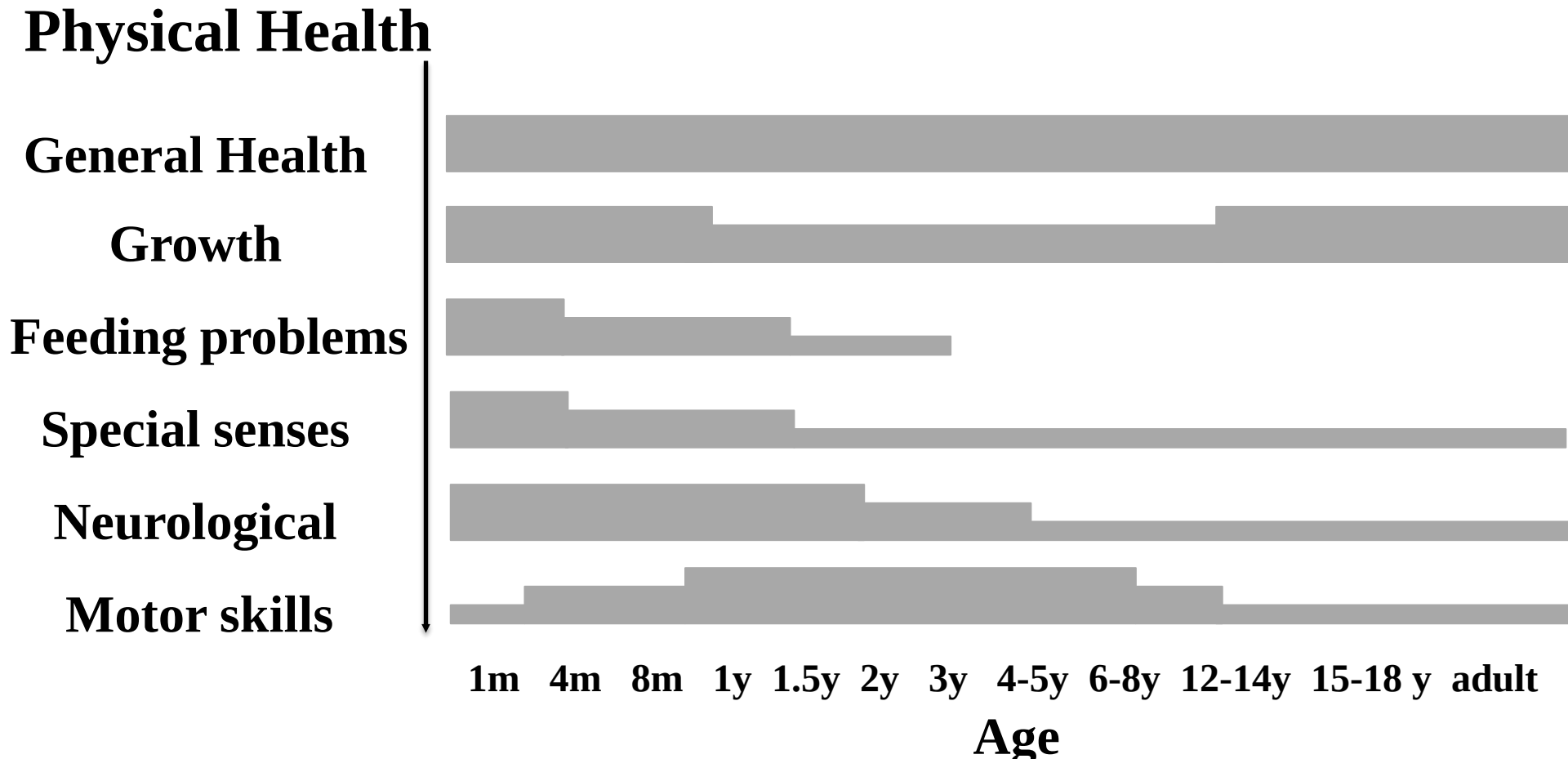
Family Outcomes

- **Parents' mental health**
- **Carer-child interaction**
- **Family function**
- **Siblings**

When?

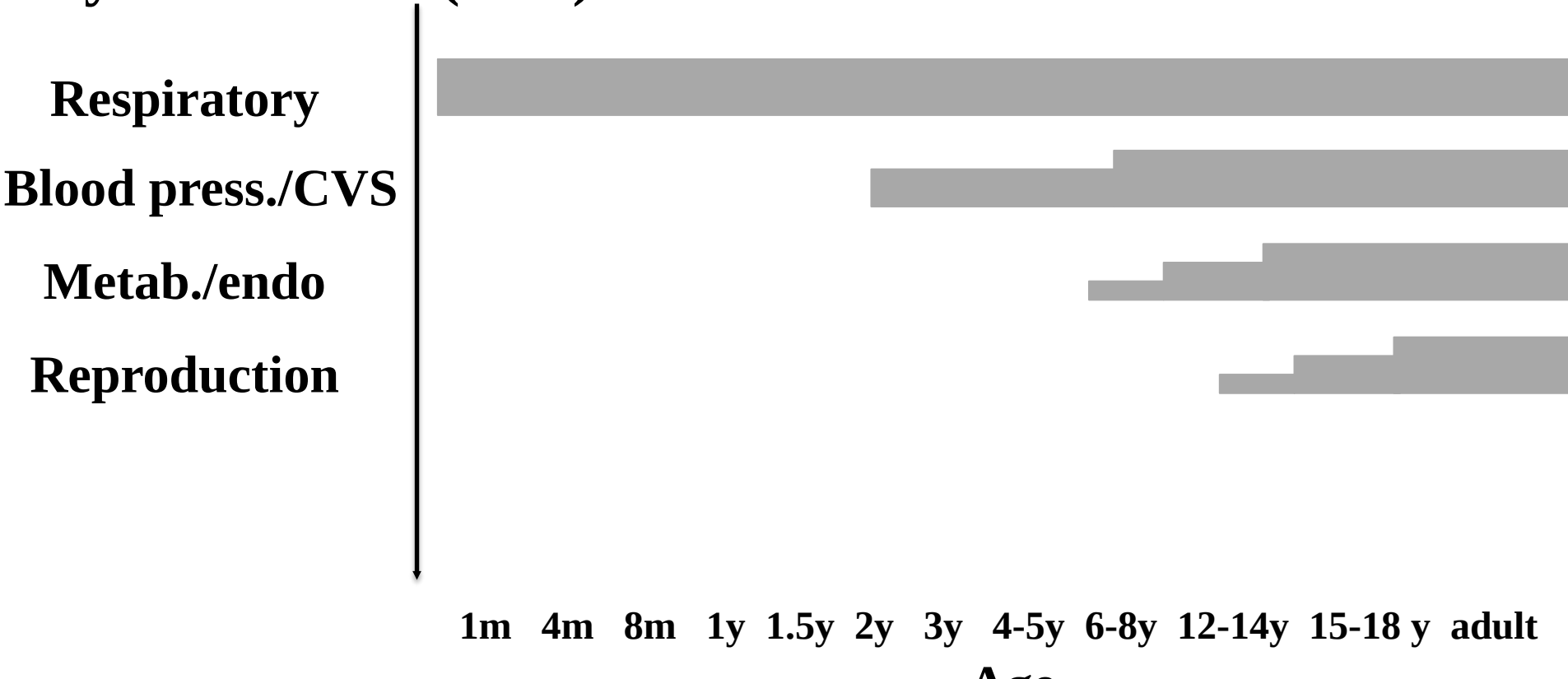
1. Child
2. Family

Child Outcomes



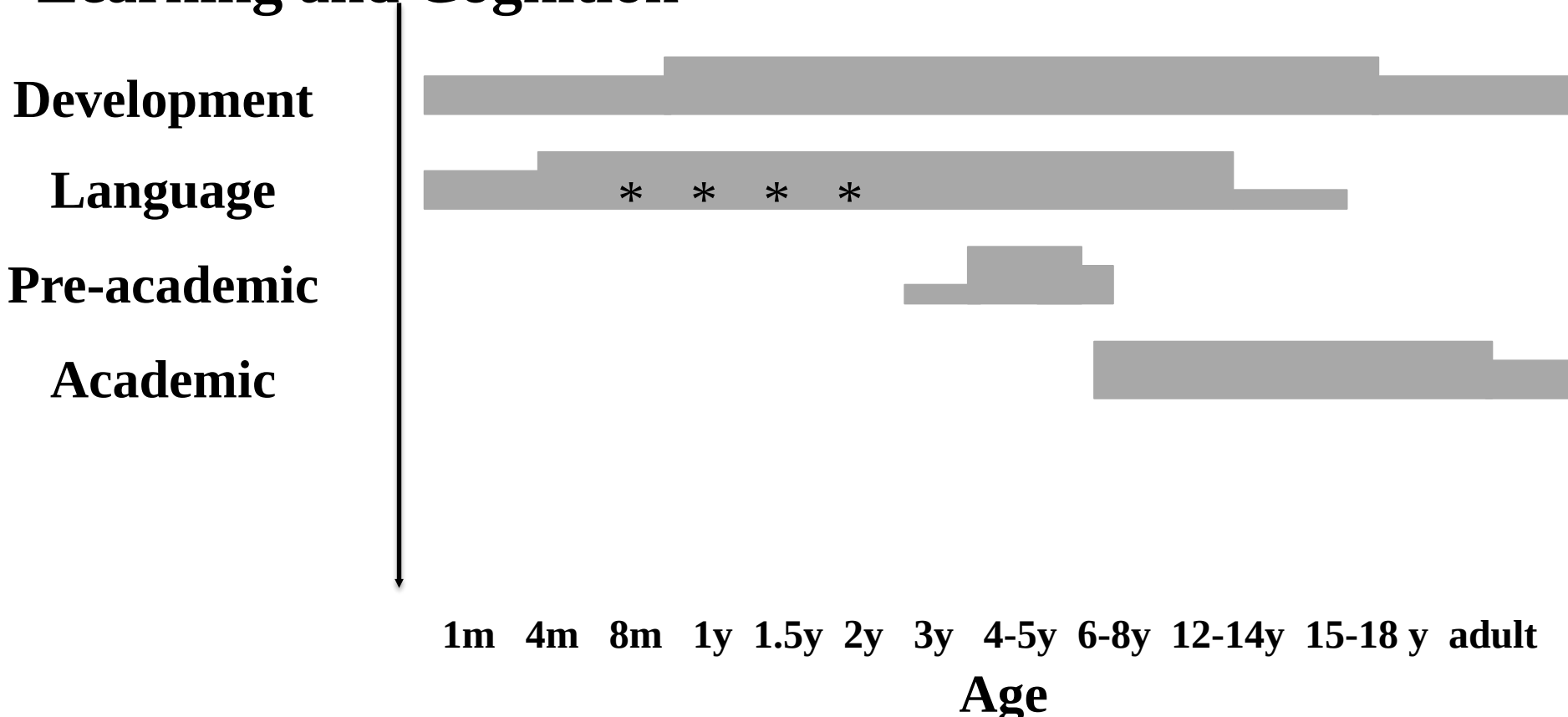
Child Outcomes

Physical Health (cont)

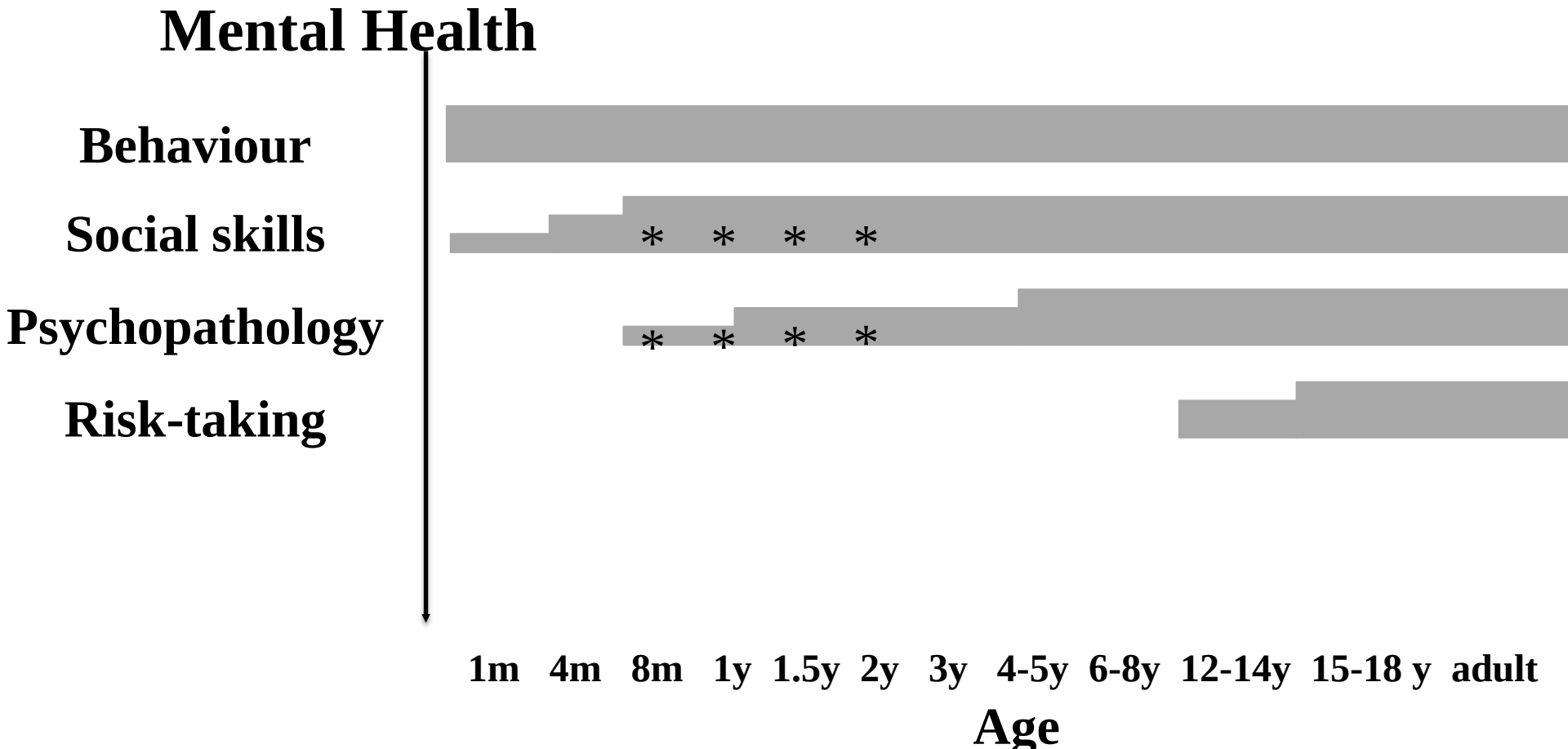


Child Outcomes

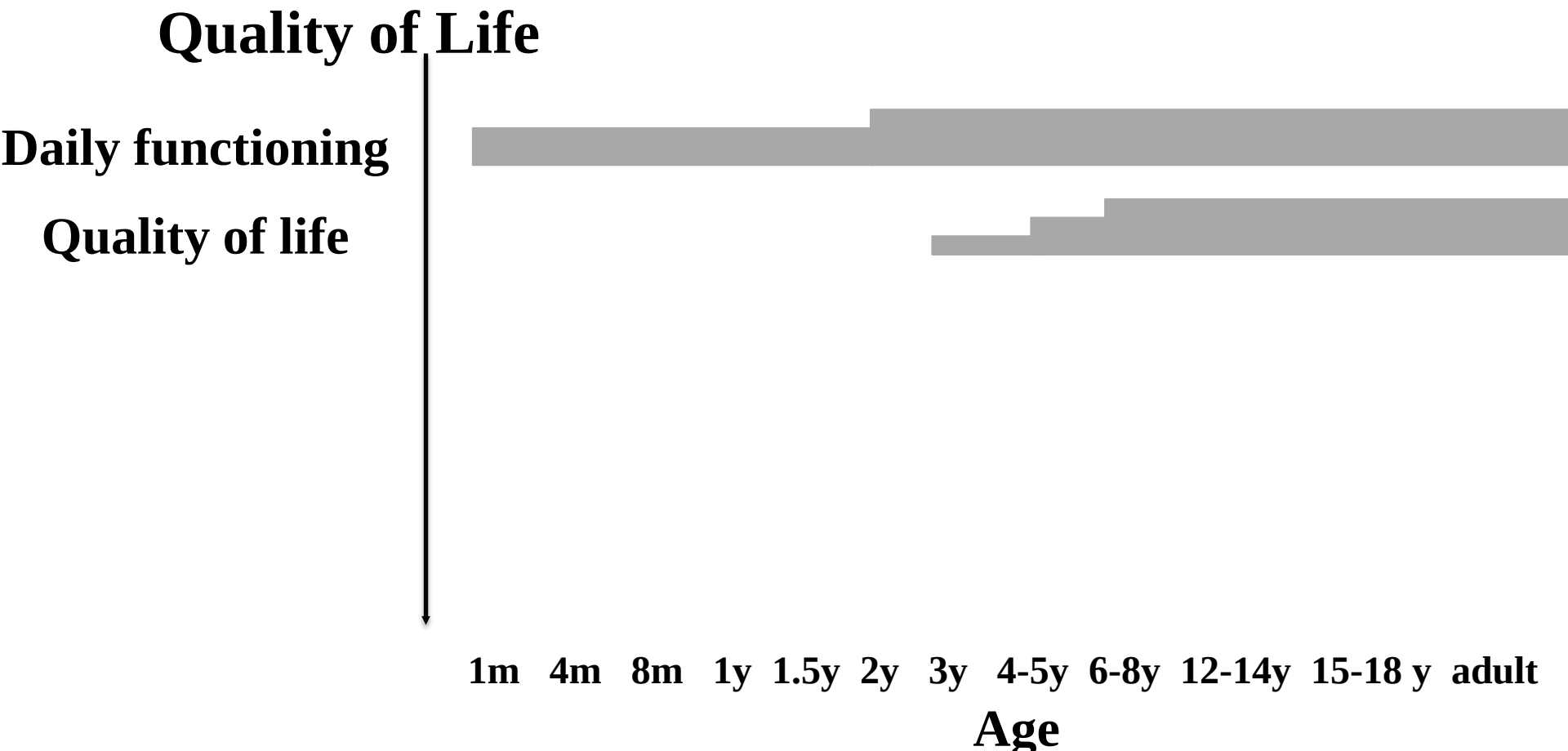
Learning and Cognition



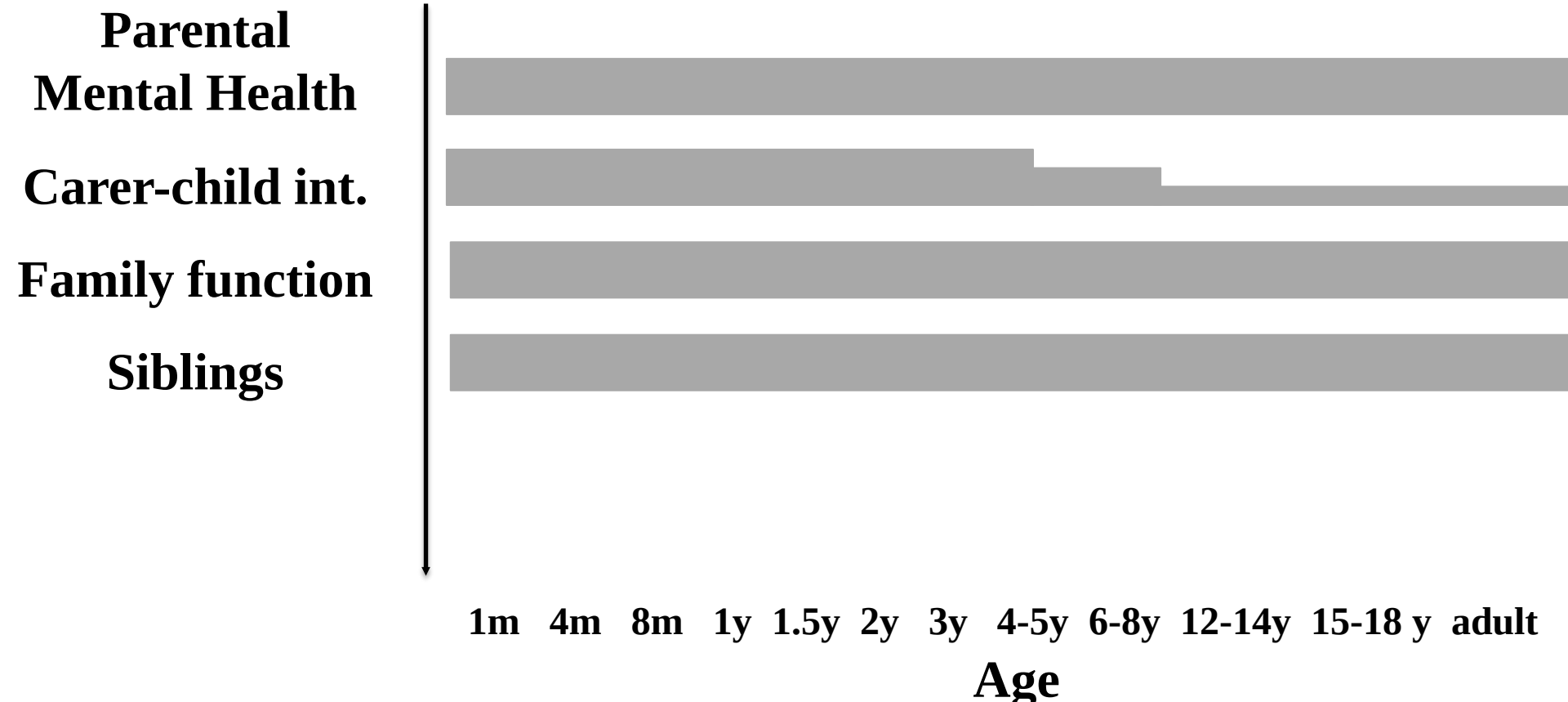
Child Outcomes



Child Outcomes



Family Outcomes



How?

Personnel/equipment will vary

Assessment tools

- **Physical health**
  - **General**
  - **Growth**
  - **Feeding**
  - **Special senses**
  - **Motor**
  - **Cardiovascular**
  - **Respiratory**
  - **Metabolic/endocrine**
  - **Reproduction**

How?

Assessment tools

- **Learning and cognition**
  - **General development**
    - **Bayley, Griffiths**
    - **Wechsler scales**
  - **Attention**
  - **Memory**
  - **Executive function**
  - **Information processing**
  - **Language development**
  - **Pre-academic skills**
  - **Academic skills**

How?

Assessment tools

- **Mental health**
  - **Newborn period**
  - **Infant/toddler**
    - **Autism**
    - **ADHD**
  - **Pre-school**
  - **School – parent and teacher**
- **Quality of life**
  - **Daily functioning**
  - **Well-being**

How?

Family variables

- **Parental mental health**
- **Child-parent interaction**
- **Family functioning**
- **Siblings**

Does the follow-up rate matter?

Guillen at al. Arch Pediatr Adol Med 2012; 166:178-84

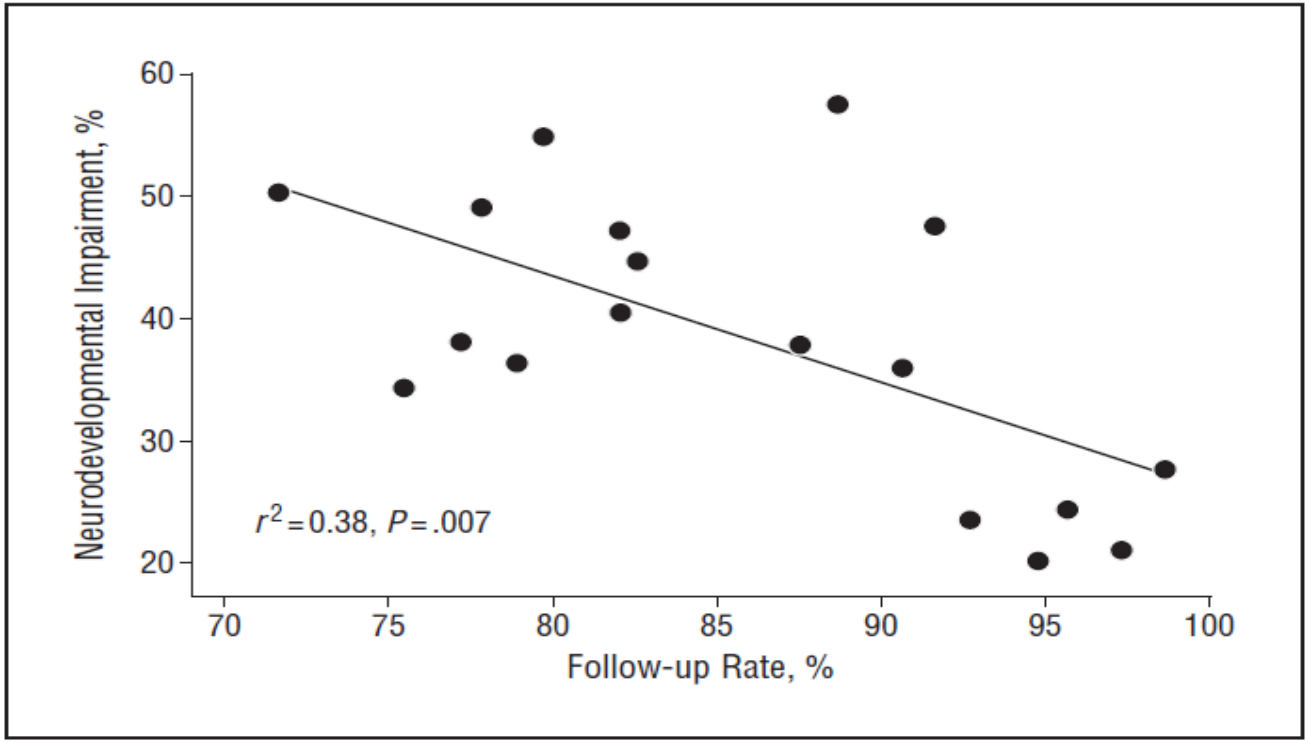


Figure 1. Scatterplot showing the relationship between neurodevelopmental impairment and follow-up rate. Solid line represents the linear regression fit

Guillen at al. Arch Pediatr Adol Med 2012; 166:178-84

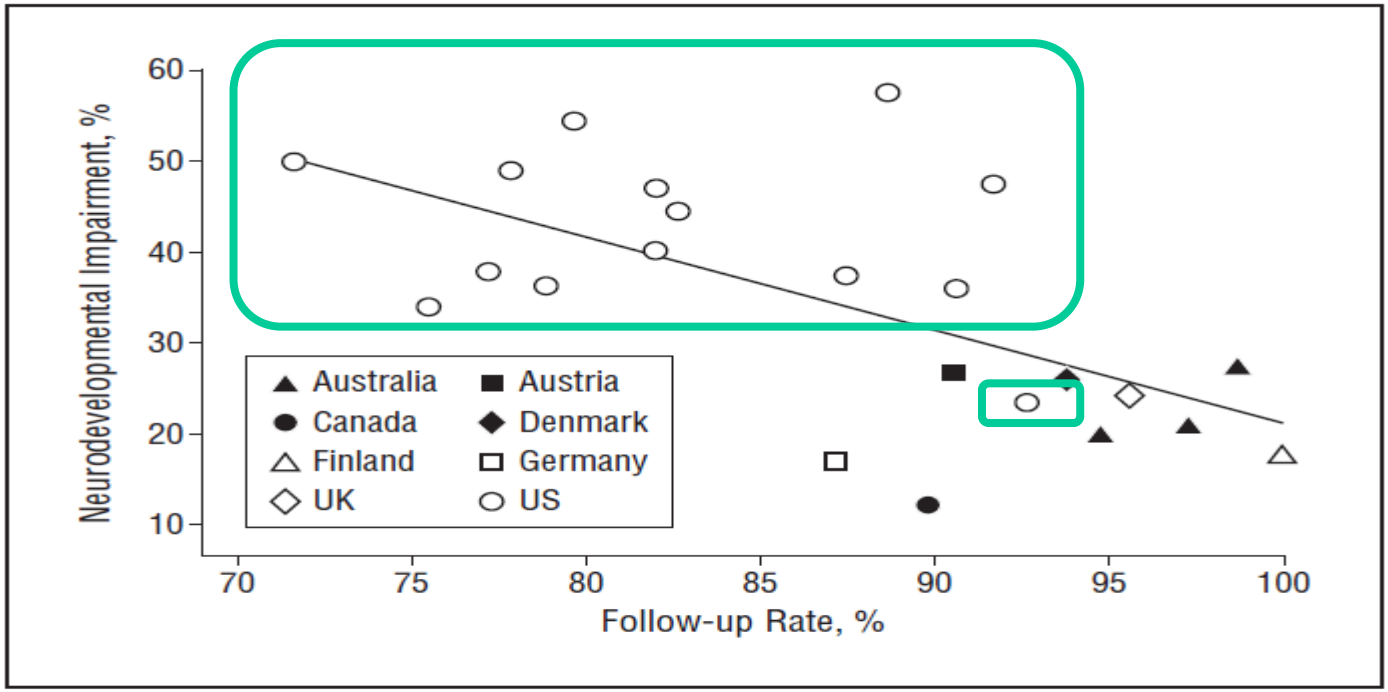


Figure 2. Scatterplot showing the relationship between neurodevelopmental impairment and follow-up rate by country. Solid line represents the linear regression fit across all subjects.

Guillen at al. Arch Pediatr Adol Med 2012; 166:178-84

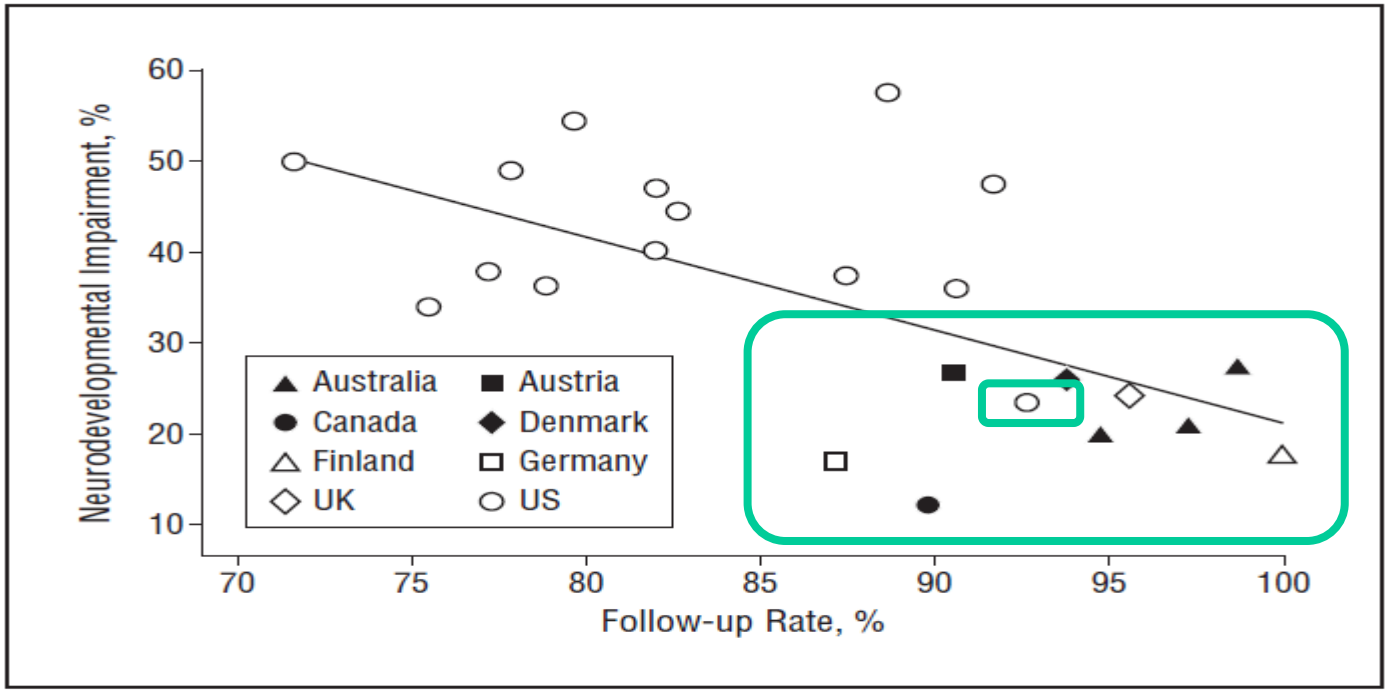


Figure 2. Scatterplot showing the relationship between neurodevelopmental impairment and follow-up rate by country. Solid line represents the linear regression fit across all subjects.

Consequences of lower follow-up rate?

VLBW infants - Easy to follow compared with hard to follow

Royal Women's Hospital

Births 1991-92

N=204/217 (94%) at age 5 years

¾ "easy", ¼ "difficult"

J Paediatr Child Health 2001; 37:152-156.

Consequences of lower follow-up rate?

	“difficult”	“easy”
	n=51	n=153
Disability	41%	19%

Consequences of lower follow-up rate?

	“difficult”	“easy”
	n=51	n=153
Disability	41%	19%
IQ <85	39%	14%

Guillen at al. Arch Pediatr Adol Med 2012; 166:178-84

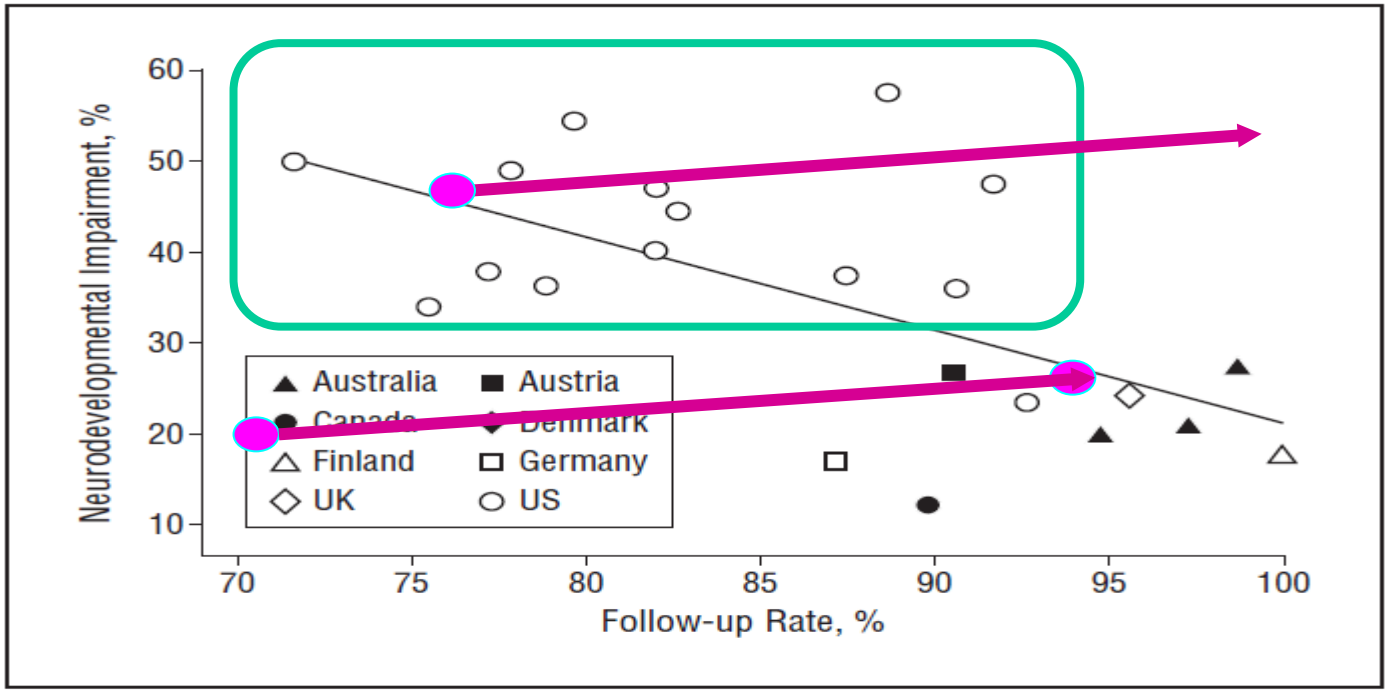


Figure 2. Scatterplot showing the relationship between neurodevelopmental impairment and follow-up rate by country. Solid line represents the linear regression fit across all subjects.

Does the follow-up rate matter?

1. **Underestimate rates of impairment**
2. **Can identify higher-risk groups before discharge**

Identify before discharge

	“difficult”	“easy”
	n=51	n=153
Family not intact	20%	5%
Lower mat. educ.	88%	54%
Multiple	43%	30%
No breast milk	22%	11%

When to stop ?

Depends on the research question

At what age is the outcome?

The later the better

Benefits – better cognitive assessments

Risks – less relevant to contemporary care

– lower FU rate

– cost

When to stop ?

Victorian cohort 1997

22-27 weeks; n=201

term controls; n=199

Assessed at 2 and 8 years

94% EPT

87% controls

Roberts et al. Arch Dis Child 2010; 95:786-90

VICS – Preterm

		8 Years			
		Nil	Mild	Moderate	Severe
2 years	Nil	59	34	3	1
	Mild	18	14	5	2
	Moderate	2	14	5	4
	Severe	3	7	7	9

VICS – Preterm

		8 Years			
		Nil	Mild	Moderate	Severe
2 years	Nil	**59**	34	3	1
	Mild	18	**14**	5	2
	Moderate	2	14	**5**	4
	Severe	3	7	7	**9**

Kappa = 0.20

When to stop ?

Agreement between disability at 2 years and disability at 8 years

EPT – kappa = 0.20

Term – kappa = 0.37

Mostly driven by change in cognitive scores

Relationships over time

Victorian cohort 1991-92

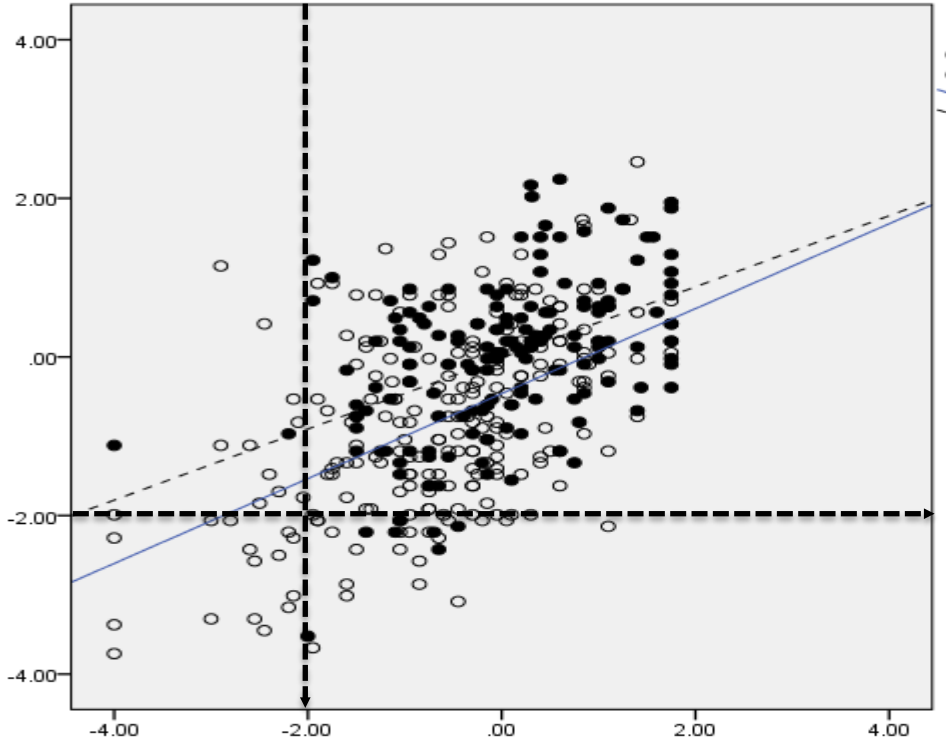
297 survivors 1000 g or <28/52

260 controls >2499 g

IQ score at 18 years

DQ at 2 years; IQ at 5 and 8

Linear regressions – 2 and 18



IQ score at 18 years

IQ SD score at 18

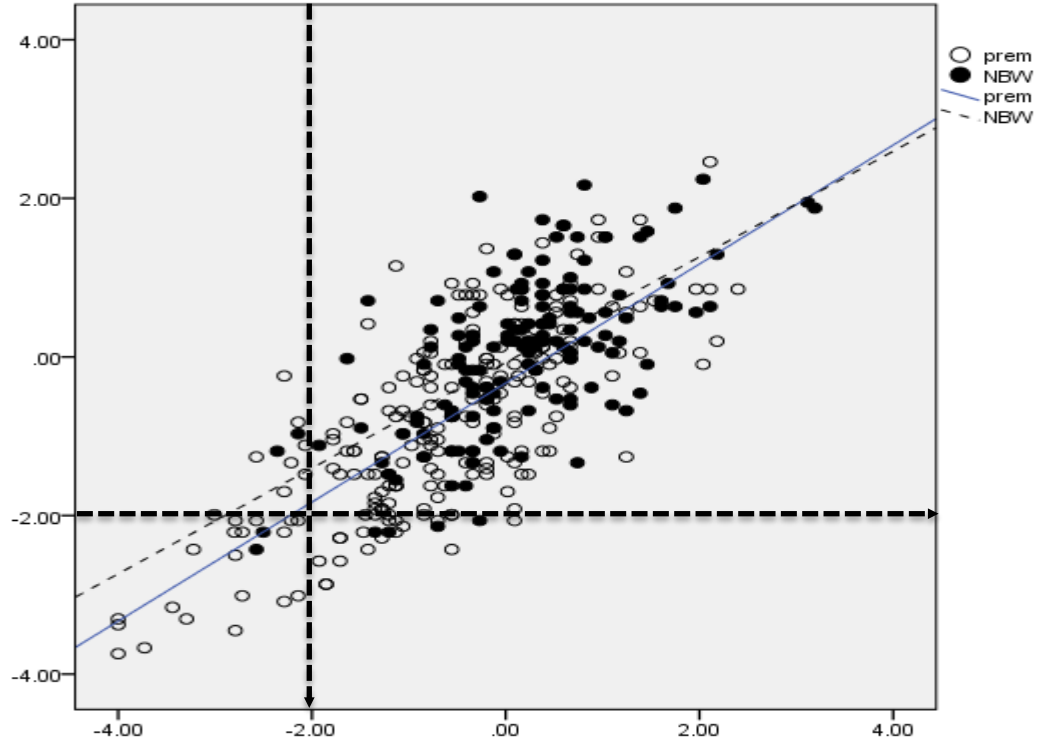
DQ SD score at 2

DQ score at 2 years

r^2=25%

r^2=21%

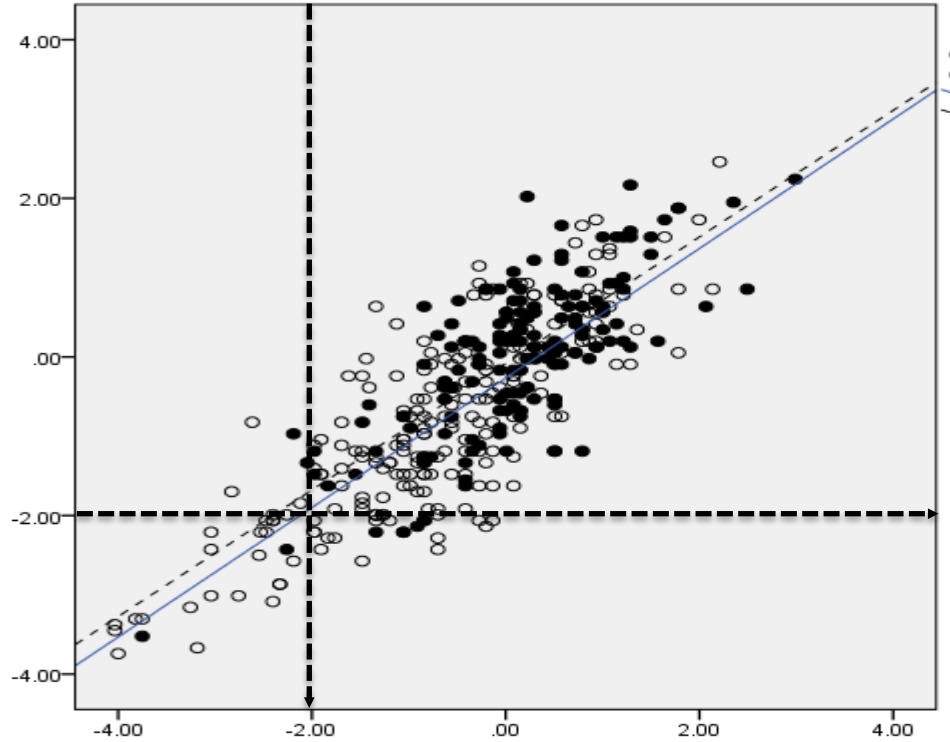
Linear regressions – 5 and 18



r^2=56%

r^2=43%

Linear regressions – 8 and 18



IQ score at 18 years

IQ SD score at 18

IQ SD score at 8

IQ score at 8 years

r^2=67%

r^2=57%

Later ages

Can assess other cognitive areas better

Memory, executive function, attention, academic achievement, etc.

Take home messages

1.	Why?	Get important answers
2.	What?	Consider more
3.	When?	Later the better
4.	How?	Variously
5.	Follow-up rates?	Expect problems
6.	When to stop?	Never!

Why follow-up?

Participants	**Among infants <1251 g**
Intervention	**how does caffeine**
Comparison	**compared with no caffeine (placebo)**
Outcome	**affect neurodevelopmental outcome**
Time	**at a) 18 mths, b) 5 yrs, c) 11 yrs?**

Profit (Professional Follow-up of Infants over Time) **Group**

- Lex Doyle, Peter Anderson, Malcolm Battin, Jennifer R Bowen, Nisha Brown, Catherine Callanan, Catherine Campbell, Samantha Chandler, Jeanie Cheong, Brian Darlow, Peter G Davis, Tony de Paoli, Noel French, Andy McPhee, Shusannah Morris, Michael O'Callaghan, Gehan Roberts, Alicia J Spittle, Dieter Wolke, Lianne Woodward
- Australia, New Zealand, UK, USA

BMC Paediatrics 2014; 14:279

Funding – NHMRC, Australia

Agenda – Long-term Outcomes

10:30 a.m.

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INC
CRITICAL PATH INSTITUTE
International Neonatal Consortium

Should long term outcome be the standard for neonatal trials?

Neil Marlow

CRITICAL PATH INSTITUTE

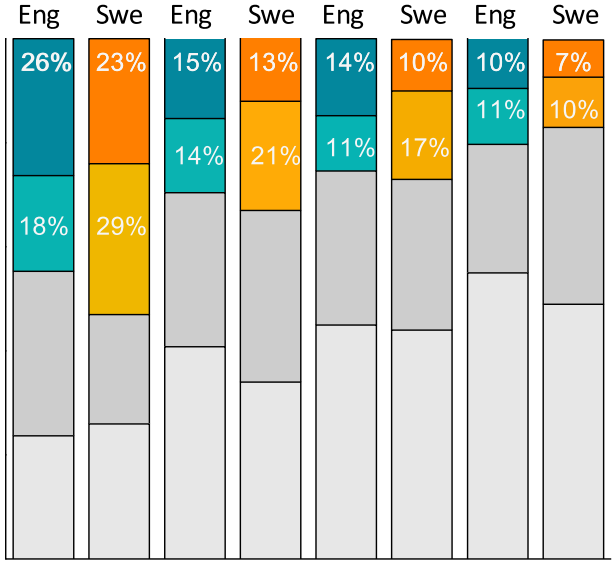
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Randomised trials in neonatology

- High risk – mortality and morbidity
- Continuing challenge:
  - Smaller effect sizes
  - Larger trial sizes
    - Enthusiasts
  - Few biomarkers of important outcomes
  - Outcomes challenging
  - Solutions not obvious
  - Some results simply confusing!

Using death or disability in preterm trials

- The value of the 2 year assessment
- Use of composite outcomes
- Issue of causal pathway v safety outcome
- Is the long term outcome the only real outcome?



ment

EPICure2: Moore et al BMJ 2012
EXPRESS: Serenius et al JAMA 2013

Two year neurodevelopmental outcomes

Table 1 Summary of definitions for recommended outcome categories (British Association of Perinatal Medicine 2008)

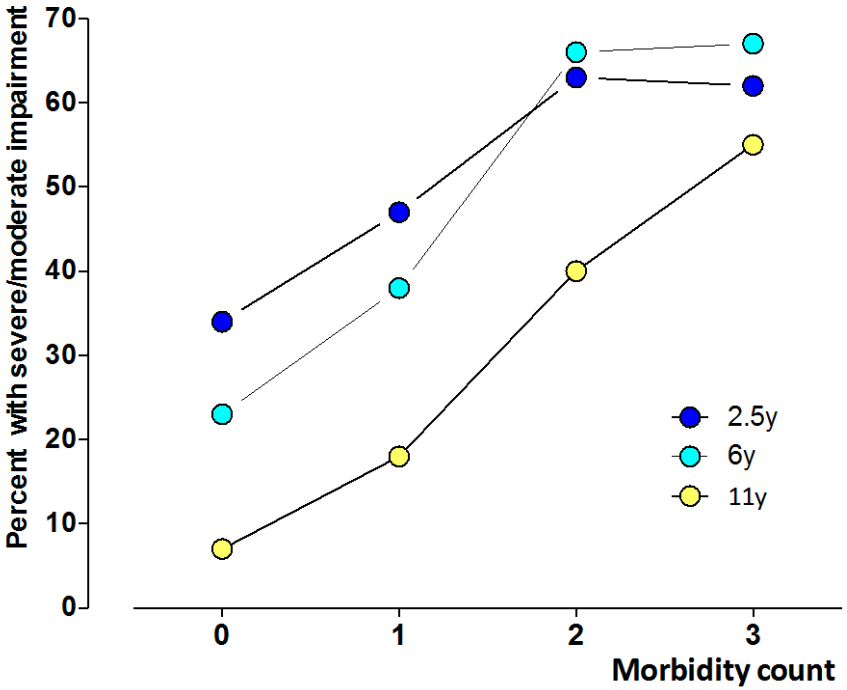
Criteria for	Severe neurodevelopmental disability	Moderate neurodevelopmental disability
Domain	*Any one of the below:*	*Any one of the below:*
Motor	Cerebral palsy with GMFCS level 3, 4 or 5	Cerebral palsy with GMFCS level 2
Cognitive function	Score <–3SDs below norm (DQ<55)	Score –2SD to -3SD below norm (DQ 55–70)
Hearing	No useful hearing even with aids (profound >90 dBHL)	Hearing loss corrected with aids (usually moderate 40–70 dBHL) or Some hearing but loss not corrected by aids (usually severe 70–90dBHL)
Speech and Language	No meaningful words/signs or unable to comprehend cued command (ie, commands only understood in a familiar situation or with visual cues eg, gestures)	Some but fewer than 5 words or signs or unable to comprehend uncued command but able to comprehend a cued command
Vision	Blind or can only perceive light or light reflecting objects	seems to have moderately reduced vision but better than severe visual impairment; or blind in one eye with good vision in the contralateral eye
Other disabilities (included as additional impairments to severe or moderate neurodevelopmental disability)		
Respiratory	Requires continued respiratory support or oxygen	Limited exercise tolerance
Gastrointestinal	Requires parenteral nutrition, gavage or gastrostomy feeding	On special diet or has stoma
Renal	Requires dialysis or awaiting organ transplant	Renal impairment requiring treatment or special diet

GMFCS; Gross Motor Function Classification System; SD, standard deviation; DQ, developmental quotient

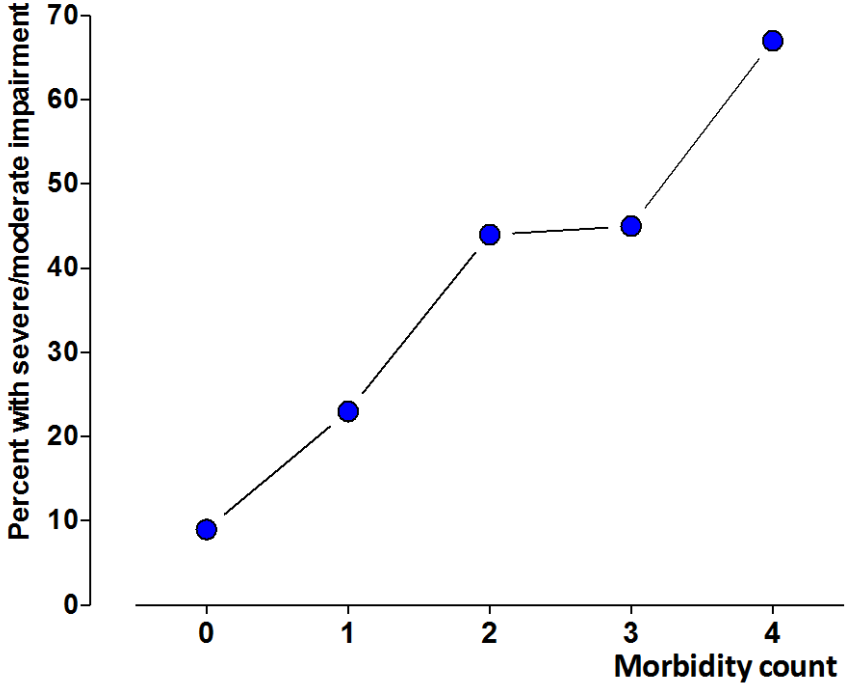
Marlow ADC F&N 2013

Neonatal factors are highly correlated with disability risk

Morbidity count in relation to disability at 3 ages
283 Babies <26w UK and Ireland: EPICure study (1995)



Morbidity count in relation to disability at 2.5y
553 Babies <27 weeks England: EPICure2 study (2006)



EPICure Studies

Long term outcomes are challenging

- Predictive in population terms
- Challenging to organise and carry out
- May require imputation
- Confounding by deaths
- Alternative strategies
  - Face-to-face assessment
  - Screener plus targeted assessments
  - Parent report – cognition: PARCA-r
    general: ASQ3

- Before discharge home:
  - Obtain contact details (landline, mobile, email, Facebook name, etc)
  - Obtain details of relative who may be contacted if contact lost
  - Leaflet explaining importance of the follow examination
  - Study gift (small toy, t-shirt with study logo)
- After discharge before assessment due:
  - Dedicated follow-up coordinator
  - Use national tracing strategies where possible
  - Maximise mailing appearance, appropriate reading age, etc[28]
  - Prospective contacts to ascertain health status
    - Telephone (use mobile with unblocked number)
    - Interim letters with change of address cards
  - Newsletters, Facebook page, website
  - Birthday and Christmas, New Year holiday cards
  - Short interim questionnaires
    - To minimise recall bias for health contacts
    - Focused on relevant issues for the child and family
- Main outcome assessment
  - Arrange well before time
  - Ring to confirm attendance
  - Pay travel expenses
  - Flexibility over time and site of assessment
- Following assessment
  - Always write with thanks
  - Feedback results of assessments
  - Offer research summary at end of study

Marlow ADC F&N 2013

External influences on child development

- Other factors affect developmental outcomes
  - Social/genetic factors
  - Noise in outcome measure
  - Increases need for large trial size

Socio-environmental factors are important

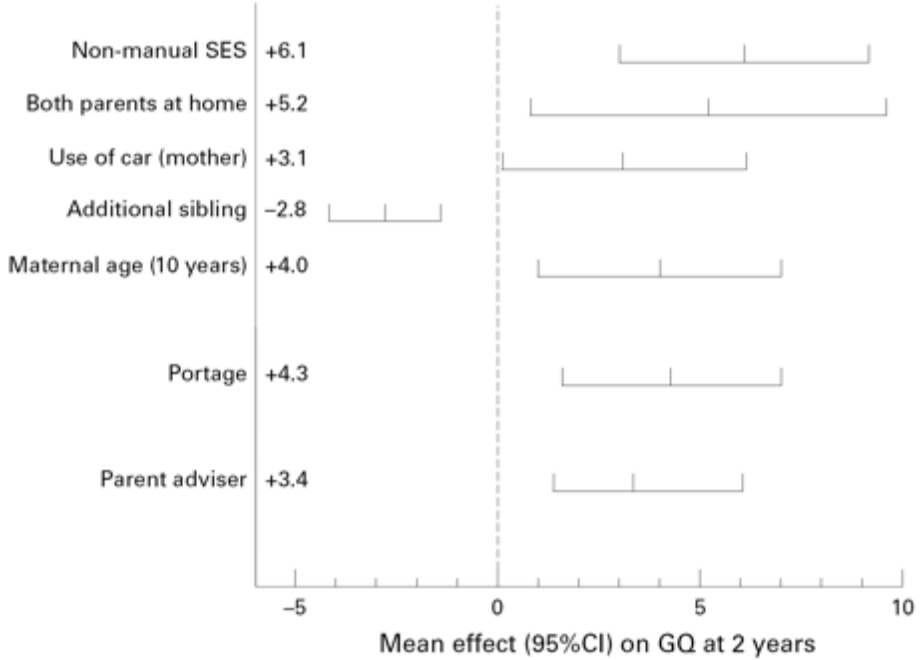


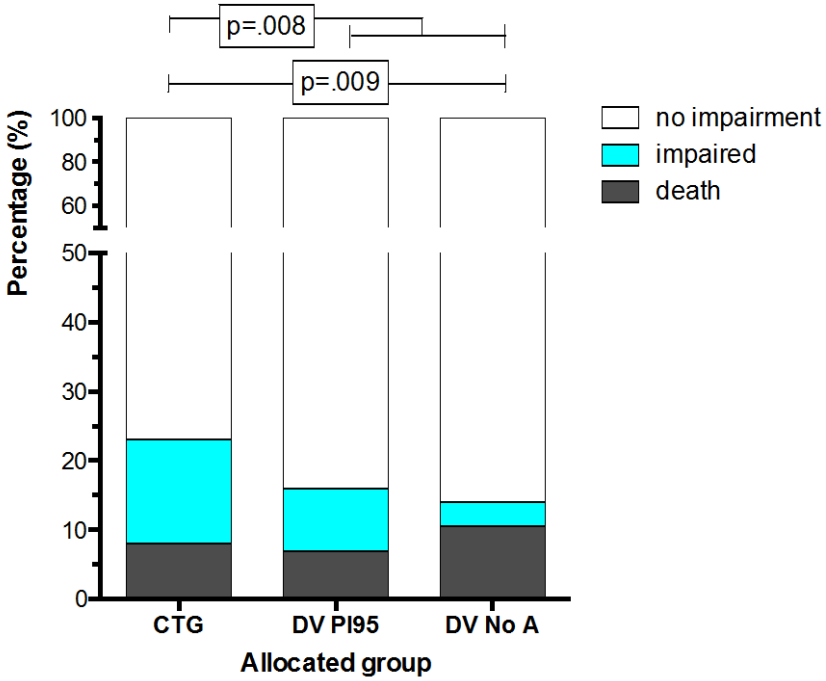
Figure 3 Effect size (95% CI) of social variables and intervention on Griffiths scores (GQ points) at 2 years.

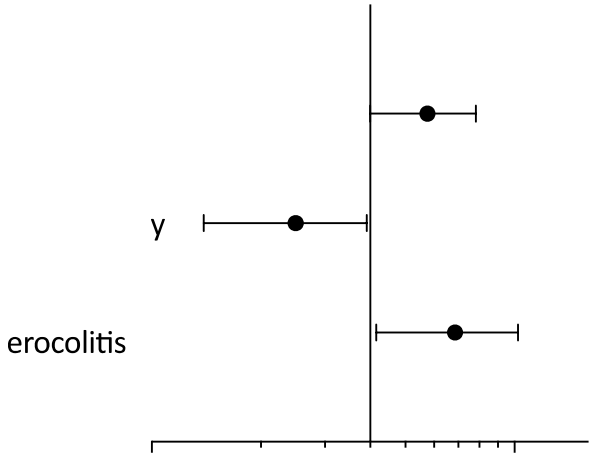
Influences on outcomes

Interventions under test

APIP Arch Dis Child 1998

Competing outcomes

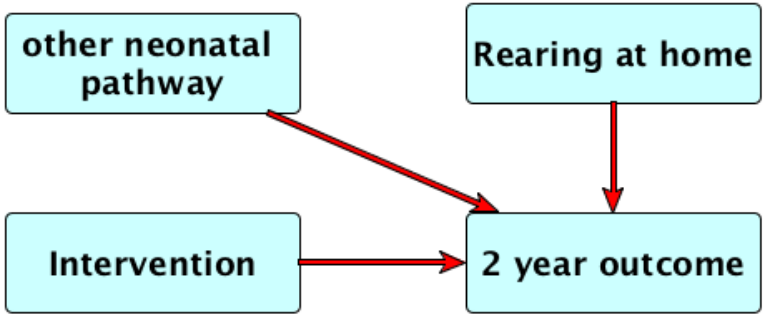




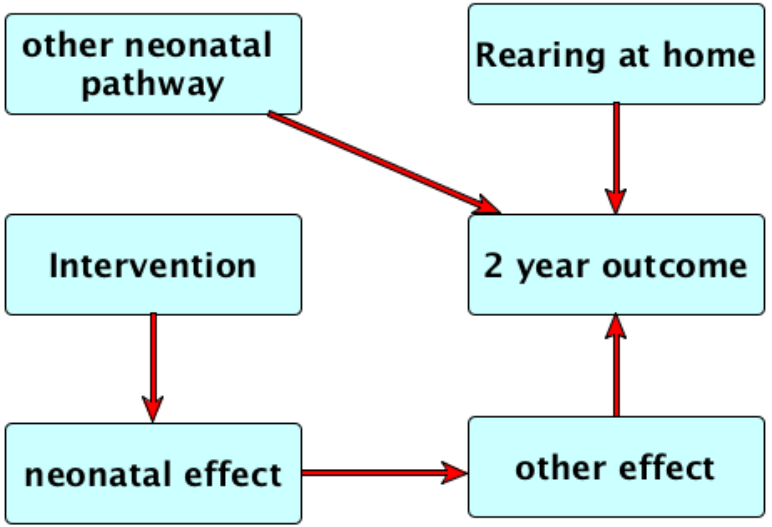
TRUFFLE: Lees, Marlow et al Lancet 2015

BOOST-II collaboration NEJM 2013

Failure to consider direct causation



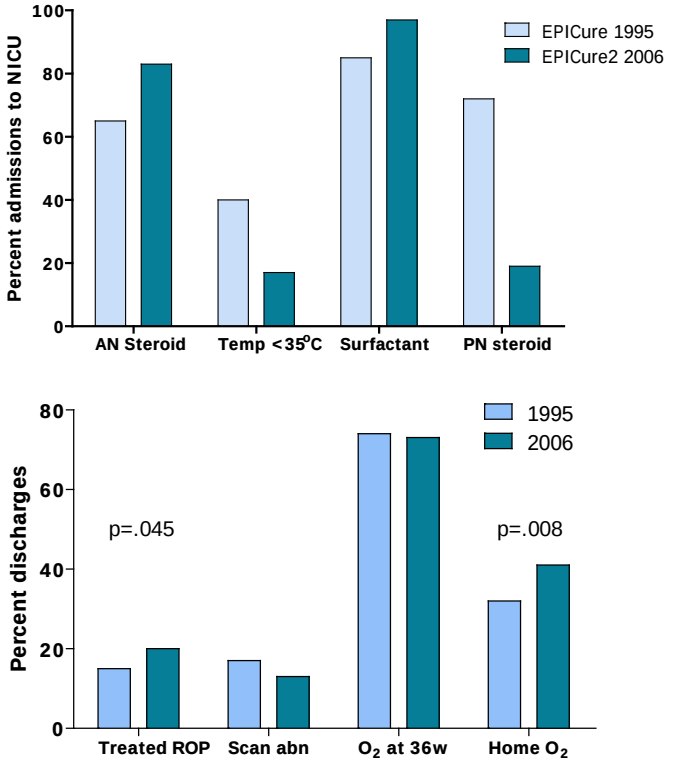
e.g.
MgSO4
Melatonin
Developental intervention



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

Effect on outcomes versus incremental gain

- Unclear causation
  - Cord clamping trials
  - Postnatal steroids
  - Caffeine
  - Indometacin
  - Macrolide antibiotics
  - Reduced painful intervention
- Concept of incremental gain



Costeloe et al BMJ 2012

Critical to show outcomes are safe

- Critical that we show interventions are safe
- In most trials 2y outcomes are safety outcomes
- Negative trial outcomes with neonatal benefit:
  - ORACLE = PPROM (nb spontaneous labour group)
  - Indomethacin
  - Caffeine – benefit at 2y, none at 5y
  - Oxygen saturation targets
  - *Not useless therapies*

Conclusion

- 2 year outcomes important
  - As targets for trials
  - To demonstrate safety
  - But may compete with mortality

  but
  - Routine part of neonatal care
  - For research outcomes these may not be enough
  - Need consistency and training
- At later ages
  - External influences more important
  - Dropout a major issue inflating ‘n’


© Jan Jordaan 2004

Agenda – Long-term Outcomes

10:30 a.m.

Session V: *Long-term Outcomes*

LEX DOYLE (UNIVERSITY OF MELBOURNE) & NEIL MARLOW (UNIVERSITY COLLEGE LONDON), CO-CHAIRS

Long-term outcomes from clinical trials – why, what, when and how? **:**
LEX DOYLE (UNIVERSITY OF MELBOURNE)

Should Long-term Outcomes be the Standard for Neonatal Trials?
NEIL MARLOW (UNIVERSITY COLLEGE LONDON)

Session V Panel:
MARILEE ALLEN (JOHNS HOPKINS)
PETER ANDERSON (UNIVERSITY OF MELBOURNE)
DINA APELE-FREIMANE (PDCO)
SUSAN HINTZ (STANFORD)
SAMANTHA JOHNSON (LEICESTER)
GIANCARLO NATALUCCI (UNIVERSITY OF ZURICH)
A.G. VAN WASSENAER-LEEDMHUIS (AMC)
SUSAN McCUNE (CDER/FDA) *by Webex*

International Neonatal Consortium

EARLY ASSESSMENT OF NEURODEVELOPMENT

Marilee C. Allen MD
Johns Hopkins School of Medicine, Baltimore MD

Early Assessment of Infant Brain Function

- Infant's rapidly developing brain: Neuronal migration; glial cell development; synaptogenesis; programmed cell death; formation of neural networks; refinement; myelination
- Developmental timing: Choreographed and synchronized
- Brain development is shaped by environmental input
- Vulnerability to a variety of environmental insults
- Long-term consequences: Neuromotor control; sensory processing; cognition; behavior
- Early assessments of brain function are an important safety measure in neonatal drug trials

Emergence of Brain Function

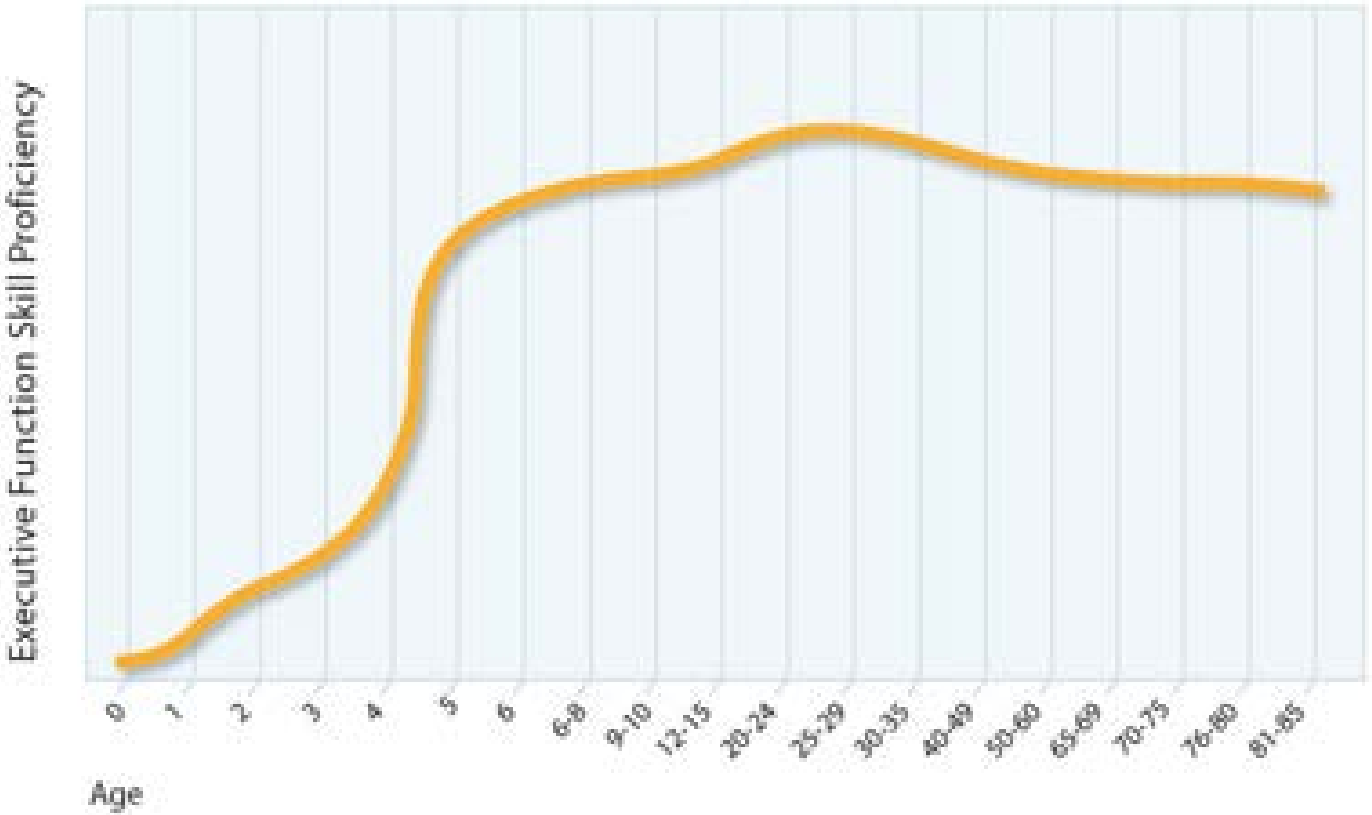
Neuromotor control: Upright posture and balance; mobility; fine motor coordination

Sensory processing: Hearing; vision; multisensory processing and integration

Neurocognition: Ability to process and use information in a meaningful way

- Memory: Sensory memory; working memory; long-term memory
- Communication: Facial expressions/gestures; receptive/expressive language
- Visual processing: Visual motor, visual perceptual, and visual spatial abilities
- Core knowledge and learning by calculations of conditional probability
- Basic self regulation of state (arousal, sleep) and emotions
- Social signaling, turn taking, and eventually, theory of mind
- Pattern recognition, concept formation and abstract thinking
- Computation: Approximate number system, mathematics
- Executive function: Selective attention, inhibition, mental flexibility

From the NIH Toolbox Project: Building the Brain's "Air Traffic Control" System: How Early Experiences Shape the Development of Executive Function, Working Paper #11



Challenges and Limitations to Early Assessment

- Determining significance of an abnormal finding:
  - Absence vs delayed acquisition of an ability
  - May be due to illness and/or weakness
- Immense plasticity of the developing brain
  - Other areas can take over function of injured area
  - The foundation of learning is synaptic plasticity
  - Targeted early intervention strategies could improve outcomes (generally not controlled for or reported)
- Ability has not yet emerged so therefore cannot be assessed
- Despite these concerns, severity of possible adverse effects of a drug on infant brain development make it necessary to assess brain function early as well as over the long-term.

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Brain MRI as a measure for perinatal/neonatal trials outcome

Peter Anderson
Murdoch Childrens Research Institute / The University of Melbourne

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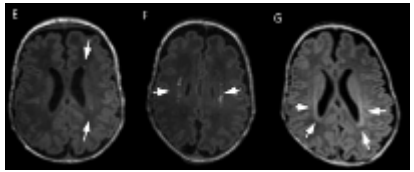
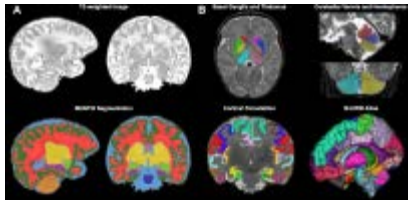
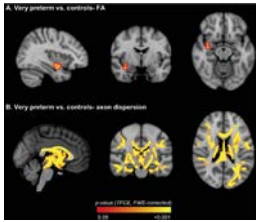
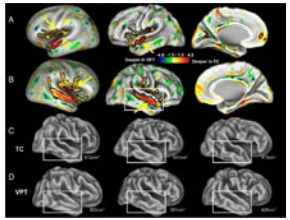
Neonatal / infant brain MRI

- Direct neuroanatomical effects (immediate or short-term outcomes)
- Potential to assess:
  - brain injury/abnormality,
  - growth/size,
  - myelination,
  - structural and functional brain connectivity,
  - cortical folding,
  - neural activation









Recombinant human erythropoietin for the neuroprotection of premature infants

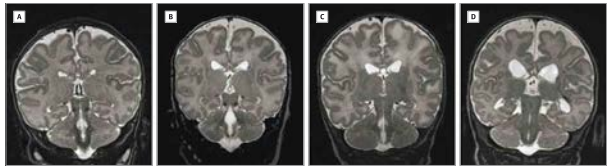
Original Investigation

Association Between Early Administration of High-Dose Erythropoietin in Preterm Infants and Brain MRI Abnormality at Term-Equivalent Age

Russia Ha-Vinh Leuchter, MD; Laura Gui, PhD; Antoine Poncet, MSc; Cornelia Hagmann, MD, PhD; Gregory Anton Lodygensky, MD; Ernst Martin, MD; Brigitte Koller, MD; Alexandra Darqué, MSc; Hans Ulrich Bucher, MD; Petra Susan Hüppi, MD

JAMA. 2014;312(8):817-824. doi:10.1001/jama.2014.9645

Total WMI score[e]	17 (22)	32 (36)	.07	0.61 (0.37-1.00)	0.58 (0.35-0.96)	.03
Subscores of the WMI score[f]						
White matter signal abnormality	2 (3)	10 (11)	.06	0.23 (0.05-1.01)	0.20 (0.05-0.90)	.04
Periventricular white matter loss	14 (18)	29 (33)	.048	0.55 (0.32-0.97)	0.53 (0.30-0.92)	.02
Cystic abnormalities	5 (6)	10 (11)	.42	0.57 (0.20-1.60)	0.51 (0.18-1.44)	.20
Ventricular dilatation	36 (47)	46 (52)	.58	0.89 (0.66-1.22)	0.87 (0.64-1.18)	.37
Thinning of corpus callosum	5 (6)	8 (9)	.74	0.71 (0.24-2.09)	0.67 (0.22-2.00)	.47
Total GMI score[g]	5 (7)	17 (19)	.03	0.34 (0.13-0.88)	0.34 (0.13-0.89)	.03
Subscores of the GMI score[f]						
Cortical abnormality	1 (1)	2 (2)	>.99	0.58 (0.05-6.26)	ND	ND
Gyral maturation	11 (14)	20 (23)	.25	0.64 (0.33-1.24)	0.67 (0.34-1.30)	.24
Subarachnoid space	34 (45)	44 (50)	.61	0.89 (0.65-1.24)	0.91 (0.66-1.26)	.57



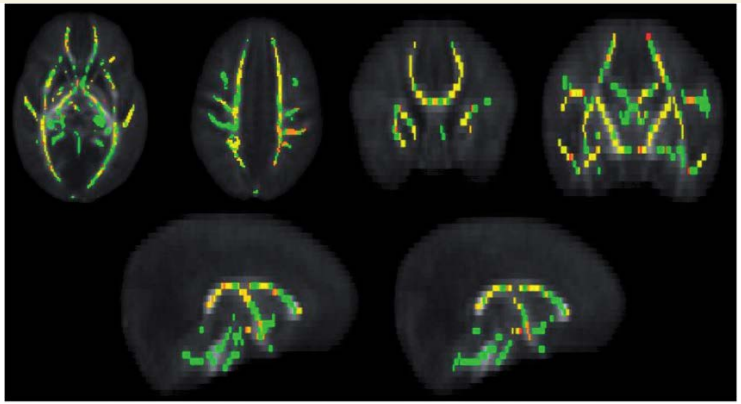


Figure 3 Mean fractional anisotropy skeleton (green) overlaid on the mean fractional anisotropy map in the axial and coronal planes. Regions of the fractional anisotropy skeleton in green represent voxels where there was no difference in fractional anisotropy between infants treated with erythropoietin and placebo. Voxels demonstrating significantly higher fractional anisotropy in the erythropoietin-treated group are overlaid in red-yellow.

Limitations of neonatal / infant MRI

- Expensive (acquisition & analysis)
- Not available at all sites
- Scanner issues
- Infant preparation
- Age at scanning
- Non-compliance of infants
- Artifacts (e.g. motion)
- Consent of families

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Regulatory and scientific challenges related to evaluation of long-term outcomes in neonates

Dr. Dina Apele-Freimane
P. Stradins Clinical university Hospital
MCH Clinic, Head of Neonatal and NIC Department (Riga, Latvia)
PDCO

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Regulatory and Scientific Issues

1. **Lack of consistency – need for harmonization of requirements**

   - timing for evaluation of the long-term neurodevelopmental outcome (vary from 18 to 36 mo)
   - validated tools
   - standardised protocols

2. **Need for validated predictive tools - is it possible to shorten the duration of the study?**

   - predictive value of mid-term outcomes e.g. neurological assessment at term equivalent (40 weeks PMA)

3. **Safety vs efficacy outcomes**

   - safety, efficacy or both?
   - long-term outcome as a primary endpoint?

Regulatory and Scientific Issues

4. **Assessment of long-term outcomes for neonatal studies – mandatory for all neonatal studies?**

   - When long-term outcomes might be accepted as a part of post-marketing surveillance?

   - Individual, flexible approach or need for standardised protocol?

5. **New trends in neonatal studies – new challenges**

   - Substitution of hormones dropping after premature birth for prevention of prematurity related conditions, e.g. IGF1 for ROP prevention

   - How should we assess long-term safety?

6. **Practical challenges for multinational studies**

   - differences in local standards (timing for assessment, quality of care – confounding factors)
   - long-term follow-up programs – not available in all countries
   - missing data – a significant impediment for evaluation of long-term outcomes

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Using routine data for long term developmental outcome assessment

Samantha Johnson
Leicester

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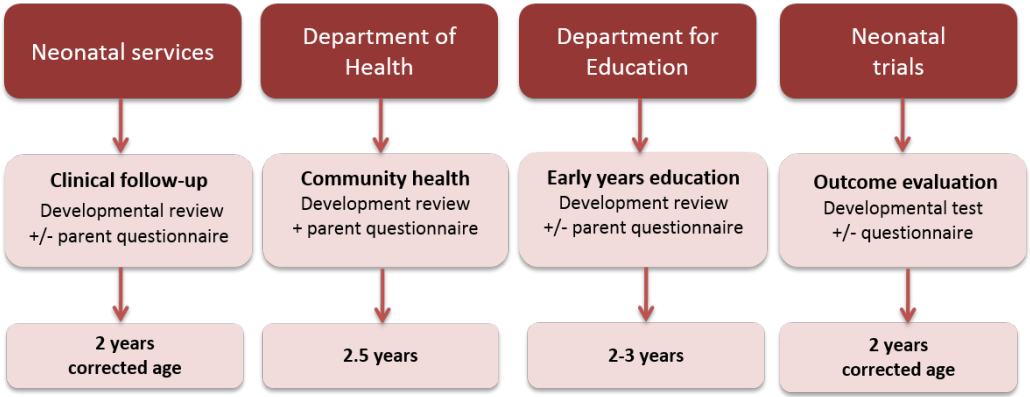
Assessing long term developmental outcomes

- Clinical assessments / research based outcome evaluations
  - Require considerable resources
  - Different outcome measures
  - Training & quality assurance of examiners needed
  - Difficult to implement in large scale trials
  - Added burden on families
  - Participant attrition



Feasibility of routine data for outcome evaluation

- Routine national health or education data as proxy measures of neuro-development
  - Data linkage of trial cohort to routine data, anonymised by treatment group
  - Minimal resources required and potential for longer term follow-up
  - Common, national standardised outcome measure
  - Minimises ascertainment bias
  - No added burden to families

- Issues of consent, validity, quality and relevance

The ORACLE Children Study: educational outcomes at 11 years of age following antenatal prescription of erythromycin or co-amoxiclav

Neil Marlow,[1] Hannah Bower,[2] David Jones,[2] Peter Brocklehurst,[1] Sara Kenyon,[3] Katie Pike,[4] David Taylor,[5] Alison Salt[6]

ABSTRACT

Background Antibiotics used for women in spontaneous preterm labour without overt infection, in contrast to those with preterm rupture of membranes, are associated with altered functional outcomes in their children.

Methods From the National Pupil Database, we used Key Stage 2 scores, national test scores in school year 6 at 11 years of age, to explore the hypothesis that erythromycin and co-amoxiclav were associated with poorer educational outcomes within the ORACLE Children Study.

Results Anonymised scores for 97% of surviving children born to mothers recruited to ORACLE and resident in England were analysed against treatment group adjusting for key available socio-demographic potential confounders. No association with crude or with adjusted scores for English, mathematics or science was observed by maternal antibiotic group in either women with preterm rupture of membranes or spontaneous preterm labour with intact membranes. While the proportion receiving special educational needs was similar in each group (range 31.6–34.4%), it was higher than the national rate of 19%.

Conclusions Despite evidence that antibiotics are associated with increased functional impairment at 7 years, educational test scores and special needs at 11 years of age show no differences between trial groups.

Trial registration number ISCRT Number 52995660 (original ORACLE trial number).

What is already known on this topic?

- Antibiotics given to women with preterm rupture of membranes and no overt infection have neonatal benefit and appear safe in terms of childhood outcomes at 7 years of age.
- In contrast, when administered to women with spontaneous preterm labour with intact membranes there is no neonatal benefit and evidence of poorer outcomes in terms of neurodevelopmental impairment and cerebral palsy at 7 years of age.
- Previous studies are open to ascertainment bias in outcomes in middle childhood.

What this study adds?

- Using independently collected and scored national attainment tests of English, mathematics and science, we demonstrate no differences in long-term educational outcomes at 11 years, or in special needs, following antenatal prescription of antibiotics.
- While attainment test results are within national norms, special needs requirements among these children are higher.
- The use of anonymised educational national data provides good coverage of the population and a robust middle childhood outcome.

Marlow et al Arch Dis Child Fetal Neonatal Ed 2016

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The proper measures

Daily neonatal and follow-up data quality challenges

GIANCARLO NATALUCCI
UNIVERSITY OF ZURICH

CRITICAL PATH INSTITUTE

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Quality of data definition

Quality	Prenatal	Postnatal	Post-discharge
Estabilshed variable definition ¶	Multiple pregnancy Antenatal steroids Mortality …	Gestational age Sex Birth weight BPD, ROP, NEC, Brain lesions …	SD of developmental scores Cerebral palsy and its severity Hearing impairment …
Heterogeneous variable definition	IUGR Chorioamnionitis US Doppler …	Sepsis Hypoxic-ischaemic insult Arterial Hypotonia Patent ductus arteriosus “Noxious/painful stimuli” …	Disability Functioning Parent-child interaction Intervention policy Social support …

¶ established but not always consistently applied

Quality of data acquisition

Quality	Data source	Dataset	Improvement
Bias ↓	Feasibility ? Clinician report	Form type	→ Minimal Dataset → Electronic form (plausibility, completeness) → Relevant outcome for the patient ?
Bias ↑	Heterogeneity Low follow-up rate ? Proxy report		→ Networking / Definitions → Patient oriented follow-up → Standardisation

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Course over time and outcomes

Time:
Over gestation
Over episodes
At different ages

Aleid van Wassenaer-Leemhuis, Amsterdam

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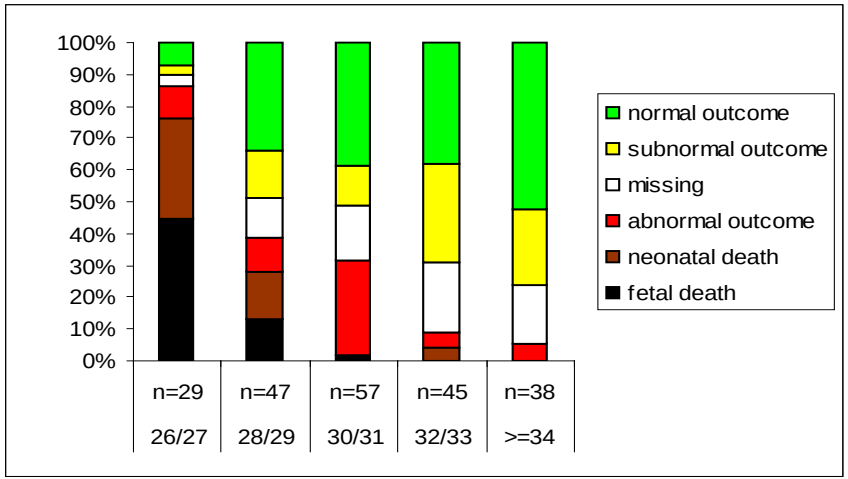
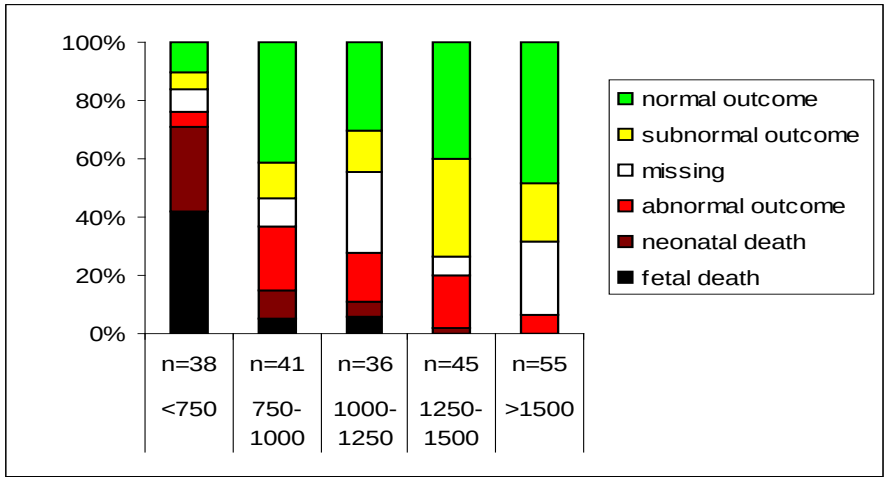
Survival and outcome example

Cohort: children born to mothers with early-onset preeclampsia and HELLP



In relation with gestational age

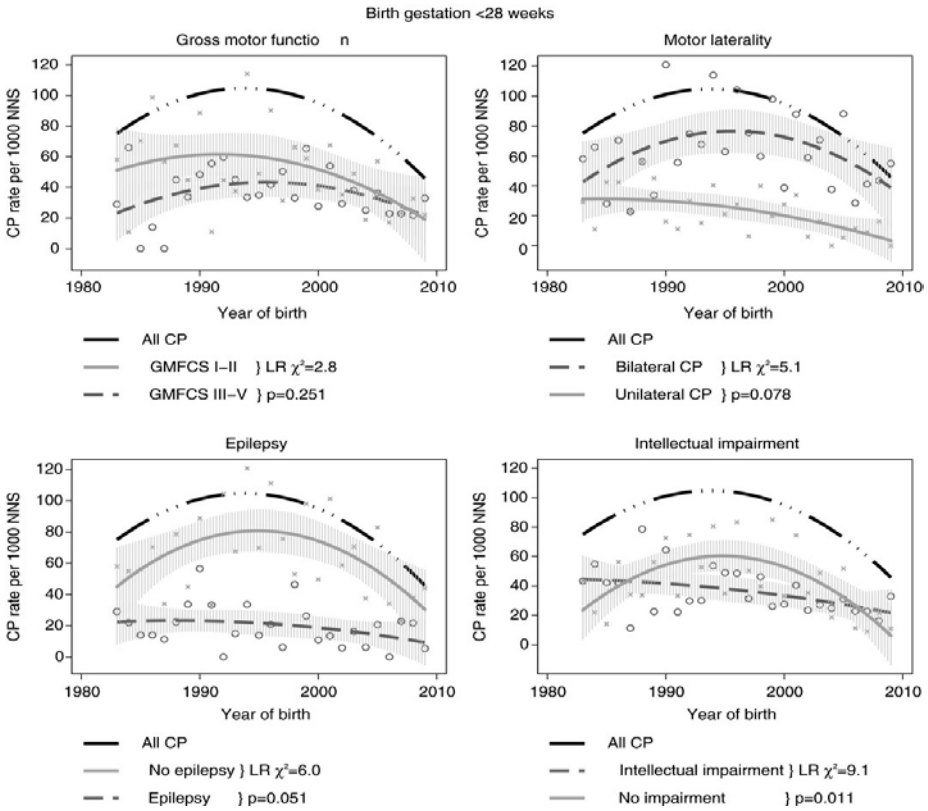


In relation with birthweight

- **Mortality is part of outcome; antenatal morbidity affects postnatal sample**
- **Importance studying whole sample that had a certain exposure**
- **Effects differ over gestational age range**

Am J Obstet Gynecol 2011;204:510.e1-9.

Temporal trends of important outcomes



Importance of including up to date numbers, when studying effects of new therapies

- **For power calculation**
- **For describing need for new therapy**
- **It may be that concurrent strategies work together effectively**

Developmental Medicine & Child Neurology
2016, 58 (Suppl. 2): 25–35

Loss of relationship over time (fetal growth restriction and growth)

Cohort: children born to mothers with early-onset preeclampsia and HELLP

Growth characteristics	3 months	1 year	4.5 years
Participating children	N=88	N=130	N=135
Height			
Mean (cm)	57 (3)	74 (3)	108 (5)
Mean SDS	−1.4 (1.3)*	−0.6 (1.1)*	−0.5 (1.1)*
Mean SDS − target height SDS	−1.1 (1.2)	−0.31 (1.0)	−0.21 (1.0)
Complete catch-up growth‡‡	65% (56)	89% (114)	94% (125)

Knowledge of course time in specific patient populations necessary

Arch Dis Child 2013,98, 30–35

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH

APPLYING REGULATORY SCIENCE TO NEONATES: SECOND ANNUAL SCIENTIFIC WORKSHOP AT EMA

LONG TERM OUTCOMES PANEL

Susan McCune, M.D.

Deputy Director, Office of Translational Sciences, CDER/FDA

September 13, 2016

Long Term Outcome Studies

- What is the purpose of long term outcome studies?
  - Dictates the organ system(s) to be studied and potentially the timing of the evaluation
    - Efficacy (e.g., neurologic injury, pulmonary function)
    - Safety (e.g. growth, neurodevelopmental outcome)
- Is the treatment acute or chronic?
- What needs to be measured, when is the optimal time to measure, what is the right tool?
  - Registry
  - Formal exam (e.g. cognition)
  - Clinical outcome assessment tool

Do We Know the Drugs Are Safe?

- Cloramphenicol
  (Gray Baby Syndrome)
  - Immature UDP-glucuronyl transferase enzyme system
  - Insufficient renal excretion of unconjugated drug

Chloramphenicol toxicity in neonates: its incidence and prevention

ANNE MULHALL, JOHN de LOUVOIS, ROSALINDE HURLEY

Br. Med. J. 287:1424-1427, 1983

- Postnatal steroids to treat or prevent chronic lung disease in preterm infants
  - Increased short term adverse events (hyperglycemia, hypertension, poor weight gain)
  - Increased long term adverse events (increased neurodevelopmental delay and cerebral palsy)

AMERICAN ACADEMY OF PEDIATRICS

Committee on Fetus and Newborn

CANADIAN PAEDIATRIC SOCIETY

Fetus and Newborn Committee

Postnatal Corticosteroids to Treat or Prevent Chronic Lung Disease in Preterm Infants

Pediatrics 109:300-338, 2002

Innovative Trials in Rare Diseases

- Carglumic acid for N-acetylglutamate synthase (NAGS) deficiency
  - Rare urea cycle disorder (~ 10 patients in U.S.)
  - Retrospective review of a 23 patient case series in Europe
  - Short-term (ammonia) and long-term (neurocognitive) outcomes
  - Compared to historical control (not formally conducted)

Support for Use of Surrogate Biomarkers

Table 1. Support for Surrogates

Factor	Favors Surrogate	Does Not Favor Surrogate
Biological plausibility	Epidemiologic evidence extensive and consistent	Inconsistent epidemiology
	Quantitative epidemiologic relationship	No quantitative epidemiologic relationship
	Credible animal model shows drug response	No animal model
	Well-understood disease pathogenesis	Pathogenesis not clear
	Drug mechanism of action well understood	Novel actions not previously studied
	Surrogate relatively late on biological path	Surrogate remote from clinical outcome
Success in clinical trials	Effect on surrogate has predicted outcome with other drugs of same pharmacologic class (supports surrogate in class)	A negative outcome without clear explanation
	Effect on surrogate has predicted outcome in several classes (supports more general use)	Inconsistent results across classes
Risk-benefit, public health considerations	Serious or life-threatening illness and no alternative therapy	Nonserious disease and alternative therapy with different pharmacologic action known to affect outcome
	Large safety database	Little safety data
	Short-term use	Long-term use
	Difficulty of studying clinical end point (rare, delayed)	Easy to study clinical end point (short-term study)
		Long-delayed, small effect in healthy people

Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA 282:790-795, 1999.

Voting Slide – Long-Term Outcomes

Considering both impact and feasibility, which of the following projects is your **first** choice?

1. Optimal age of recording childhood neurodevelopmental outcomes to support regulatory approval.
2. Optimal definition of childhood neurodevelopmental outcome at that age.
3. 1&2 as one choice.
4. Duration of safety monitoring post-regulatory approval.
5. Optimal method of collecting data on LTOs.
6. Potential for using neonatal data as biomarkers for LTOs.
7. “Walk-in Option A” (offered up by audience)
8. None of the above

Voting Slide – Long-Term Outcomes

Considering both impact and feasibility, which of the following projects is your **second** choice?

1. Optimal age of recording childhood neurodevelopmental outcomes to support regulatory approval.
2. Optimal definition of childhood neurodevelopmental outcome at that age.
3. 1&2 as one choice.
4. Duration of safety monitoring post-regulatory approval.
5. Optimal method of collecting data on LTOs.
6. Potential for using neonatal data as biomarkers for LTOs.
7. “Walk-in Option A” (offered up by audience)
8. None of the above