The protocol

Investigator-initiated, randomized, multinational, pragmatic phase-III trial

Hypothesis

"Treatment based on near-infrared spectroscopy monitoring for extremely preterm infants during the first 72 hours of life will result in a reduction in severe brain injury or death at 36 weeks postmenstrual age."

Population: <28 weeks

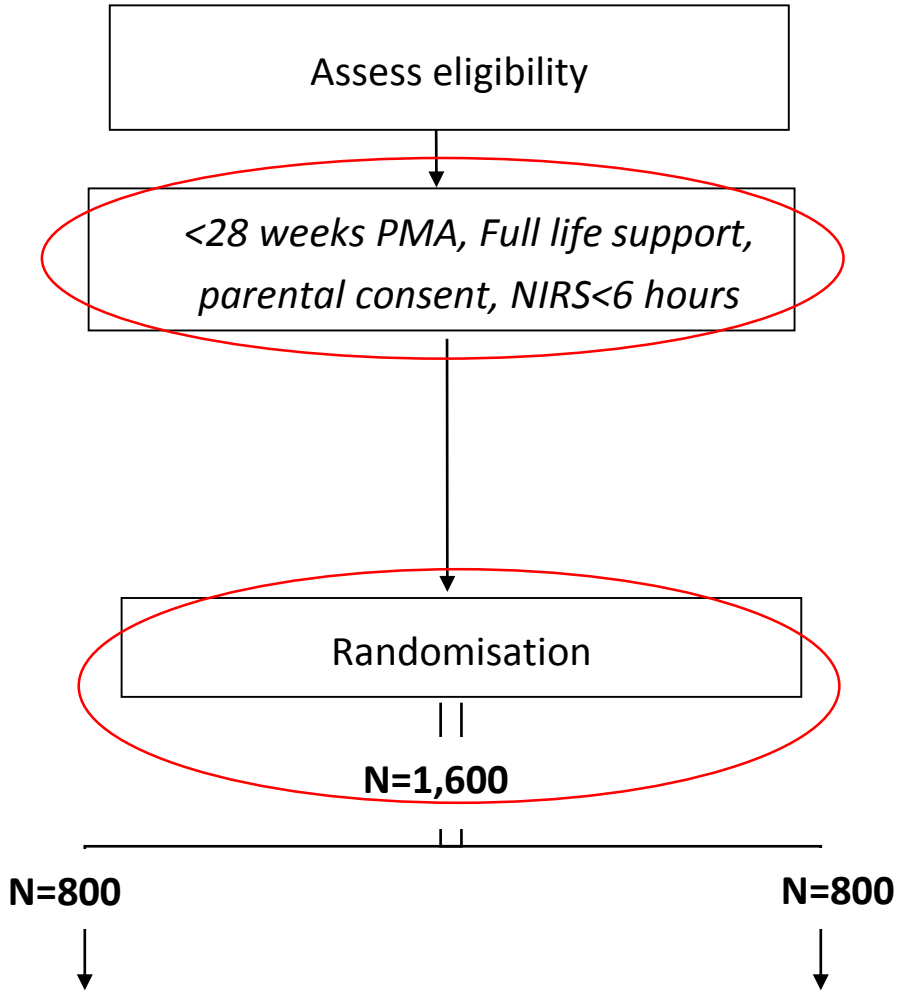
Intervention: treatment based on cerebral oximetry monitoring

Control: treatment as usual

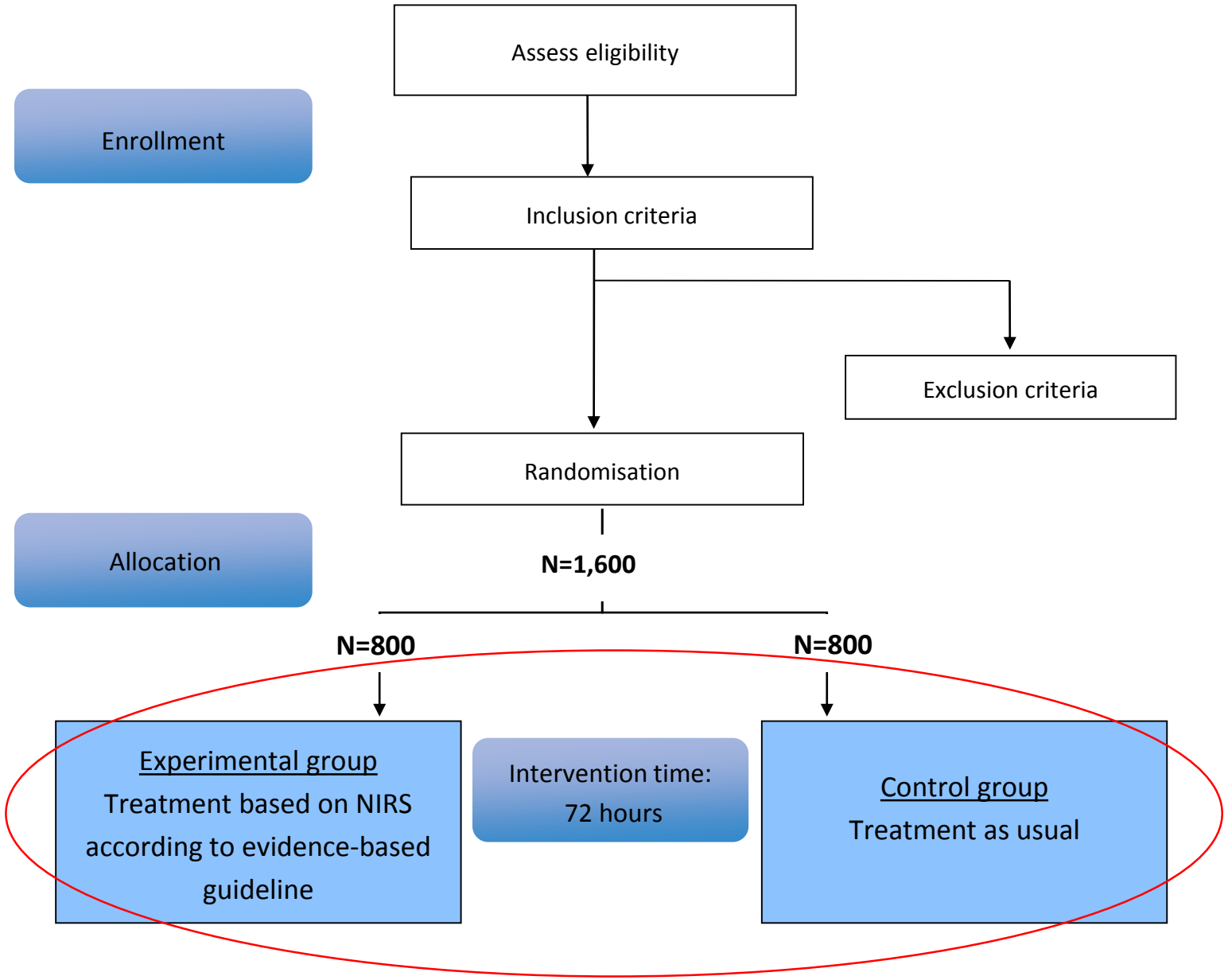
Outcome: severe brain injury or death at 36 weeks PMA

SafeBoosC phase III trial

Enrollment



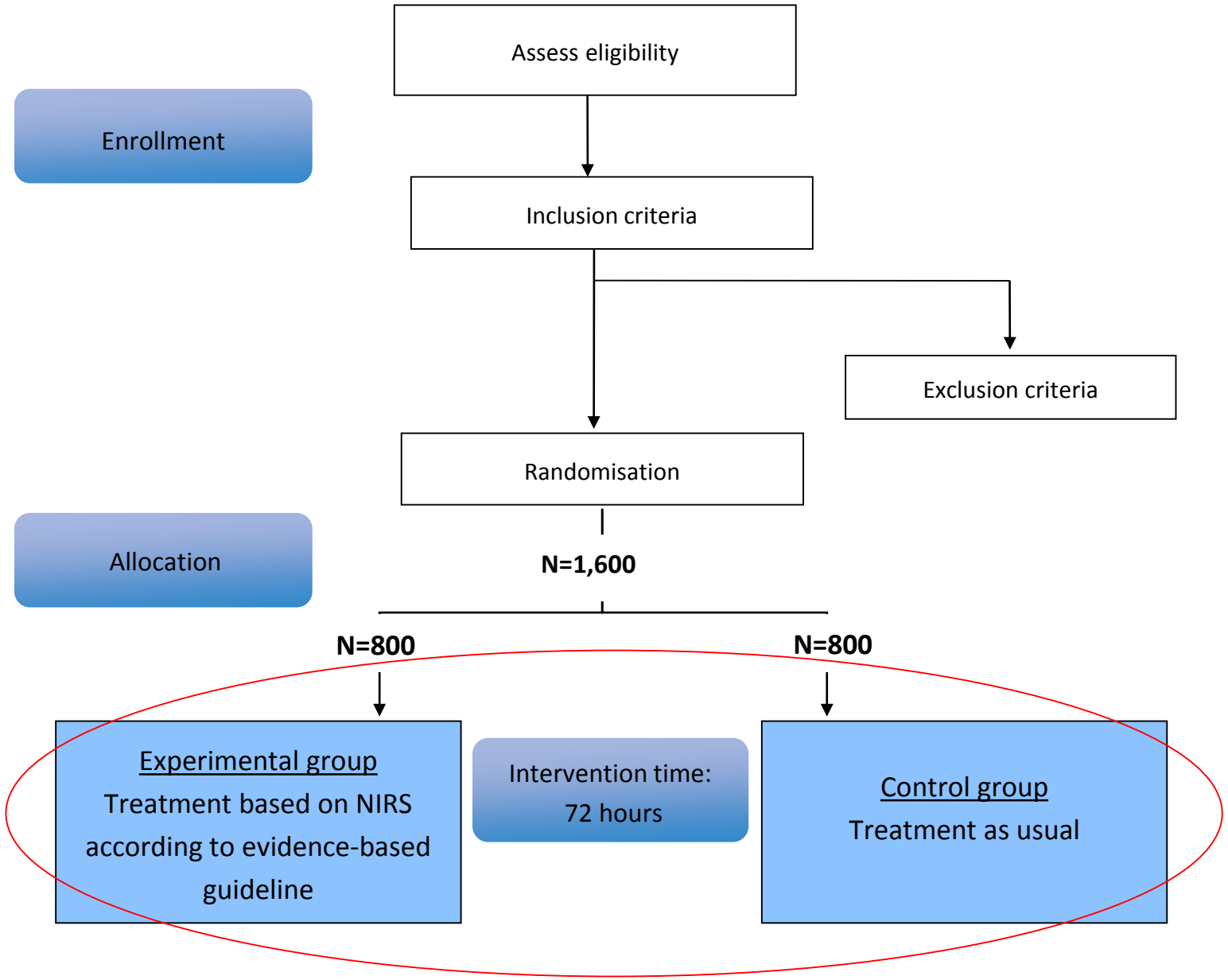
SafeBoosC phase III trial

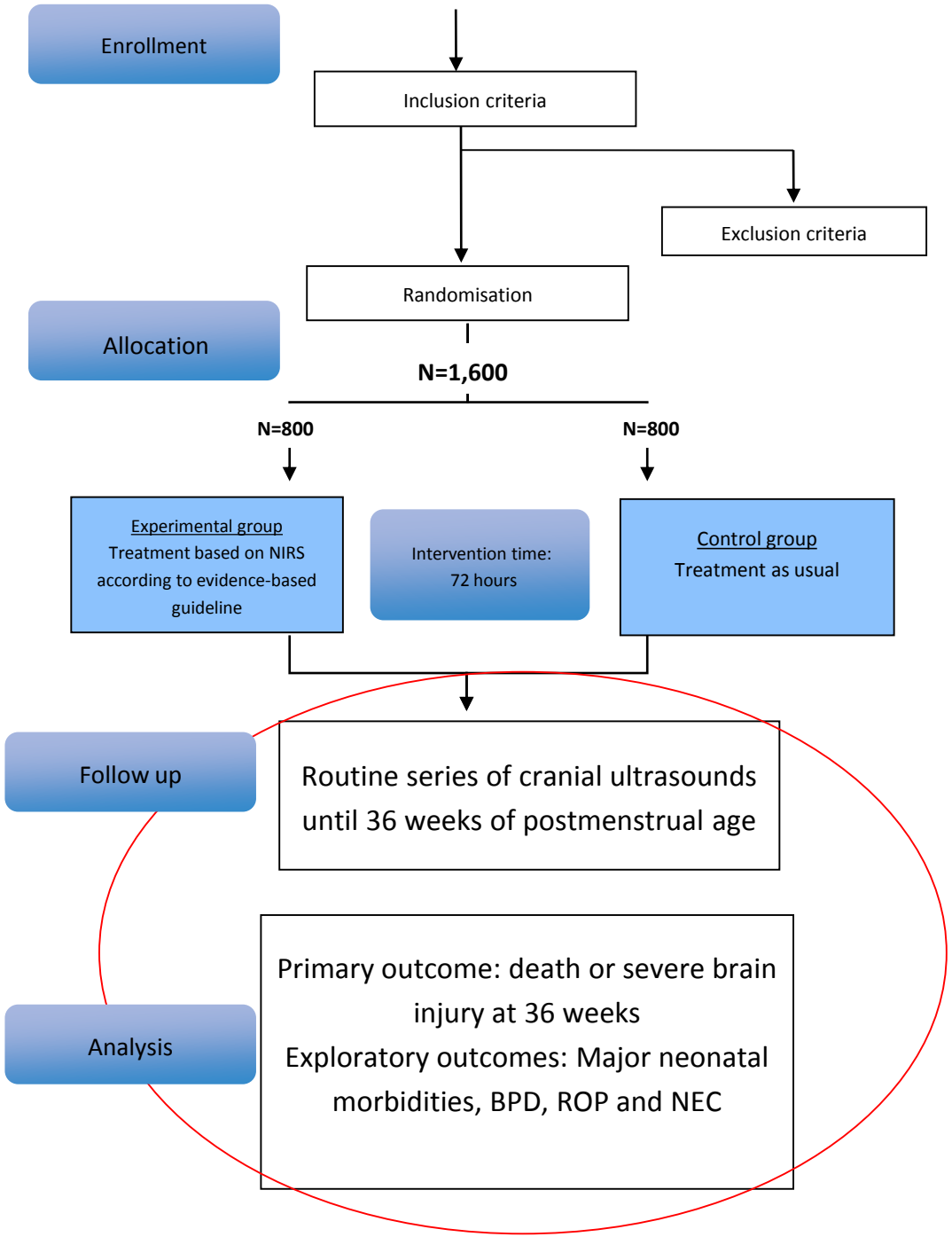



with EQUANOX Advance™ Sensor,
Model 8004CA
Near infrared oxygenation monitor
NIRO-200NX C10448
Foresight Tissue Oximeter
FORE-SIGHT
Absolute Tissue Oximetry
L 67
R 67
S 79
S 55

48

SafeBoosC phase III trial




Enrollment
Inclusion criteria
Exclusion criteria
Randomisation
Allocation
N=1,600
N=800
N=800
Experimental group
Treatment based on NIRS according to evidence-based guideline
Intervention time: 72 hours
Control group
Treatment as usual
Follow up
Routine series of cranial ultrasounds until 36 weeks of postmenstrual age
Analysis
Primary outcome: death or severe brain injury at 36 weeks
Exploratory outcomes: Major neonatal morbidities, BPD, ROP and NEC

Data entry

- At randomization
- At 72 hours of age
- At 36 weeks postmenstrual age

See all data appendix I in protocol

Data needed at randomization

- Birth date and hour
- Gestational age less than 28 weeks or less than 26 weeks

Data needed at 72 hours of age

- Gestational age in weeks and days
- Birth weight
- Apgar 1 and Apgar 5
- Resuscitation
- Age in hours when cerebral oximetry was started
- Cerebral oximetry monitoring stopped prematurely with reason
- Severe incidents due to monitoring
- Change of medical management due to cerebral hypoxia in patient record
- Surfactant therapy
- Cardiovascular support (volume, vasopressors, inotropes) before 72 hrs
- SARs

Data needed at 36 weeks of postmenstrual age (or referring to age at discharge home if that happened before 36 weeks)

- Major congenital anomaly
- SARs
- Mechanical ventilation, and number of days of mechanical ventilation
- Sepsis
- Treatment for patent ductus arteriosus
- Cranial ultrasound performed before 8 days of age and/or after 35 days of age
- Intraventricular haemorrhage grade 3 or 4
- Cystic periventricular leukomalacia
- If relevant cUS information is available, post-haemorrhagic ventricular dilatation, cerebellar haemorrhage or cerebral atrophy
- Bronchopulmonary dysplasia
- Necrotizing enterocolitis stage 2 or greater via modified Bell's staging system or focal intestinal perforation
- Retinopathy of prematurity stage 3 or higher

Q/A session

Members of the Steering Committee

Why have we chosen the primary outcome ‘severe brain injury’ or death at 36 weeks postmenstrual age?

Eugene Dempsey, Cork, Ireland

Primary outcome

- Composite of severe brain injury detected on **any** of the serial cranial ultrasound scans routinely performed or death until 36 weeks of postmenstrual age.

Severe Brain injury

- Intra-ventricular haemorrhage grade III
- Parenchymal/periventricular haemorrhagic infarction (grade IV)
- Cystic periventricular leukomalacia (cPVL)
- Post-hemorrhagic ventricular dilatation
- Cerebellar haemorrhage
- Cerebral atrophy

Primary Outcome

- Pragmatic
  - Sequential scans
  - No additional resources
- Meaningful
  - Measuring brain oxygenation
  - Severe injury on scan good correlation with long-term outcome
- Consistent
  - Safeboosc II
  - Other trials

Cranial Ultrasound

- Web based Training

- Local PI ensures training program is conducted

Why have we chosen 1600 children?
and
How should we do this statistically?

Janus Christian Jakobsen

Janus Christian Jakobsen

- Chief physician, PhD at The Copenhagen Trial Unit, Centre for Intervention Research, Denmark
- Director of Research, Chief Physician, Department of Internal Medicine, Holbæk, Denmark
- Deputy Co-Ordination Editor, Cochrane Hepato-Biliary Group

CTU Copenhagen Trial Unit
Centre for Clinical Intervention Research

THE COCHRANE HEPATO-BILIARY GROUP

A REVIEW GROUP OF
THE COCHRANE COLLABORATION®

Why have we chosen 1600 children?

Why sample size?

- Interpreting a neutral trial result?
  - Indications of no difference in effect between the compared interventions, or indications of too small sample size to demonstrate or discard the anticipated intervention effect
- Interpreting a result favouring one of the interventions?
  - Trials with too small accrued sample size have an increased risk of either overestimating or underestimating the effect size and variance

Remember to limit the overall type I error to 5%!!!!

How?

- Based on a patient centred primary outcome
- Anticipated intervention effect?
- Proportion of participants with the event in the control group?
- Acceptable risk of type I and type II errors?

Safeboost outcomes

- The primary outcome: a composite outcome of death or severe brain injury
- Exploratory outcomes: bronchopulmonary dysplasia, retinopathy of prematurity, and necrotising enterocolitis
- All outcomes will be assessed at 36 weeks after randomisation

Anticipated intervention effect?

- In the SafeBoosC-II trial the proportion of trial participants in the control group with the primary outcome was approximately 34% and in the experimental group 26%
- We anticipate a similar intervention effect: 34% to 26.5%; a RRR of 22%, or a 7% absolute risk reduction

Acceptable risks of type I and type II errors?

- Risk of type I error 5%
- Risk of type II errors 10%

Sample size estimation

- 800 experimental infants and 800 control infants, i.e., a total of 1,600 participants
- NNT 15

Power estimations of non-primary outcomes

- Bronchopulmonary dysplasia: 89% power
- Retinopathy: 68% power
- Necrotising enterocolitis: 23% power

Questions?
Comments?

How should we do this statistically?

Twins

- SafeBoosC-II: ICC of the burden of hypoxia within pairs of twins was negligible and other studies have shown also shown negligible ICCs
- First, we will analyse infant data as independent observations
- Second, we will analyse data where we remove the first and the last infant from twin pairs, respectively
- Last, we will analyse data taking the possible correlation into consideration

How should we do this statistically?

- The analyses will be intention-to-treat
- The primary analyses for all outcomes will be adjusted for the stratification variables, i.e., ‘site’ and ‘gestational age’
- Analysis of ‘infants’ using the generalized linear model (‘logit link’, ‘site’ as random intercept)
- Analysis where we remove the first and the last infant from twin pairs, respectively (GLM)
- Analysis of ‘births’ using generalized linear model (‘logit link’, ‘births’ and ‘site’ as random intercepts)

Missing outcomes

- We plan to consider using multiple imputation and present best-worst and worst-best case scenarios if it is not valid to ignore missing data (Jakobsen et al. 2017)

Questions?
Comments?

Why do the children have to be under 28 weeks postmenstrual age in order to be included?

Jonathan Mintzer

Inclusion Criteria

Jonathan Mintzer, Stony Brook Children's, Stony Brook, NY

"Why do the children have to be under 28 weeks' postmenstrual age in order to be included?"

Key points: Simplicity, generalizability

-Proof-of-concept for future extrapolation

-SafeBoosC-II experience

-Avoid confounding across large study population

Inclusion Criteria

Jonathan Mintzer, Stony Brook Children's, Stony Brook, NY

-Older, growth-restricted neonates?

-Older neonates requiring advanced cardiorespiratory support?

-Septic neonates?

*Comparable to <28wk?

*Confounding concerns

*Homogeneous population

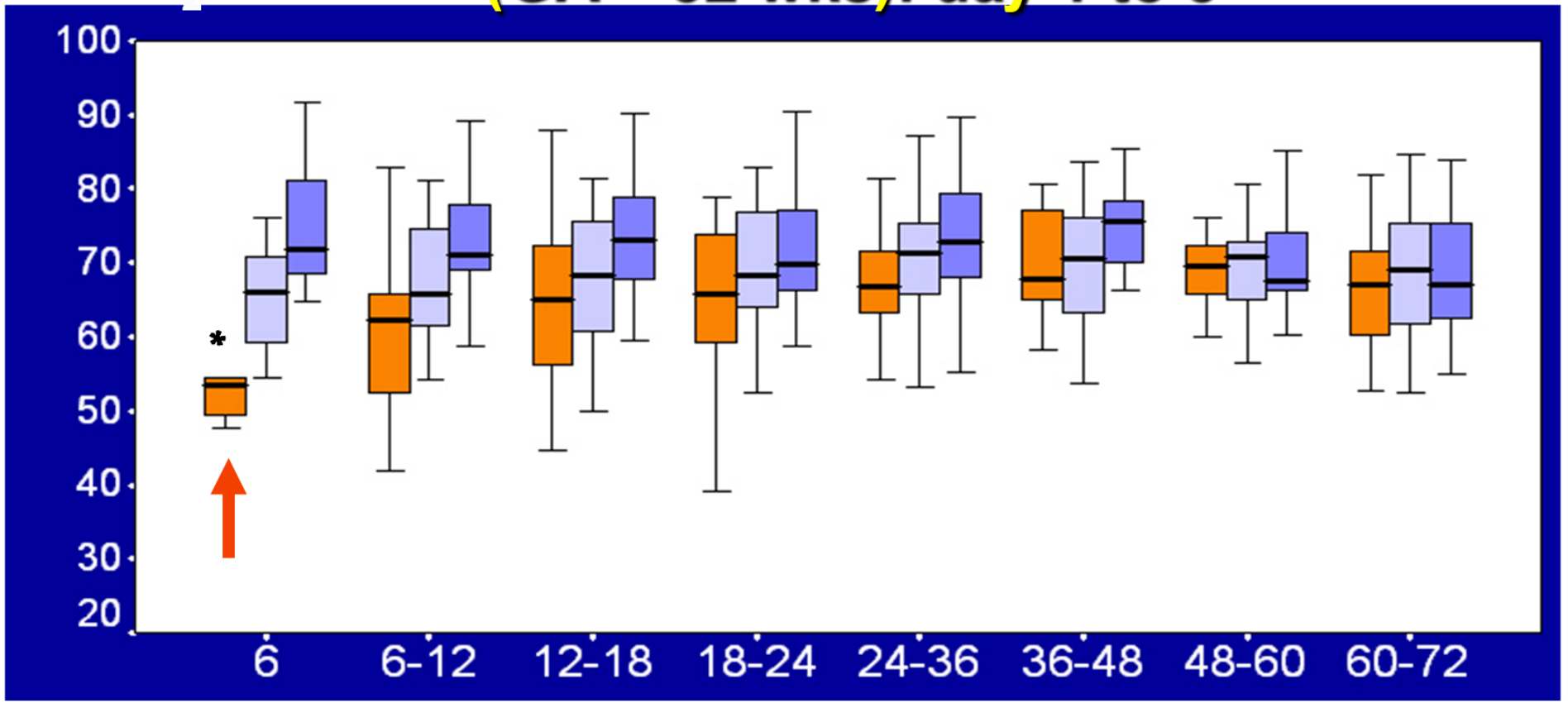
-Effective data collection and interpretation

*Potential future studies based on SafeBoosC-III findings

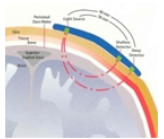
Why have we chosen 55-85% as the hypoxic threshold in this population?

Petra Lemmers

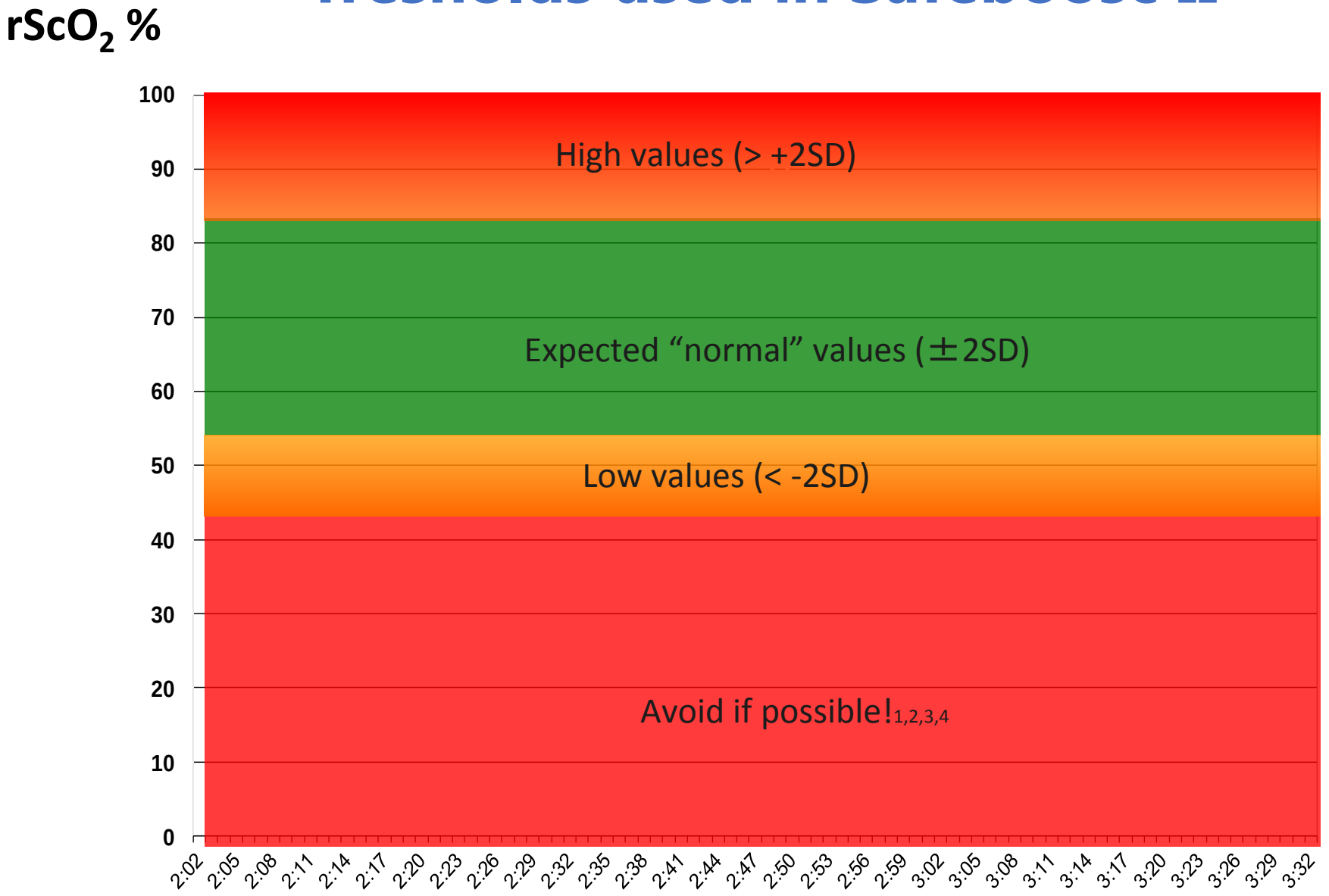
Pattern of $rScO_2$ in preterm infants (GA < 32 wks): day 1 to 3



Postnatal age (h)



Tresholds used in Safeboosc II



1) Hou, Physiol Meas 2007; 2) Kurth, J Cereb Blood Flow Metab 2005;
3) Dent, J Thorac Cardiovasc Surg 2002 4) Alderliesten T J Pediatr 2013

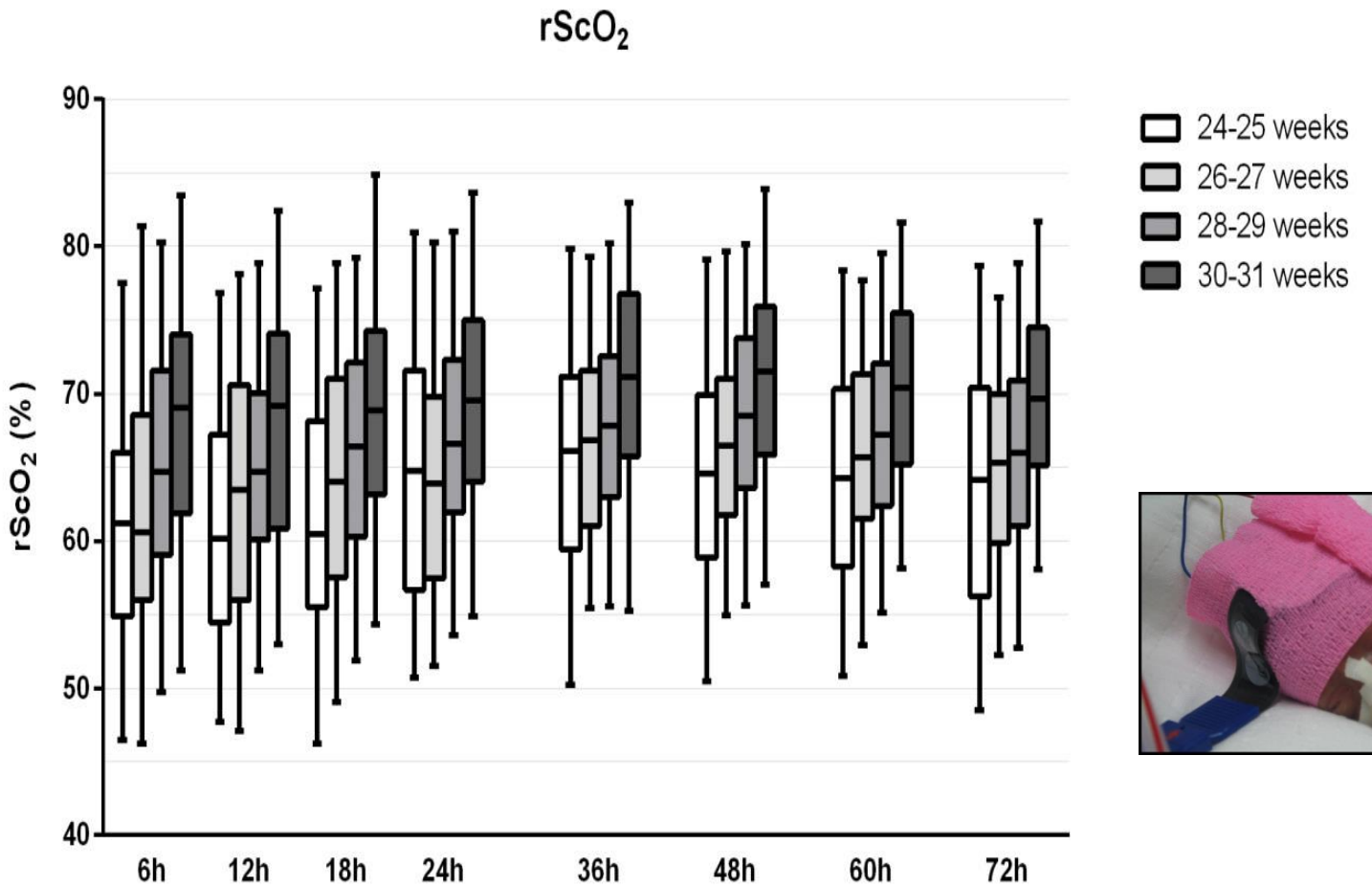
Reference values

	Literature values					Current study		Difference
Author	Time	Measure	GA (wk)	*N*	$rScO_2$/TOI (%)	Ref. GA group	$rScO_2$ (%)	Literature – current
0–72 h of life								
Naulaers *et al.* (9)	day 1	TOI	28 (25–30)	15	57 (54–66)	28–29 (12 h)	67.2	10.2
	day 2	—	—	—	66 (62–82)	28-29 (36 h)	68.7	2.7
	day 3	—	—	—	76 (68–80)	28–29 (60 h)	67.7	−8.3
Lemmers *et al.* (17)	6–12 h	$rScO_2$	29.3 (1.7)	20	70 (61–77)	28–29 (12 h)	67.2	−2.8
	18–24 h	—	—	—	68 (63–75]	28–29 (24 h)	68.3	0.3
	36–48 h	—	—	—	73 (65–84)	28–29 (48 h)	68.5	4.5
	60–72 h	—	—	—	71 (64–75)	28–29 (72 h)	66.3	−4.7
Sorensen *et al.* (11)	19 h (6)	TOI	27.6 (23.9–33)	37	74.6 (8.5)	26–27 (18 h)	66.5	−8.1
Moran *et al.* (19)	day 1	TOI	29 (25.3–31.5)	27	68.1 (7.9)	28–29 (12 h)	67.2	−0.9
Pichler *et al.* (20)	<1 h	$rScO_2$	34.9 (1.4)	27	80 (62–92)	34–35 (1 h)[a]	79.5[ab]	−0.5
Sirc *et al.* (18)	6 h	TOI	25.9 (1.7)	22	65.2 (10)	24–25 (6 h)	62.8	−2.4
	12 h	—	—	—	63.9 (5.9)	24–25 (12 h)	63.6	−0.3
	24 h	—	—	—	68.8 (5.7)	24–25 (24 h)	64.7	−4.1
	48 h	—	—	—	67.2 (7.2)	24–25 (48 h)	64.9	−2.3
Hyttel-Sørensen *et al.* (10)	Average 3 d	$rScO_2$	26.3 (–)	10	64.2 (4.5)	26–27 (36 h)	66.9	2.7
Average difference								−0.9
>7 d of life								
van Hoften *et al.* (21)	17 d (1–93 d)	$rScO_2$	27.3 (25–34)	33	71 (65–96)	26–27 (72 h)	74.7[b]	3.7
Petrova *et al.* (12)	>7 d	$rScO_2$	(24–32)	20	66 (8.8)	28–29 (72 h)	66.3	0.3
Petrova *et al.* (13)	~5 wk	$rScO_2$	26 (2.4)	10	68.5 (4.6)	26–27 (72 h)	66.3	−2.2
Pocivalnik *et al.* (15)	3.9 d (4.8)	$rScO_2$	35.2 (3.0)	37	84.1 (6.4)	34–35 (72 h)[a]	80.0[a,b]	−4.1
	—	TOI	—	—	72.2 (6.0)	34–35 (72 h)[a]	71.3[a]	−0.9

GA, gestational age; rScO2, regional cerebral oxygen saturation; TOI, tissue oxygenation index.
[a]Model fit was obtained in subjects ≤32 wk GA; therefore, data >32 wk GA was extrapolated. [b]Study used a neonatal sensor; for comparison, the following conversion was used: $rScO_{2\text{-neo}} = 0.8481 \times rScO_{2\text{-adult}} + 19.11$.

Reference values

N=999



Thomas Alderliesten
Pediatr Res (2016) **79**, 55-64. doi:10.1038/pr.2015.186

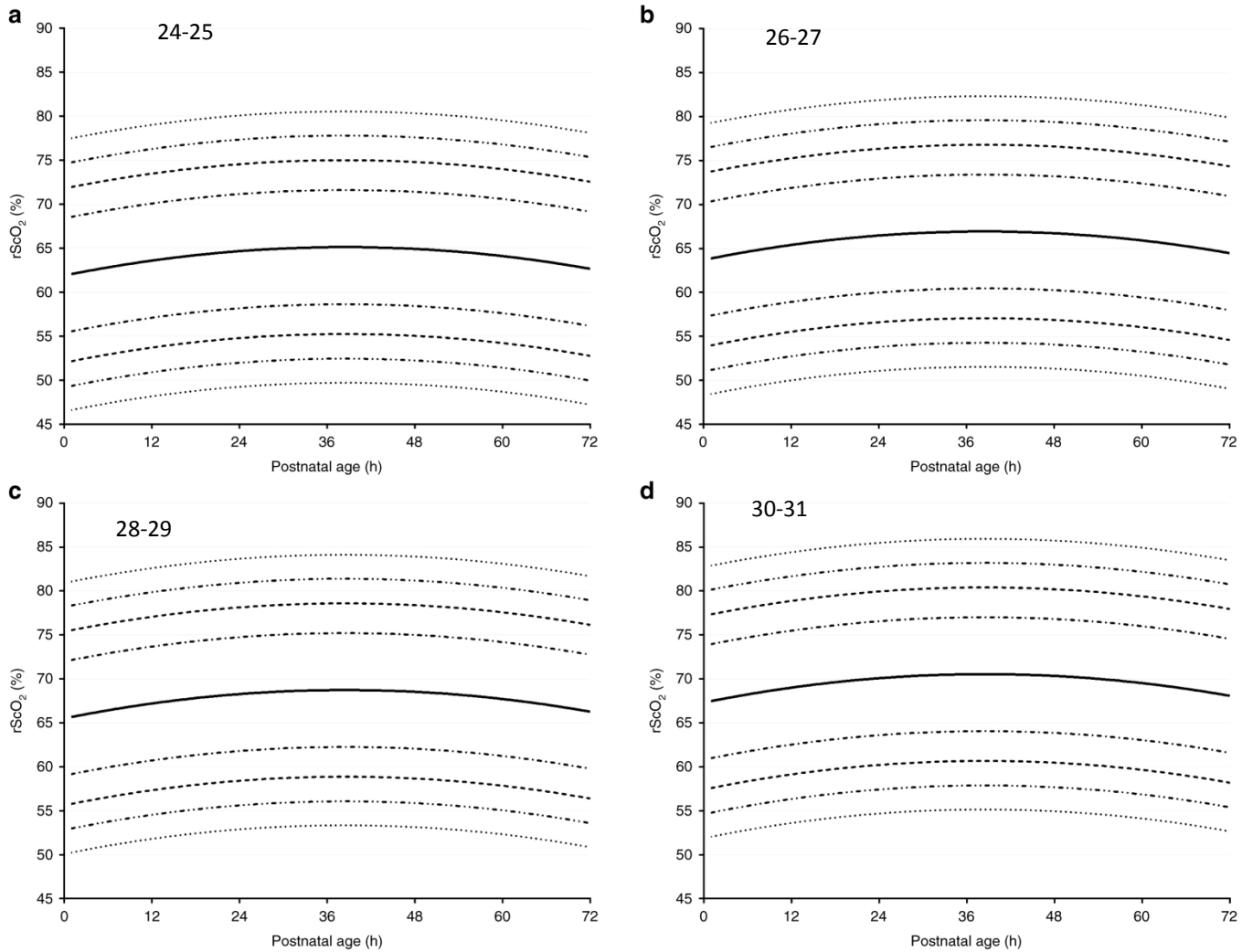


Figure 2

Thomas Alderliesten
Pediatr Res (2016) **79**, 55-64. doi:10.1038/pr.2015.186

Evidence for adverse neurodevelopmental outcome in preterm infants if rScO2<55 %?

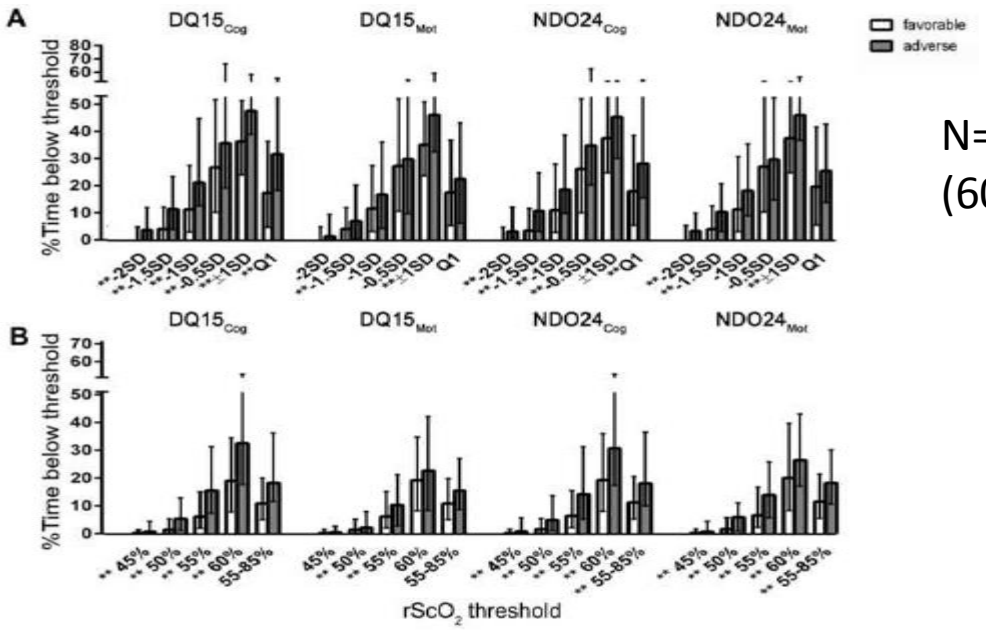
- Plomgaard AM, No neurodevelopmental benefit of cerebral oximetry in the first randomised trial(SafeBoosC II) in preterm infants during the first days of life. Acta Paediatr. 2018 Jun16;

	Intervention	Control	p value
Bayley-II (n)	14	16	
Age at Bayley-II (months)	25.0 (1.4)	24.8 (1.1)	0.65
Mental Developmental Index	96.9 (13.9)	86.4 (13.8)	0.05
Psychomotor Developmental Index	83.9 (14.3)	87.4 (16.0)	0.54
Bayley-III (n)	30	23	
Age at Bayley-III (months)	24.3 (3.6)	25.2 (2.9)	0.34
Cognitive index	95.8 (19.9)	97.6 (10.2)	0.69
Language index	94.4 (18.8)	95.6 (13.4)	0.81
Motor index	91.8 (15.6)	99.1 (9.2)	0.07
Predicted Mental Developmental Index*	85.6 (21.1)	90.0 (15.4)	0.43

Evidence for adverse neurodevelopmental outcome in preterm infants if rScO2<55 %?

- Verhagen et al Cerebral oxygenation is associated with neurodevelopmental outcome of preterm children at age 2 to 3 years. Dev Med Child Neurol. 2014 Nov 8;1–7.

- Alderliesten T et al, Hypotension in preterm neonates: low blood pressure alone does not affect neurodevelopmental outcome. J Pediatr. 2014 May;164:986–91.

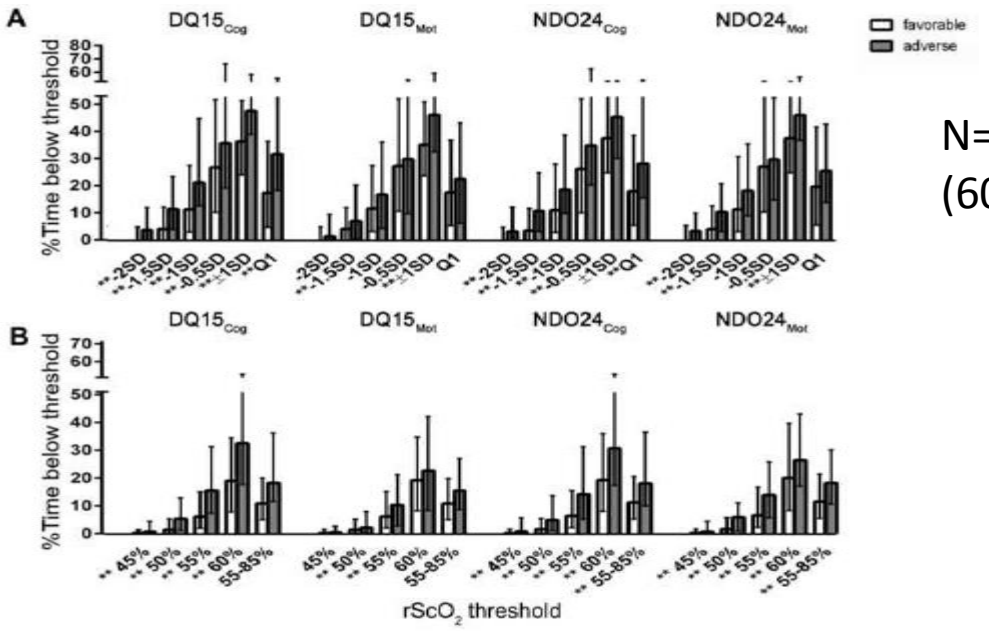


N=734
(60 died)

Results:

The median burden of hypoxia, according to the SafeBoosC trial definition, for rScO2 <55% was 18.5%hours (IQR 5.5 – 56.1%) vs. 42.3 (12.2 – 101.2) %hours for favorable and adverse cognitive outcome groups

Alderliesten 2018 under review J Pediatr

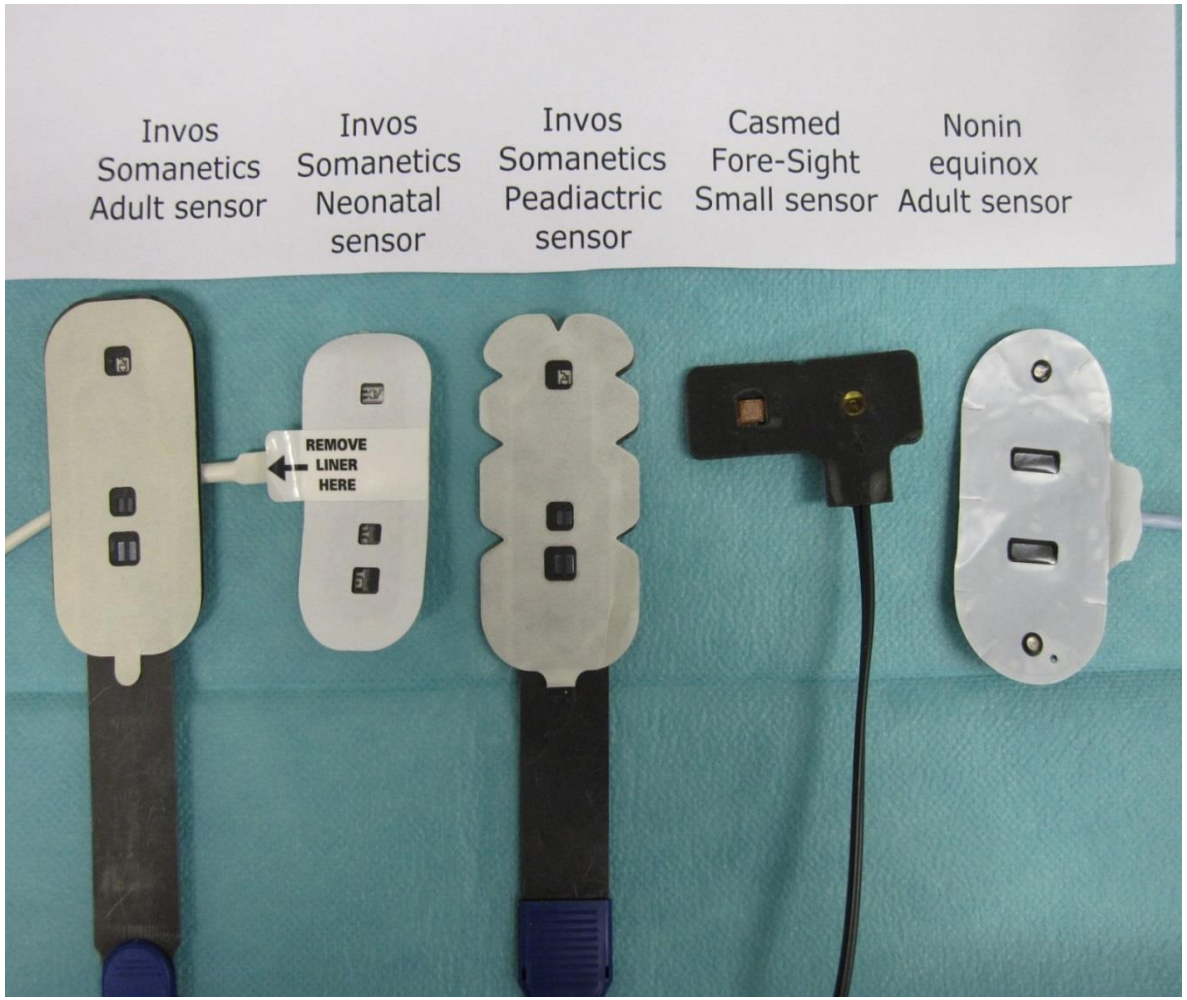


N=734
(60 died)

- Associations with unfavorable cognitive outcome in multivariable analysis were comparable for time spent with a rScO2 below 55% and -1.5SD (according to published reference values); odds-ratio 1.4 (CI1.1 – 1.7) for 20% of time below either threshold.
- Results at 15 months were comparable to results at 24 months.
- Results were not statistically significant for thresholds defining high values of rScO2.
- Composite motor outcome was not significantly related to either low or high alues or rScO2.

Conclusion: Low, but not high, rScO2 was associated to unfavorable cognitive outcome. It suggests the use of rScO2 <55% for future clinical studies when using adult Near-InfraRed sensors (rScO2 <65% for neonatal sensors, approximately).

Tresholds and sensors



Tresholds and sensors

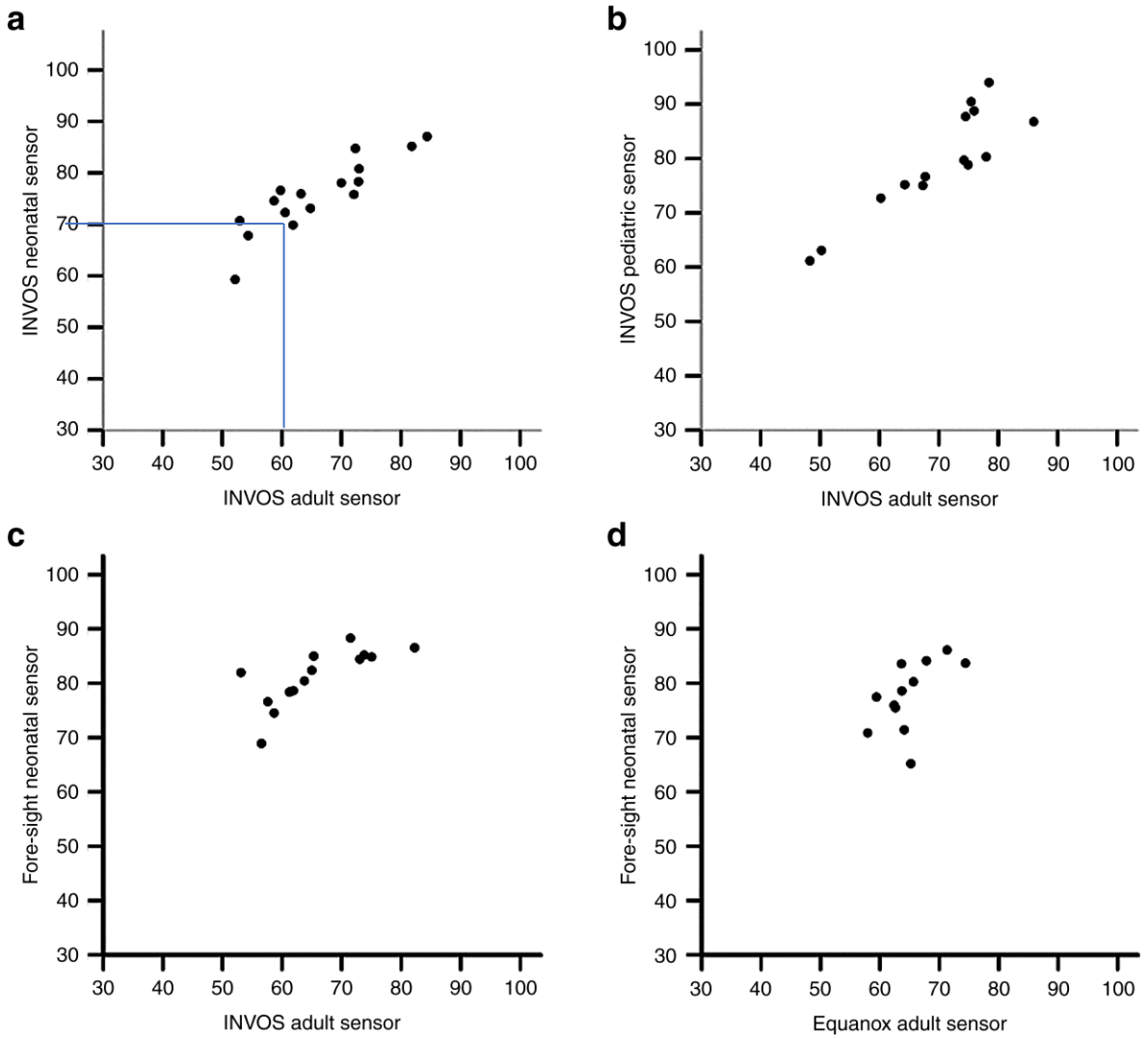
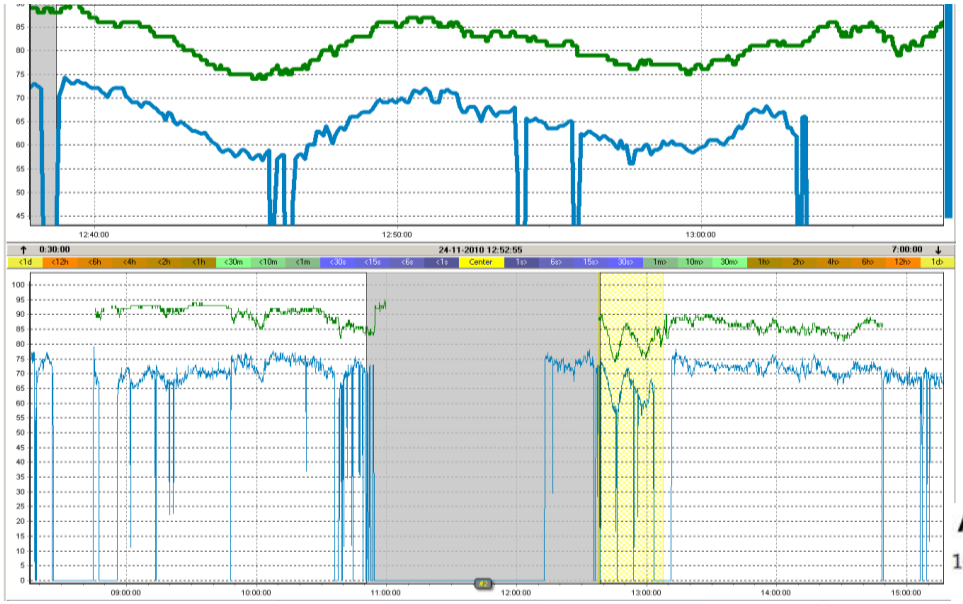
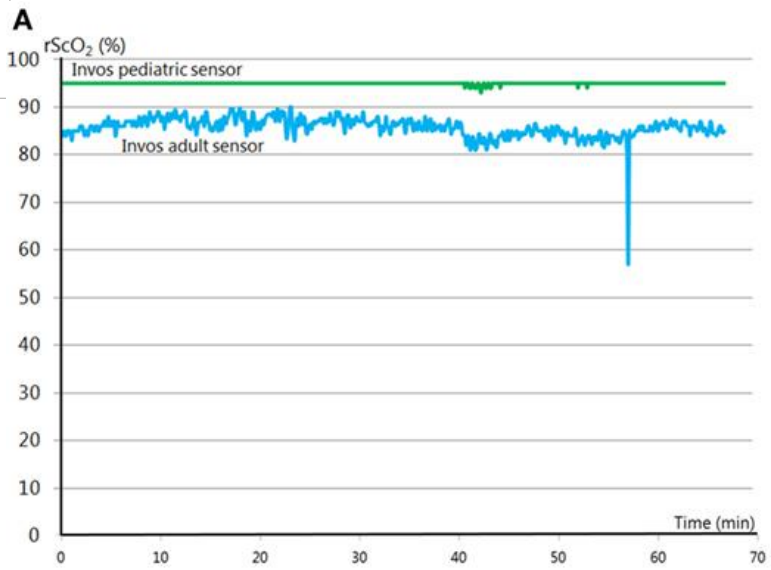


Figure 1

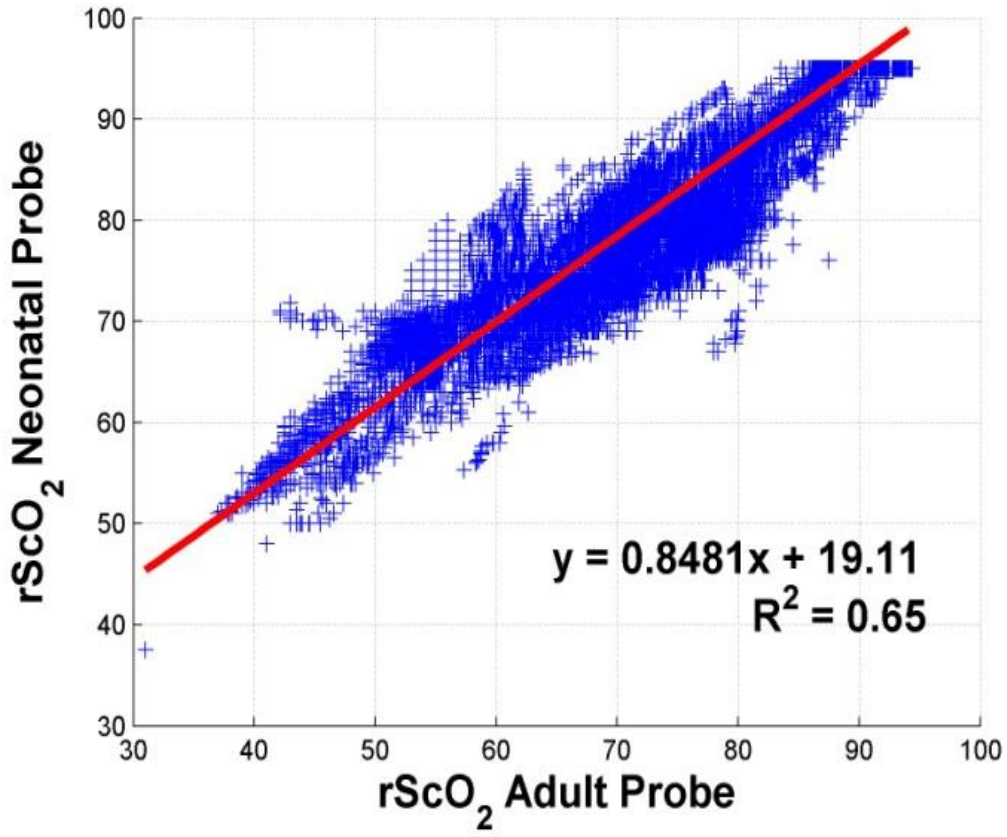
Laura M.L. Dix
Pediatr Res (2013) **74**, 00-00. doi:10.1038/pr.2013.133

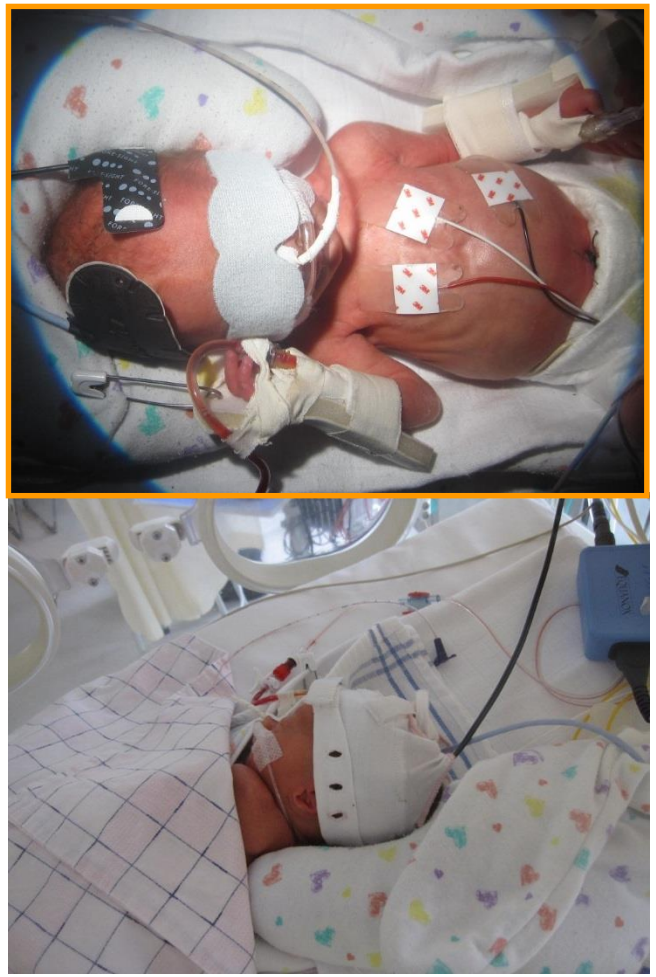
Adult vs neonatal sensor





Tresholds and sensors





Dix et al, Pediatr Res 2014

Tresholds and sensors

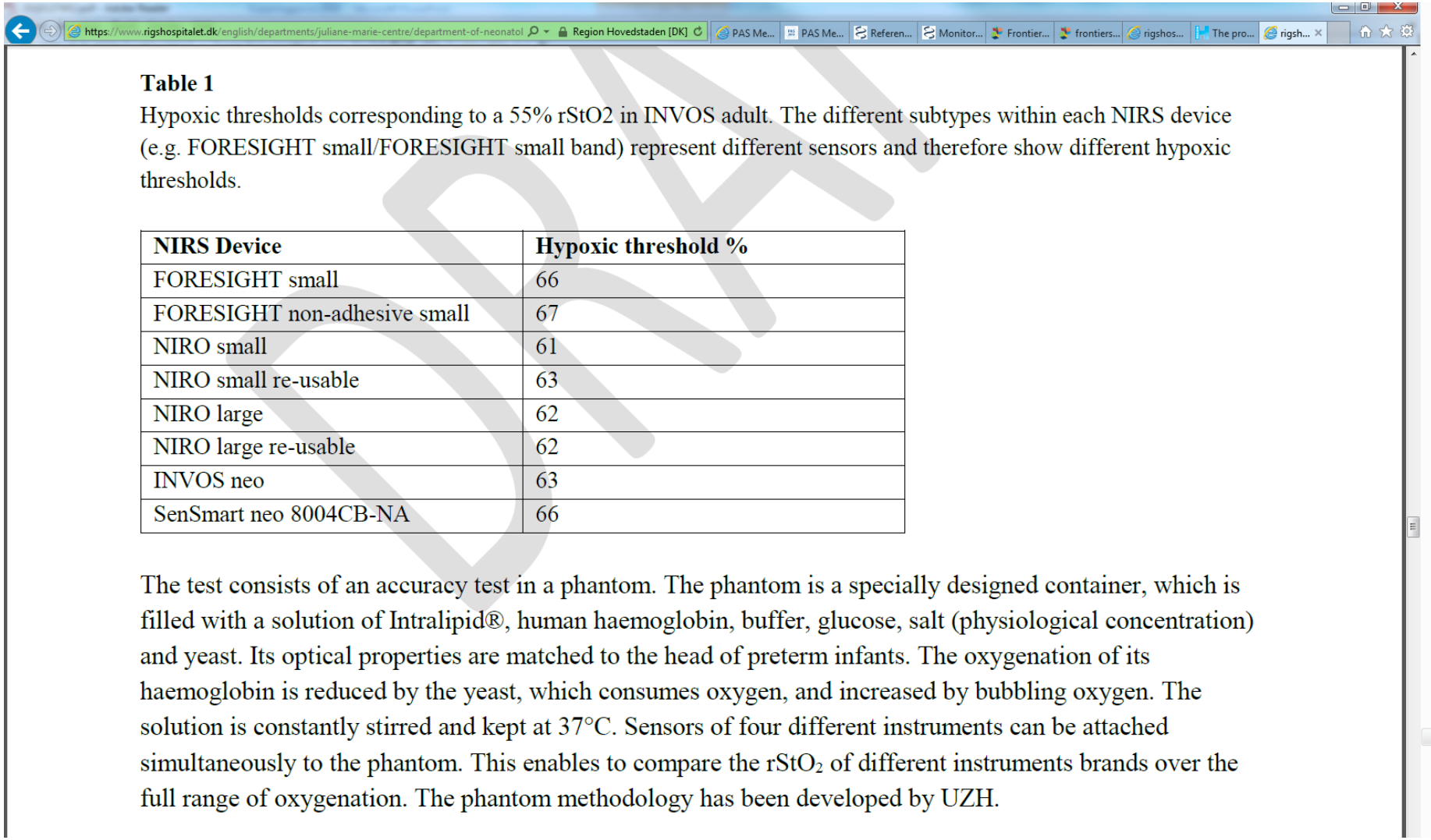


Table 1

Hypoxic thresholds corresponding to a 55% rStO2 in INVOS adult. The different subtypes within each NIRS device (e.g. FORESIGHT small/FORESIGHT small band) represent different sensors and therefore show different hypoxic thresholds.

NIRS Device	Hypoxic threshold %
FORESIGHT small	66
FORESIGHT non-adhesive small	67
NIRO small	61
NIRO small re-usable	63
NIRO large	62
NIRO large re-usable	62
INVOS neo	63
SenSmart neo 8004CB-NA	66

The test consists of an accuracy test in a phantom. The phantom is a specially designed container, which is filled with a solution of Intralipid®, human haemoglobin, buffer, glucose, salt (physiological concentration) and yeast. Its optical properties are matched to the head of preterm infants. The oxygenation of its haemoglobin is reduced by the yeast, which consumes oxygen, and increased by bubbling oxygen. The solution is constantly stirred and kept at 37°C. Sensors of four different instruments can be attached simultaneously to the phantom. This enables to compare the $rStO_2$ of different instruments brands over the full range of oxygenation. The phantom methodology has been developed by UZH.

Protocol Safeboosc III draft

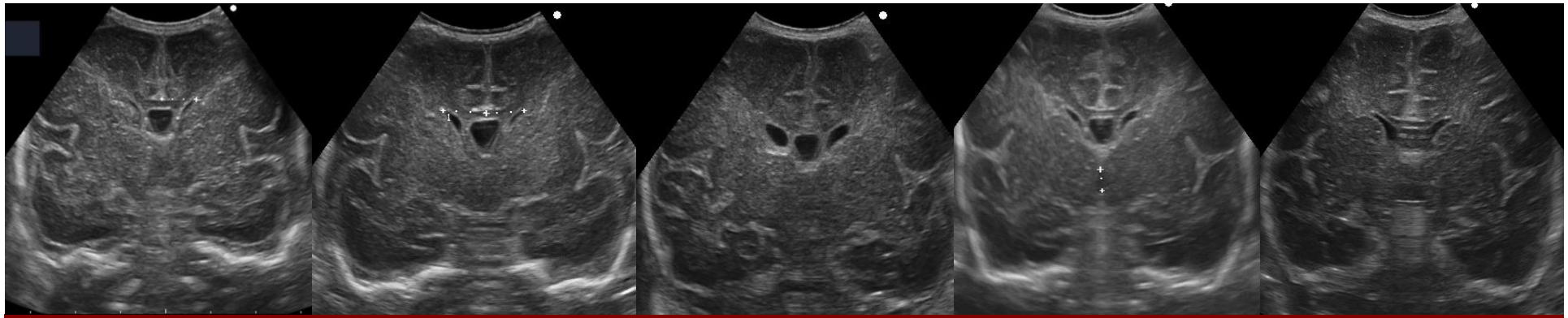
Why do we use cranial ultrasound as outcome measuring tool for severe brain injury?

Monica Fumagalli

Why do we use cranial ultrasound as outcome measuring tool for severe brain injury?

Monica Fumagalli

NICU Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico - Milan Italy
University of Milan - Department of Clinical Sciences and Community Health



SafeBoosc III - Investigator Meeting – Copenhagen 8-9 November 2018

Assessment of brain injury with cranial ultrasound

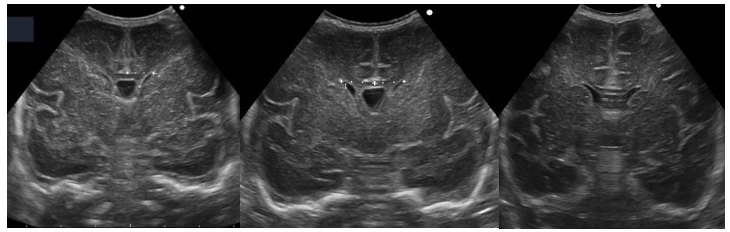
Cranial ultrasound is a standard tool for diagnosing brain injury in newborn infants

Severe brain injury

Myth: Cerebral palsy cannot be predicted by neonatal brain imaging

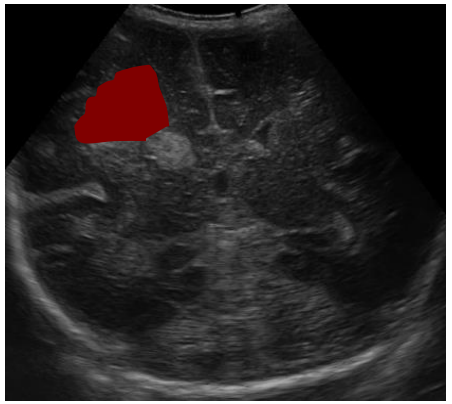
Linda S. de Vries*, Ingrid C. van Haastert, Manon J.N.L. Benders, Floris Groenendaal 2011

Sequential cranial UltraSound



Major intracranial lesions

(IVH III, IVH IV, c-PVL)



Non – ambulatory
Cerebral Palsy

Acta Paediatr. 2005 Dec;94(12):1815-21.

Ultrasound diagnosis of brain atrophy is related to neurodevelopmental outcome in preterm infants.

Horsch S[1], Muentjes C, Franz A, Roll C.

Infants with sonographic signs of brain atrophy at discharge

achieve lower scores in neurodevelopmental testing at 3 y

Yes, cranial ultrasound can be used as outcome measuring tool for severe brain injury

The primary outcome

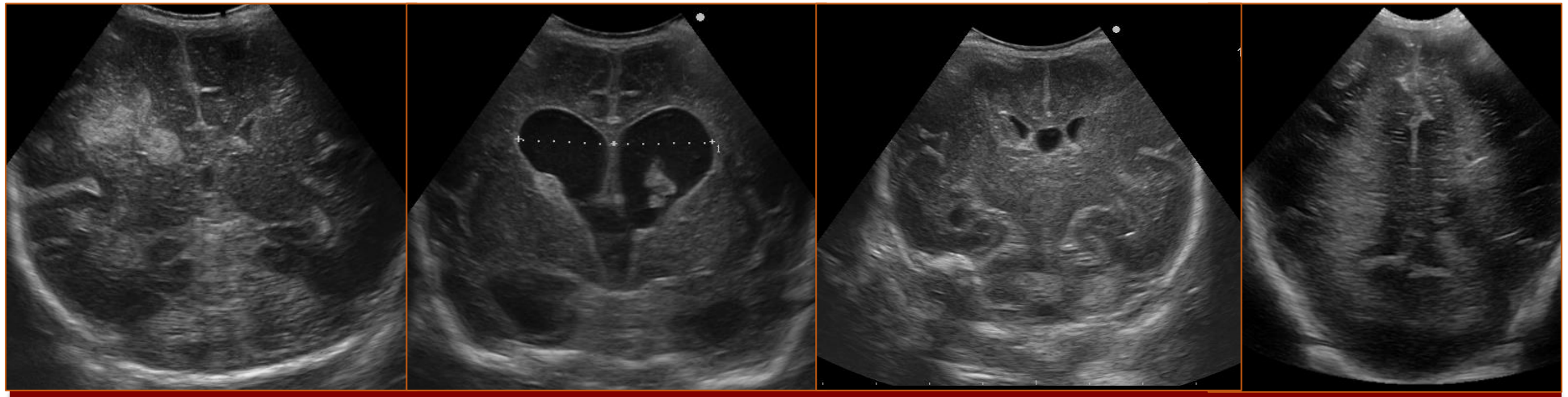
A composite of severe **brain injury** detected on any of the serial cranial ultrasound scans that are routinely performed in these infants up to that age **or death** until 36 weeks of postmenstrual age.

Yes, cranial ultrasound can be used as outcome measuring tool for severe brain injury

The primary outcome

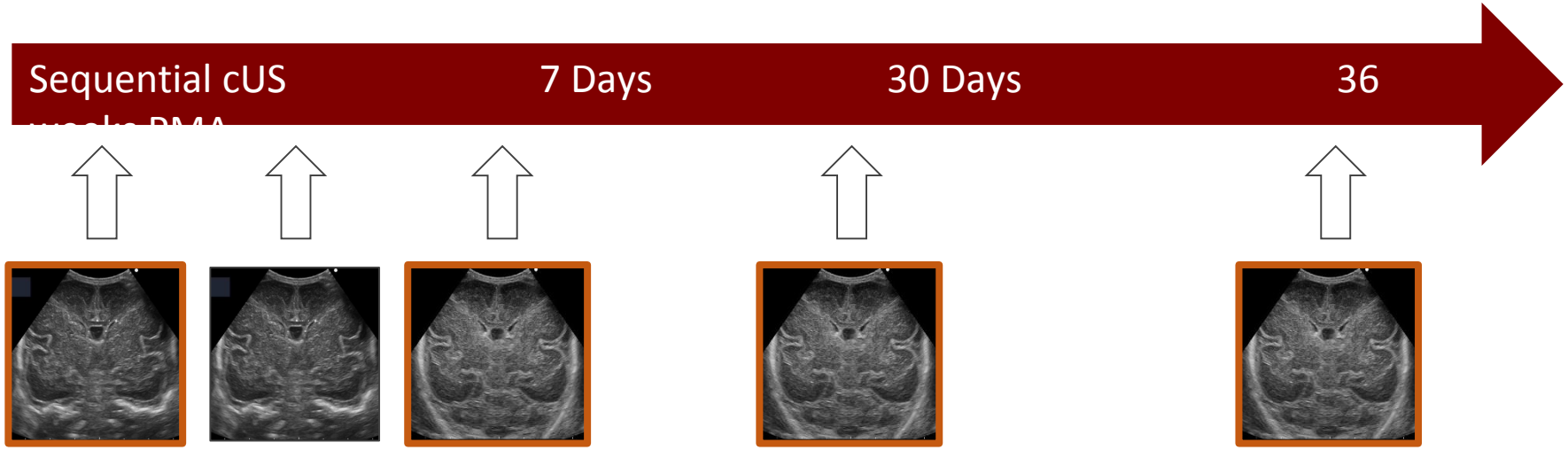
A composite of severe *brain injury (**cerebral haemorrhage grade III or IV, cystic periventricular leukomalacia, cerebellar haemorrhage, post-haemorrhagic ventricular dilatation** or cerebral atrophy) detected on any of the serial cranial ultrasound scans that are routinely performed in these infants up to that age or death until 36 weeks of postmenstrual age.*

GMH-IVH PHVD CBH cPVL



When to perform cranial ultrasound scans ?

Cranial ultrasound is a standard routine examination in preterm infants and will be performed multiple times up to the follow-up time at 36 weeks postmenstrual or first discharge home, per local NICU guidelines. These are often obtained at birth, 7 postnatal days, and 30 postnatal days or more often as clinically indicated.



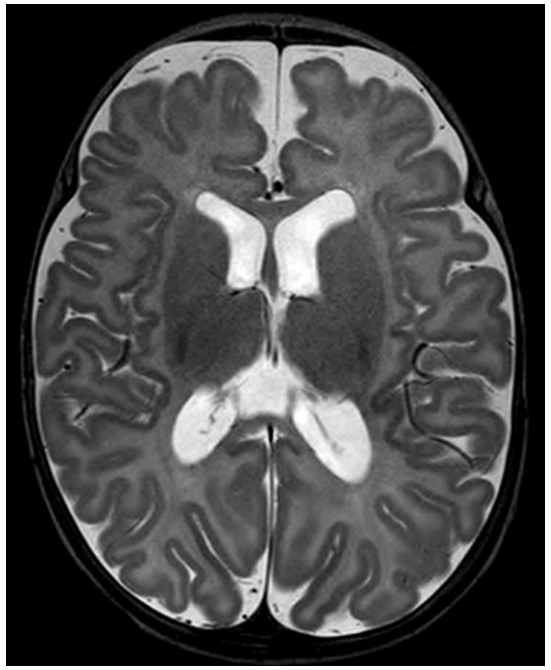
How to score cUS detected brain injury ?

At 36 weeks *of postmenstrual age or first discharge home, the series of ultrasound scans and the infant's clinical files* ***will be reviewed by experienced clinical staff in the local NICU***

Severe brain injury
• Intra-ventricular haemorrhage grade III
• Parenchymal/periventricular haemorrhagic infarction (grade IV)
• Cystic periventricular leukomalacia (cPVL) (89)
• Post-hemorrhagic ventricular dilatation
• Cerebellar hemorrhage
• Cerebral atrophy

Can we do anything better?

Brain MRI



Brain injury in the international multicenter randomized SafeBoosC phase II feasibility trial: cranial ultrasound and magnetic resonance imaging assessments

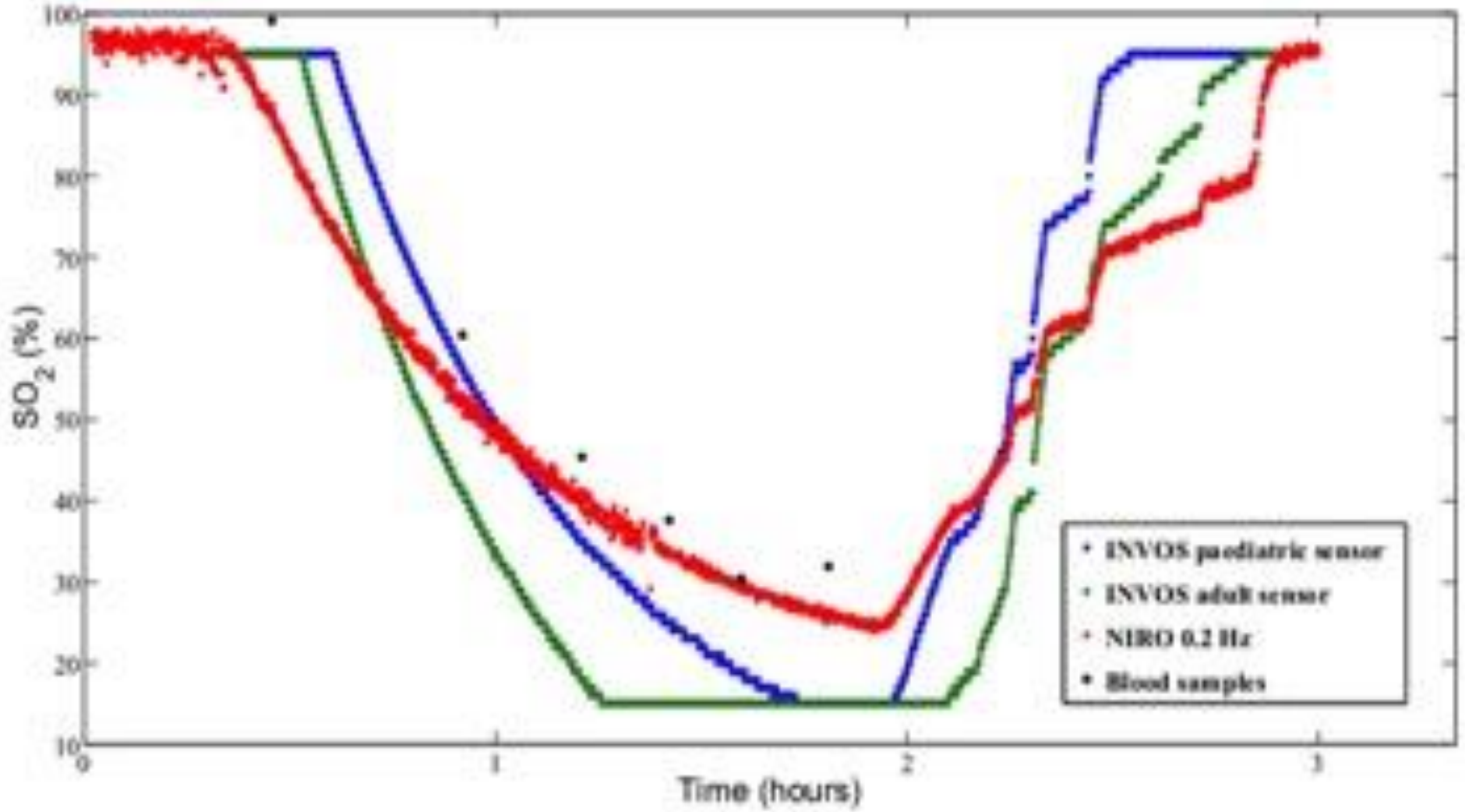
Anne M Plomgaard[1], Cornelia Hagmann[2], Thomas Alderliesten[3], Topun Austin[4], Frank van Bel[3], Olivier Claris[5], Eugene Dempsey[6], Axel Franz[7], Monica Fumagalli[8], Christian Gluud[9], Gorm Greisen[1], Simon Hyttel-Sorensen[1], Petra Lemmers[3], Adelina Pellicer[10], Gerhard Pichler[11] and Manon Benders[3]

MRI at corrected age 40–44 wk	Experimental group ($n = 24$)	Control group ($n = 24$)
Corrected age (wk), median (range)	41.4 (40.7–43.6)	41.2 (40.3–44.0)
No injury, *n* (%)	3 (13)	2 (8)
Mild/moderate injury, *n* (%)	18 (74)	19 (79)
Severe injury, *n* (%)	3 (13)	3 (13)
MRI at any time point	$n = 46$[b]	$n = 38$
Corrected age (wk), median (range)	41.4 (36.7–52.7)	41.4 (39.8–53.9)
No severe brain injury, *n* (%)	41 (89)	35 (89)
Severe injury, *n* (%)	5 (11)	3 (8)

Why have we decided to use generic/different devices?

Simon Hyttel-Sørensen

NIRS devices differ …



NIRS Device	Hypoxic threshold %
FORESIGHT small	66
FORESIGHT non-adhesive small	67
NIRO small	61
NIRO small re-usable	63
NIRO large	62
NIRO large re-usable	62
INVOS neo	63
SenSmart neo 8004CB-NA	66

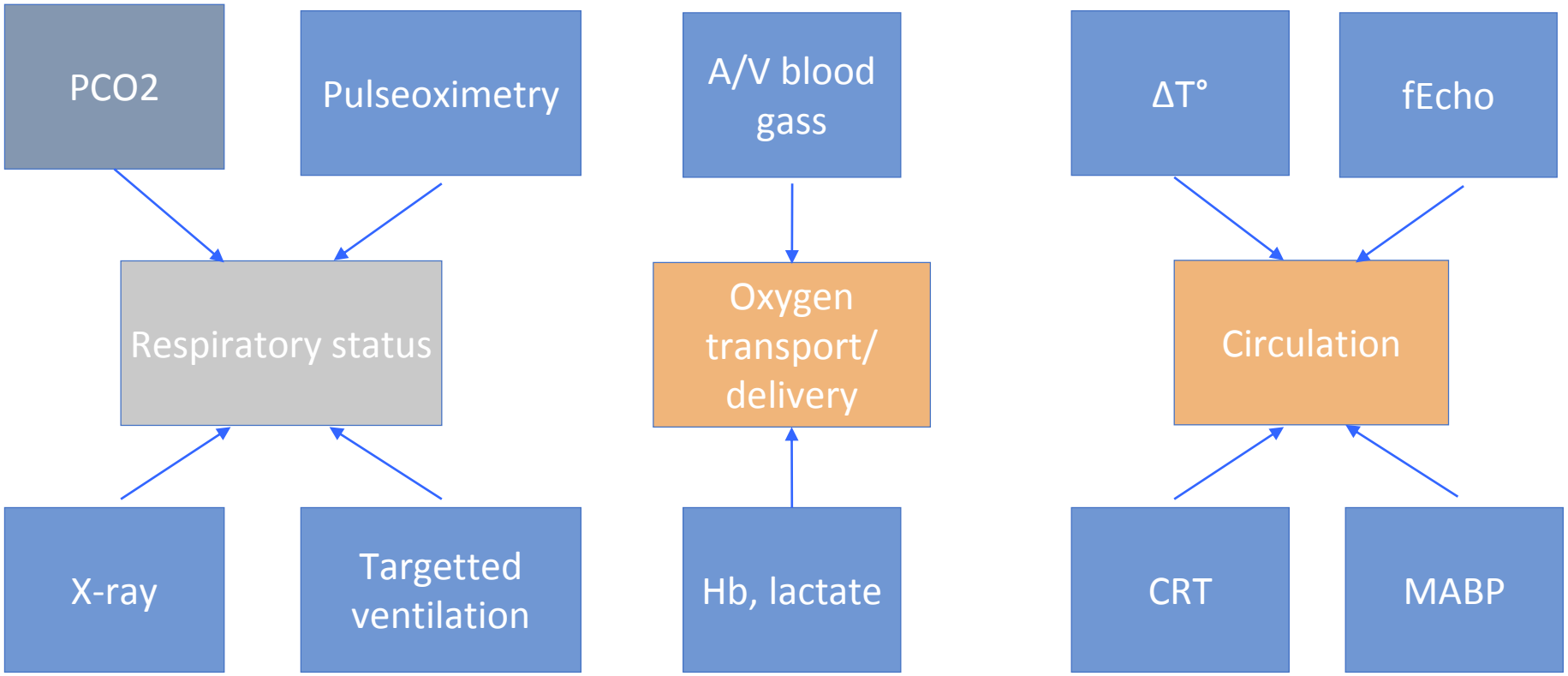
Why have we defined the Severe Adverse Reactions as ‘physical mishaps associated with managing the oximeters and sensors’ and ‘clinical mismanagement based on data from the cerebral oxygenation monitoring’?

Gorm Greisen

Why is the treatment guideline as it is?

Adelina Pellicer

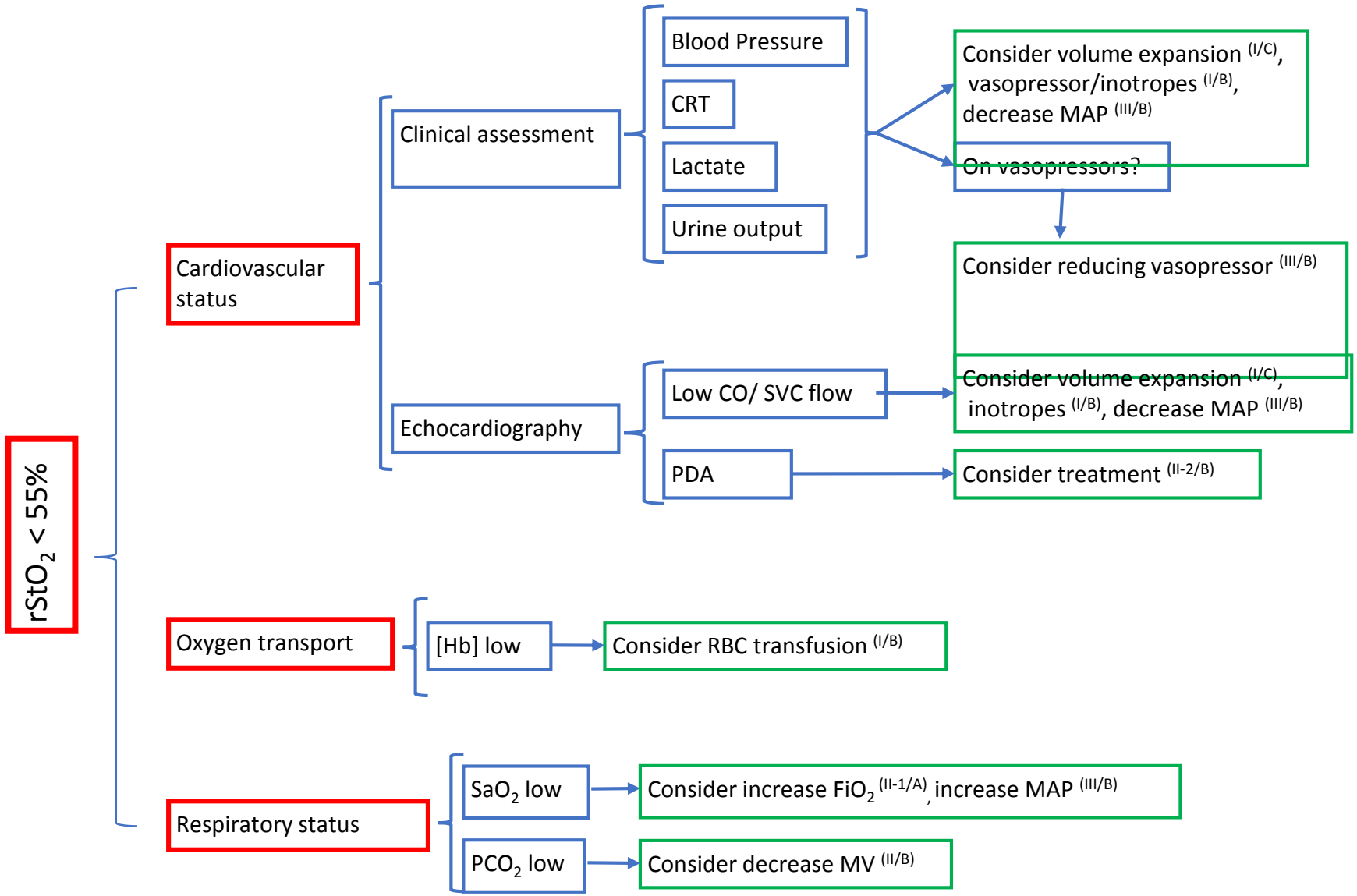
THE PATHOPHYSIOLOGY



Level of evidence	Type of study
I	Evidence obtained from at least one properly randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group
II-3	Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees

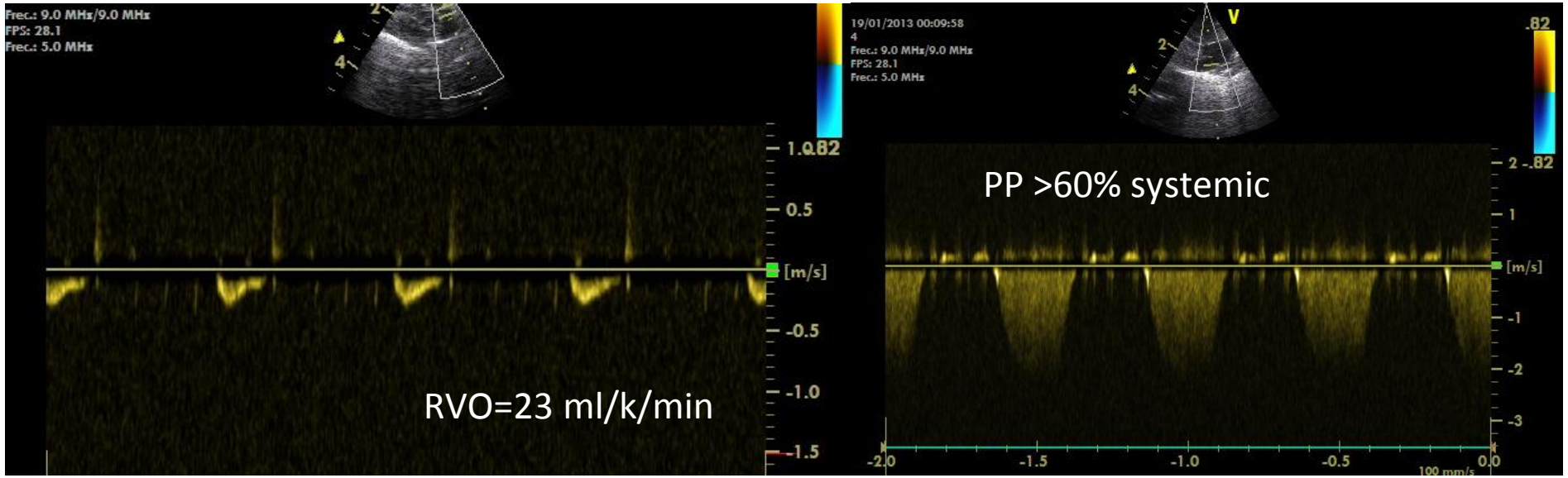
	Net benefit			
Quality of evidence	substantial	moderate	small	zero/negative
Good	A	B	C	D
Fair	B	B	C	D
Poor	E	E	E	E
Standard recommendation language	A= Strongly recommended (good evidence that the intervention improves important health outcomes and benefits substantially outweigh harms). B= Recommended (at least fair evidence that the intervention improves important health outcomes and benefits substantially outweigh harms). C= No recommendation for or against routine provision of the intervention (fair evidence that the service can improve health outcomes but the balance of the benefits and harms is too close to justify a general recommendation). D= Recommends against routinely providing the intervention (at least fair evidence that the service is ineffective or that harms outweigh benefits). E= Insufficient to recommend for or against routinely providing the intervention (evidence that the intervention is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined)			

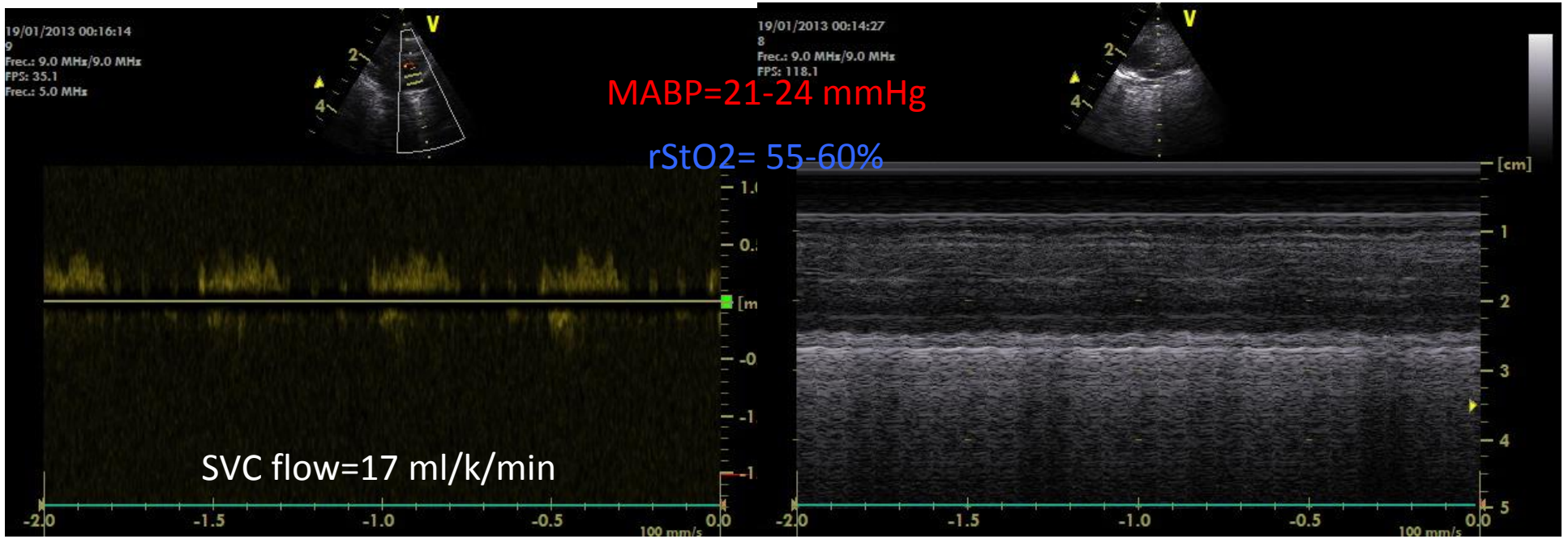
Clinical intervention algorithm in the SafeBoosC phase III trial

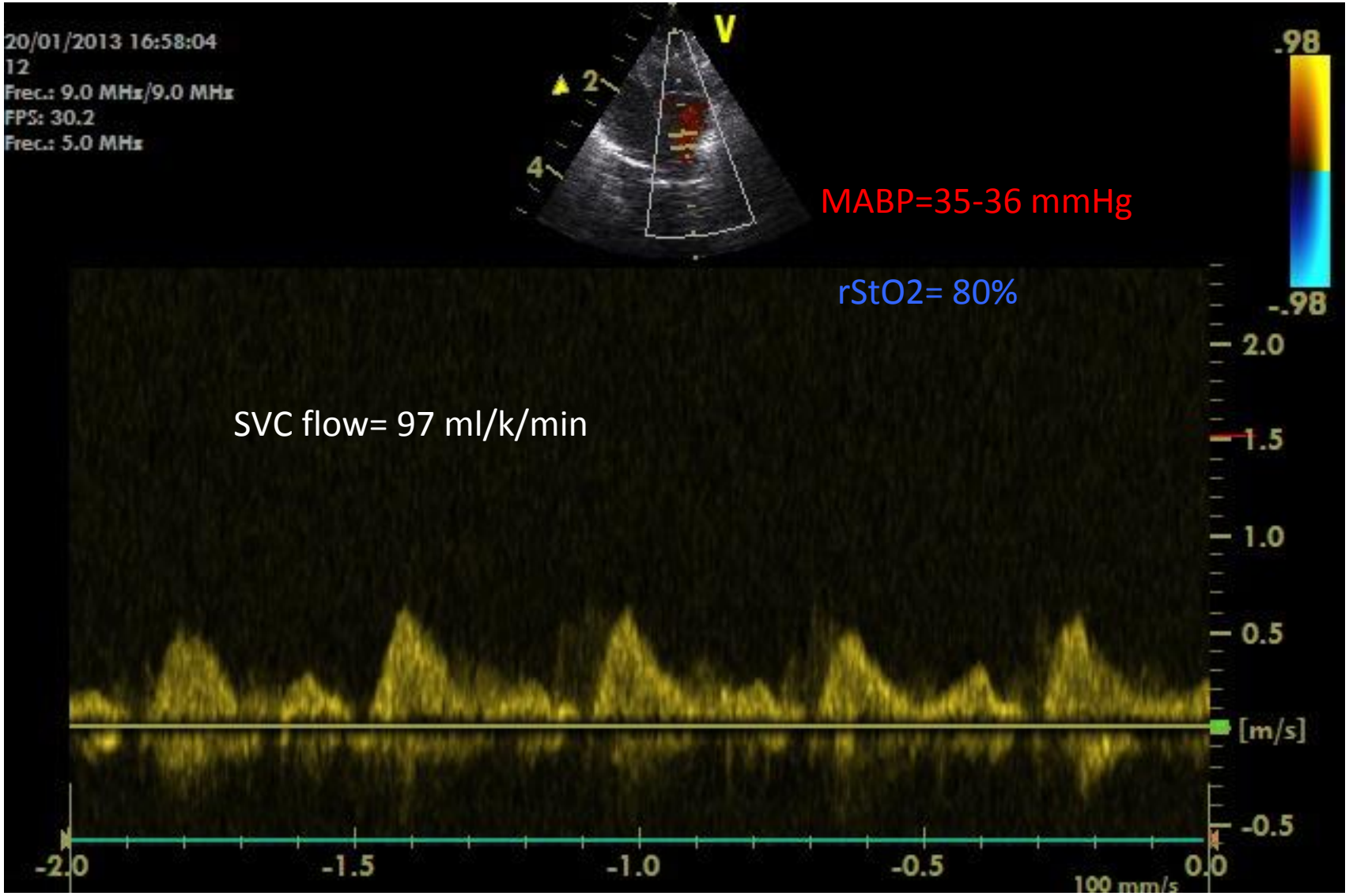


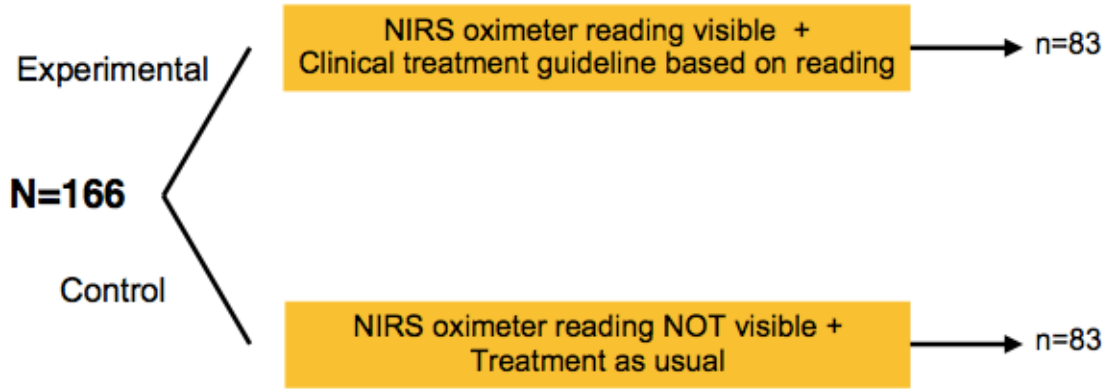

Sensor reposition
rStO2
Echo D
125,
100,
75,
50,
25,
0,
00
01
02
02
03
04
06
07
08
09
10
11
12
13
14
15

23 weeks, <24h


Frec.: 9.0 MHz/9.0 MHz
FPS: 28.1
Frec.: 5.0 MHz
1.0
0.5
[m/s]
-0.5
-1.0
-1.5
RVO=23 ml/k/min
19/01/2013 00:09:58
4
Frec.: 9.0 MHz/9.0 MHz
FPS: 28.1
Frec.: 5.0 MHz
.82
2
1
[m/s]
-1
-2
-3
-2.0
-1.5
-1.0
-0.5
0.0
100 mm/s
PP >60% systemic


19/01/2013 00:16:14
9
Frec.: 9.0 MHz/9.0 MHz
FPS: 35.1
Frec.: 5.0 MHz
SVC flow=17 ml/k/min
-2.0
-1.5
-1.0
-0.5
0.0
100 mm/s
MABP=21-24 mmHg
rStO2= 55-60%
19/01/2013 00:14:27
8
Frec.: 9.0 MHz/9.0 MHz
FPS: 118.1
[cm]
1
2
3
4
5


20/01/2013 16:58:04
12
Frec.: 9.0 MHz/9.0 MHz
FPS: 30.2
Frec.: 5.0 MHz
V
2
4
.98
-.98
MABP=35-36 mmHg
rStO2= 80%
SVC flow= 97 ml/k/min
2.0
1.5
1.0
0.5
[m/s]
-0.5
-2.0
-1.5
-1.0
-0.5
0.0
100 mm/s



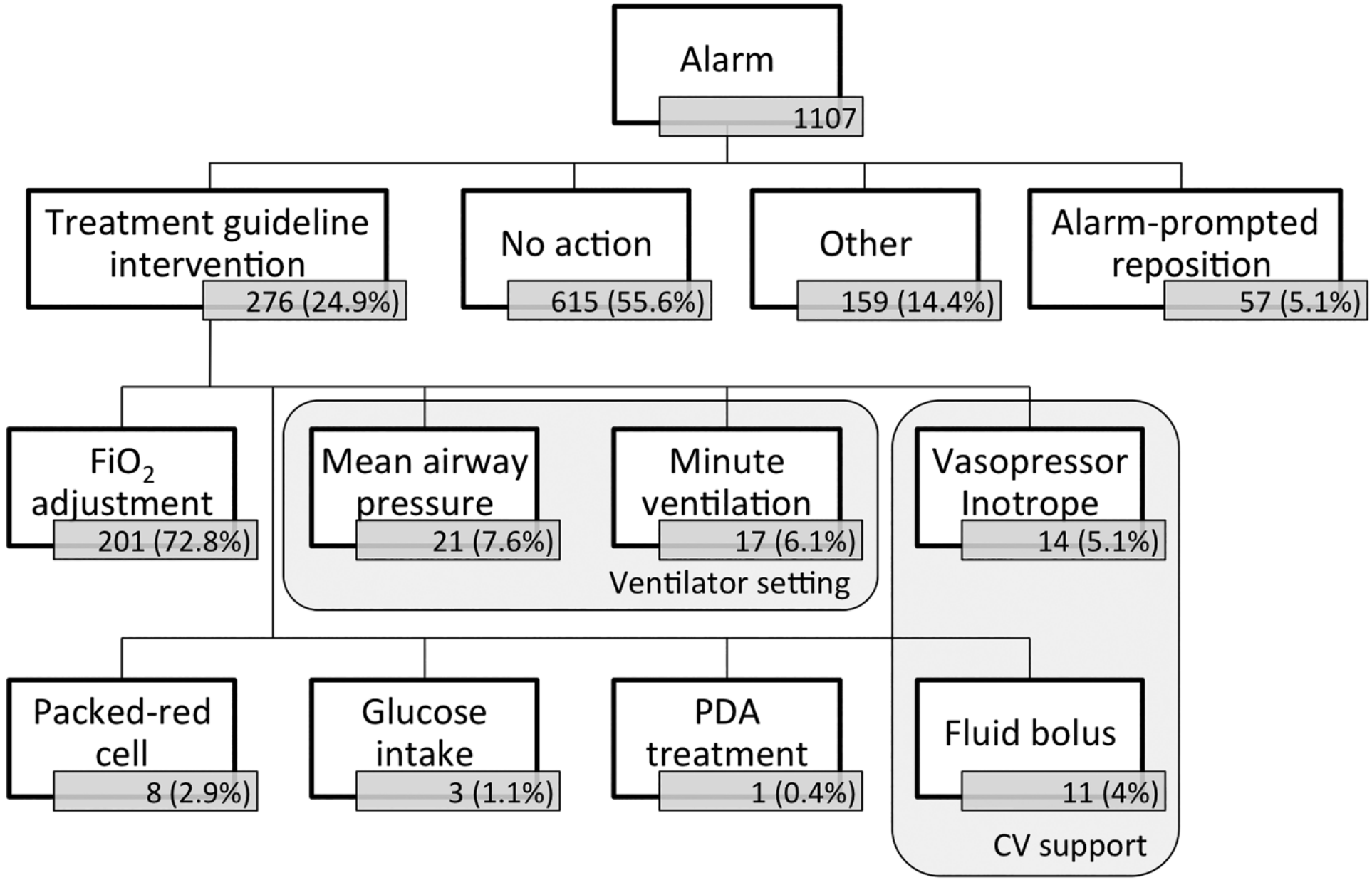
Value of NIRS in decision making

Original article

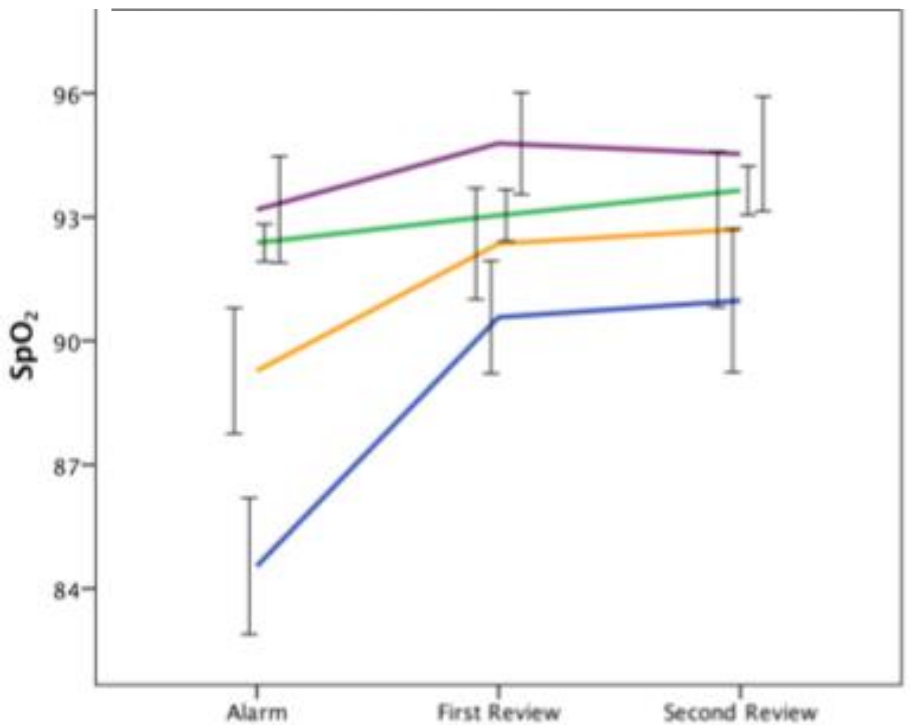
The SafeBoosC phase II clinical trial: an analysis of the interventions related with the oximeter readings

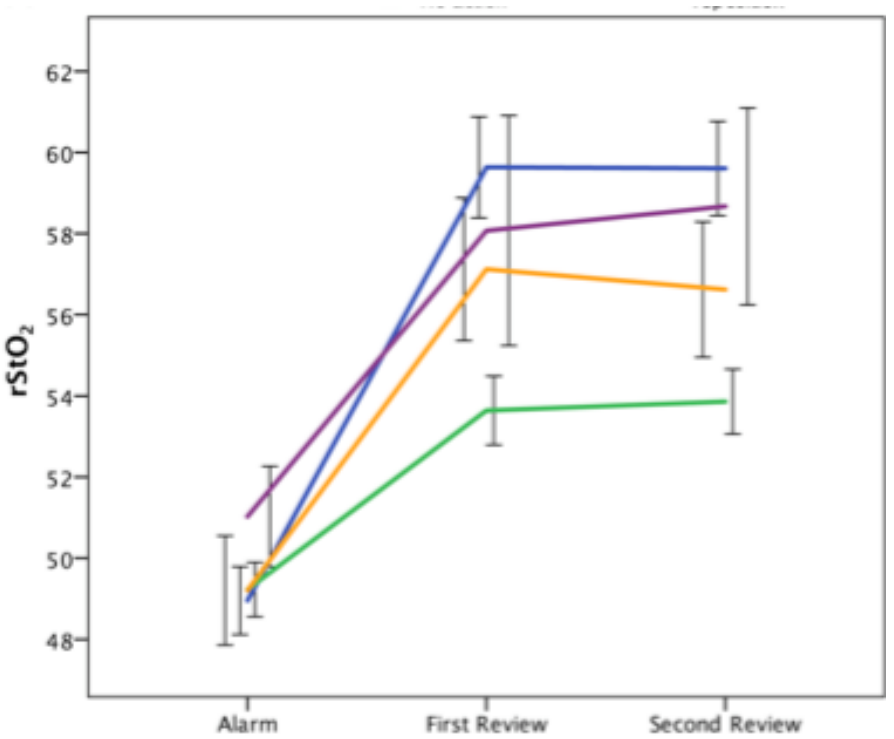
Joan Riera,[1,2] Simon Hyttel-Sorensen,[3] María Carmen Bravo,[1] Fernando Cabañas,[4] Paloma López-Ortego,[1] Laura Sanchez,[1] Marta Ybarra,[1] Eugene Dempsey,[5] Gorm Greisen,[3] Topun Austin,[6] Olivier Claris,[7] Monica Fumagalli,[8] Christian Gluud,[9] Petra Lemmers,[10] Gerhard Pichler,[11] Anne Mette Plomgaard,[1] Frank van Bel,[10] Martin Wolf,[12] Adelina Pellicer[1]

Riera J, *et al. Arch Dis Child Fetal Neonatal Ed* 2016;**101**:F333–F338. doi:10.1136/archdischild-2015-308829


Alarm
1107
Treatment guideline intervention
276 (24.9%)
No action
615 (55.6%)
Other
159 (14.4%)
Alarm-prompted reposition
57 (5.1%)
FiO2 adjustment
201 (72.8%)
Mean airway pressure
21 (7.6%)
Minute ventilation
17 (6.1%)
Ventilator setting
Vasopressor Inotrope
14 (5.1%)
Packed-red cell
8 (2.9%)
Glucose intake
3 (1.1%)
PDA treatment
1 (0.4%)
Fluid bolus
11 (4%)
CV support

Guideline intervention
No action
Other
Sensor reposition





CHALLENGES

- Heterogeneity among centres
  - Adherence to NIRS-TG
- Reliability
  - Sensor reposition
- Reaction to other devices-monitors
  - NIRS threshold alarm not retarded