Ancillary studies

“All partners are encouraged to design ancillary studies and draw on data collected by SafeBoosC-III if not compromising the blinding of assessors or the equipoise of the trial. Ancillary studies must seek approval by the SafeBoosC Steering Committee. “

Potential follow-up studies

Possible outcomes and sample size estimations

Where can I read more?

- www.safeboosc.eu (full synopsis)
- Appendix H in the protocol (www.safeboosc.eu)

Possible outcomes at follow-up

- Days alive outside hospital
- Length of hospital stay
- Bayley Scales of Infant Development
- The Ages and Stages Questionnaire

Days alive outside hospital

Relevant outcome to combine the effect of

1. In-hospital mortality
2. Length of hospital stay of survivors
3. Re-admissions
4. Post-discharge mortality

Assessment by extracting data from clinical files

Days alive outside hospital

Difficulties

1. Discharge home – *criteria for discharge home vary between NICUs*

2. Re-hospitalization – *if this does not happen to primary hospital, it might be difficult for investigators to identify re-hospitalizations at follow-up*

Solutions

1. Statistical analysis stratified for NICU
2. Contact to parents

Length of hospital stay

Social perspective

- Physically and mentally demanding for family
- Decreasing number of days hospitalized → direct value to family

Economic perspective

- Decreasing length of stay → direct value to hospital economy

  (part of health economic evaluation)

Length of hospital stay

Difficulties

1. Infants who die early ‘save’ hospitalization days (benefit)
2. Re-hospitalization issue

Solution

1. Separate assessment for survivors and non-survivors
2. Contact to parents

Neurodevelopmental impairment

Bayley Scale of Infant Development, Ages and Stages Questionnaire

The Bayley Scales of Infant Development (BSID)

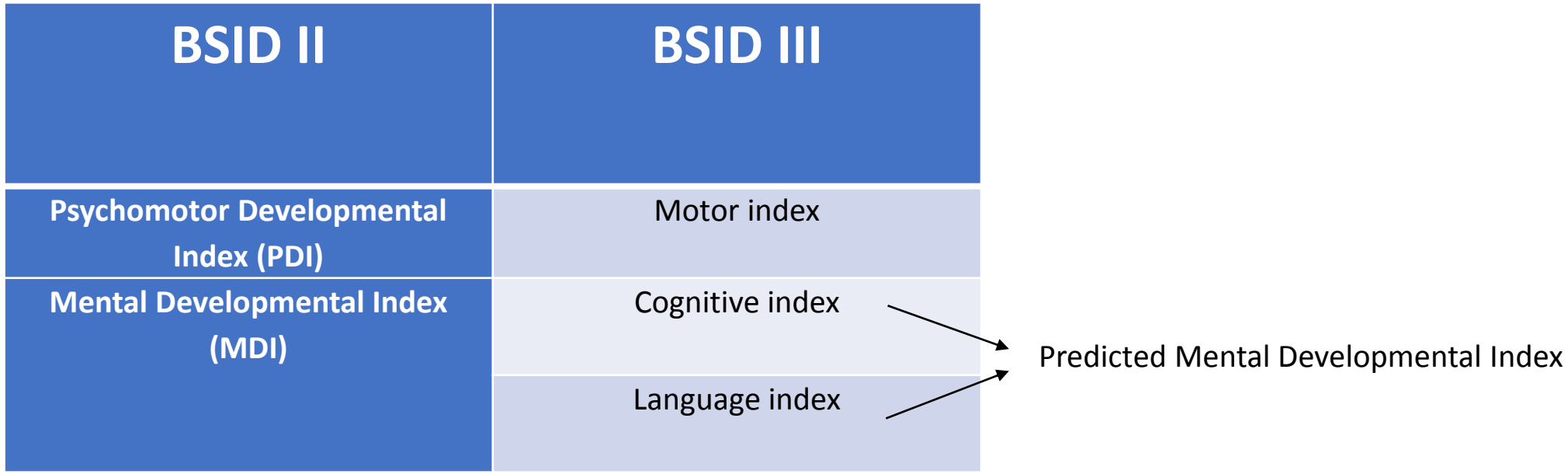
Clinical examination to predict neurodevelopmental impairment

BSID III
- Cognitive
- Language
- Motor

BSID II
- MDI
- PDI

BSID II versus BSID III

How to merge BSID II and BSID III scores (3) (4)



(3) Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between Test Scores Using the Second and Third Editions of the Bayley Scales in Extremely Preterm Children. J Pediatr. 2012 Apr;160:553–8.

(4) Plomgaard AM, Alderliesten T, van Bel F, Benders M, Claris O, Cordeiro M, et al. 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 Jul 5;1–7.

Ages and Stages Questionnaire (ASQ) III

- Validated parental questionnaire
- Good agreement between BSID og ASQ (5)

(5) Gollenberg AL, Lynch CD, Jackson LW, McGuinness BM, Msall ME. Concurrent validity of the parent-completed Ages and Stages Questionnaires, 2nd Ed. with the Bayley Scales of Infant Development II in a low-risk sample. Child Care Health Dev. 2010;36:485–90

Estimation of sample size

In this table we have outlined the number of infants needed in each group to achieve a power of 90% at a 5% significance level, for the specific outcome.

Outcome	Data type	Number of infants needed in each group
Days alive outside hospital (one year)	Continuous	657
Length of hospital stay (one year)	Continuous	237
BSID MDI score (two years)	Range	235
ASQ total score (two years)	Range	235

Feasibility

Despite only 30% of the NICUs participating in a follow-up study, it is possible to achieve significant power in multiple outcomes. Therefore, we believe a later follow-up study is feasible.

We hope that all NICUs will prepare for ancillary follow-up studies by

1. *Storing the personal information necessary to track all infants*
2. *Define the possible sources for follow-up. This is to enable the best possible data for later systematic follow-up.*

Jonathan Mintzer

Stony Brook Children's, Stony Brook, NY

Peripheral Muscle Monitoring

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

- **Observational Study**
- **Large population** – starting point for comprehensive data
- **Rationale**
  - Cerebral rSO_2 is stable measure
    - Redundant perfusion
    - Cerebral autoregulation
  - Peripheral monitoring may be more sensitive to change
    - Variability comparing cerebral to renal/splanchnic
      - Renal – affected by fluid balance/shifts, diuresis
      - Splanchnic – high variability, hollow cavity, peristalsis, feeding

Peripheral Muscle Monitoring

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

- **Why?**
  - Sensitivity of peripheral monitoring
  - Potentially less pitfalls than renal and splanchnic
  - Blood flow redistribution
    - A "true end-organ"
    - Earlier indicator of altered clinical status?

- **Peripheral Muscle**
  - Right thigh, vastus lateralis along lateral-most thigh margin
  - Longitudinal sensor placement (sensor cord projected distally)

Peripheral Muscle Monitoring

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

- **Approach**
  - Observational data gathering
  - *Protocol-based changes based on cerebral only
  - *No effect on SafeBoosC-III goals

- **Data / Outcomes**
  - Site-specific baseline and stability/variability
  - *Time-course of cerebral versus peripheral muscle perturbations
  - *Responses to therapeutic maneuvers

Zachary Vesoulis

Washington University, St. Louis MO

Big Data Ancillary Project

Zachary Vesoulis, Washington University, St. Louis MO

- **Observational Study**
- **Large population** – starting point for comprehensive data
- **Rationale**
  - NIRS monitoring is hard to do in the preterm population
  - Large studies are rare (Alderliesten 2015 the notable exception)
  - Excellent opportunity for secondary data collection

Big Data Ancillary Project

Zachary Vesoulis, Washington University, St. Louis MO

- **Approach**
  - Observational data gathering
  - Anonymization and transmission to central “data repository”
  - *No effect on SafeBoosC-III goals, merely recording of underlying physiology

- **Data / Outcomes**
  - Multi-modality data recording
    - NIRS, pulse oximetry, heart rate, arterial blood pressure, ventilator data (as available)
  - Primary outcome - cerebral hypoxia and brain injury

Big Data Ancillary Project

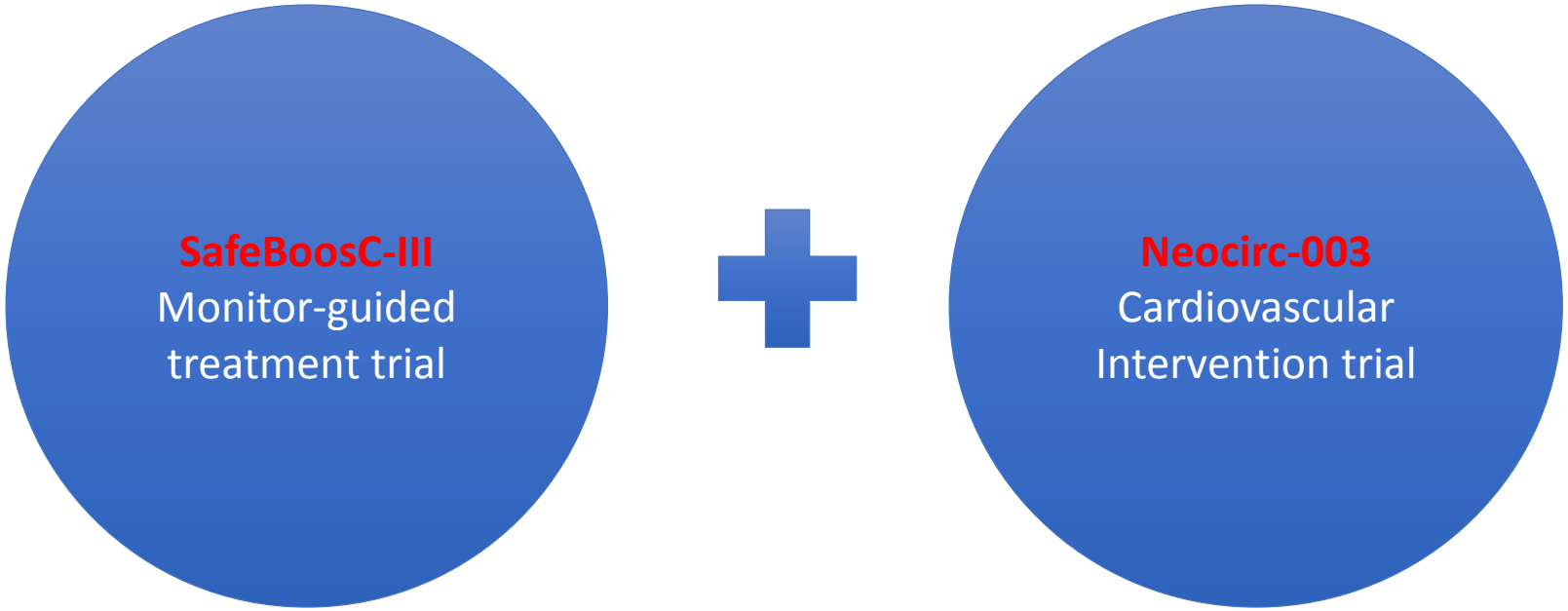
Zachary Vesoulis, Washington University, St. Louis MO

- **Additional goals**
  - Standardization of data recording platforms
  - Standardization of data interchange format
  - Standardization of central data storage
  - Evaluation of variation in cerebral saturation/FTOE by device, sensor, and center
- **Challenges**
  - Additional cost (hardware/software, time) for data collection

Adelina Pellicer

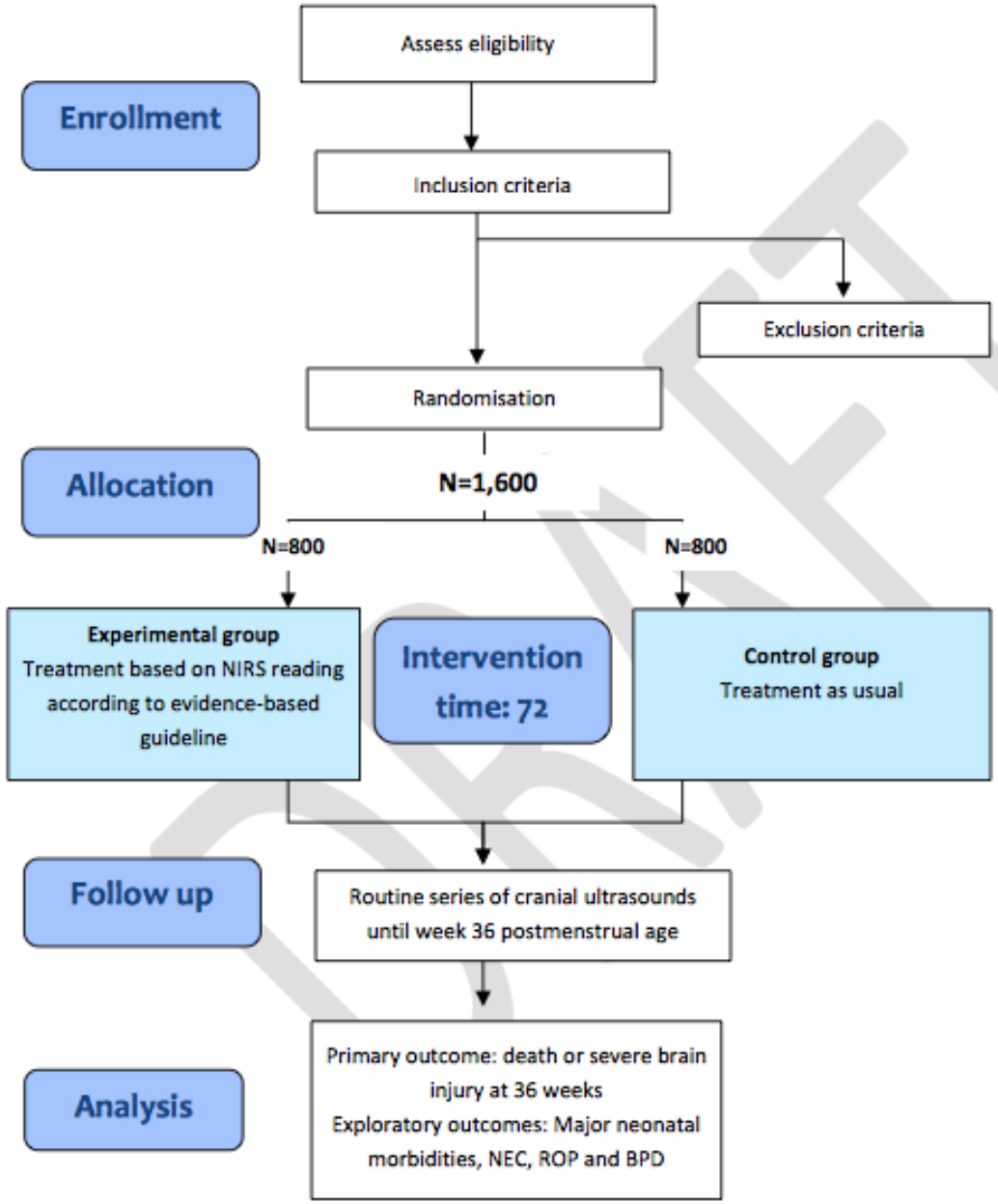
La Paz University Hospital, Madrid, Spain

Getting infants into both RCTs

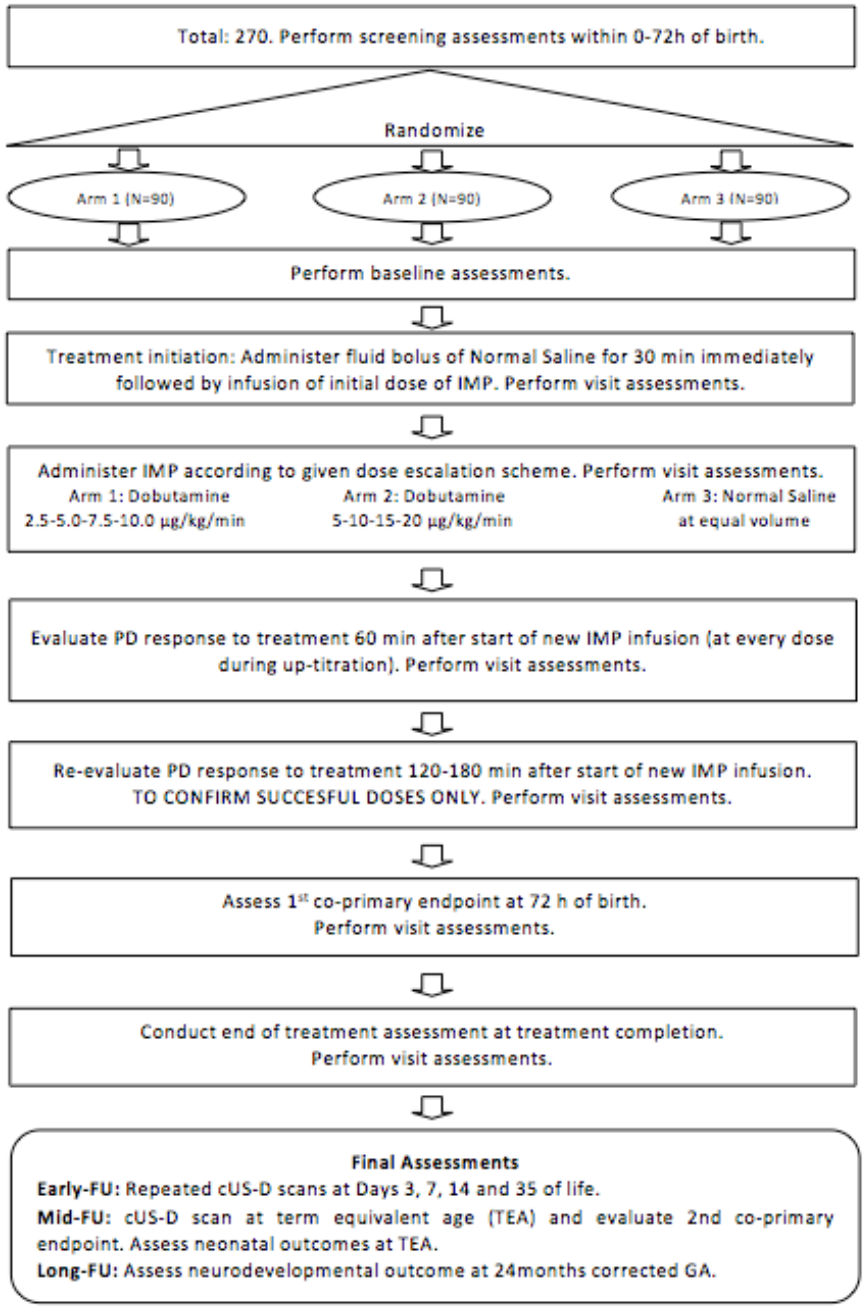


Questions to address have common pathophysiology

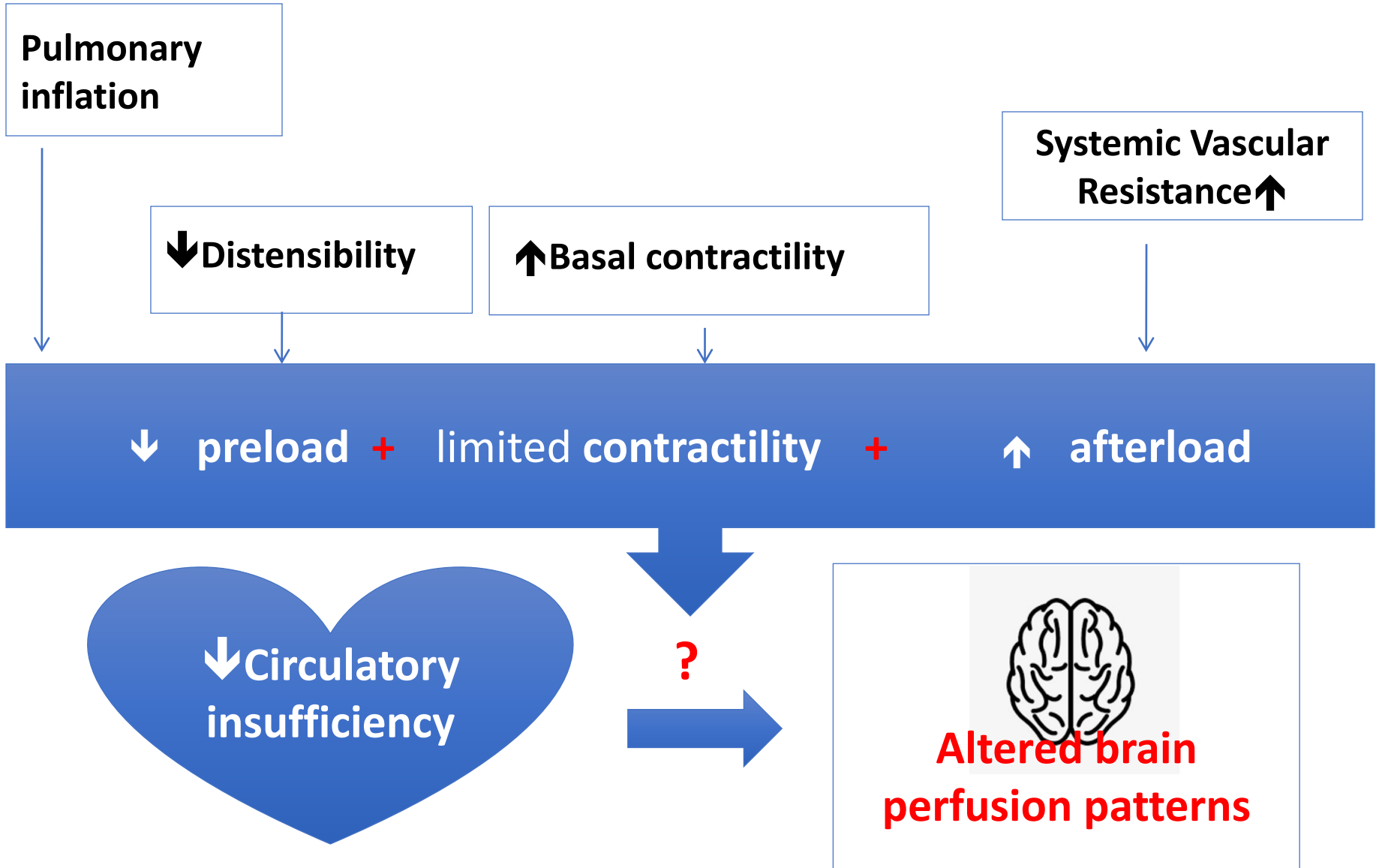
SafeBoosC phase III trial



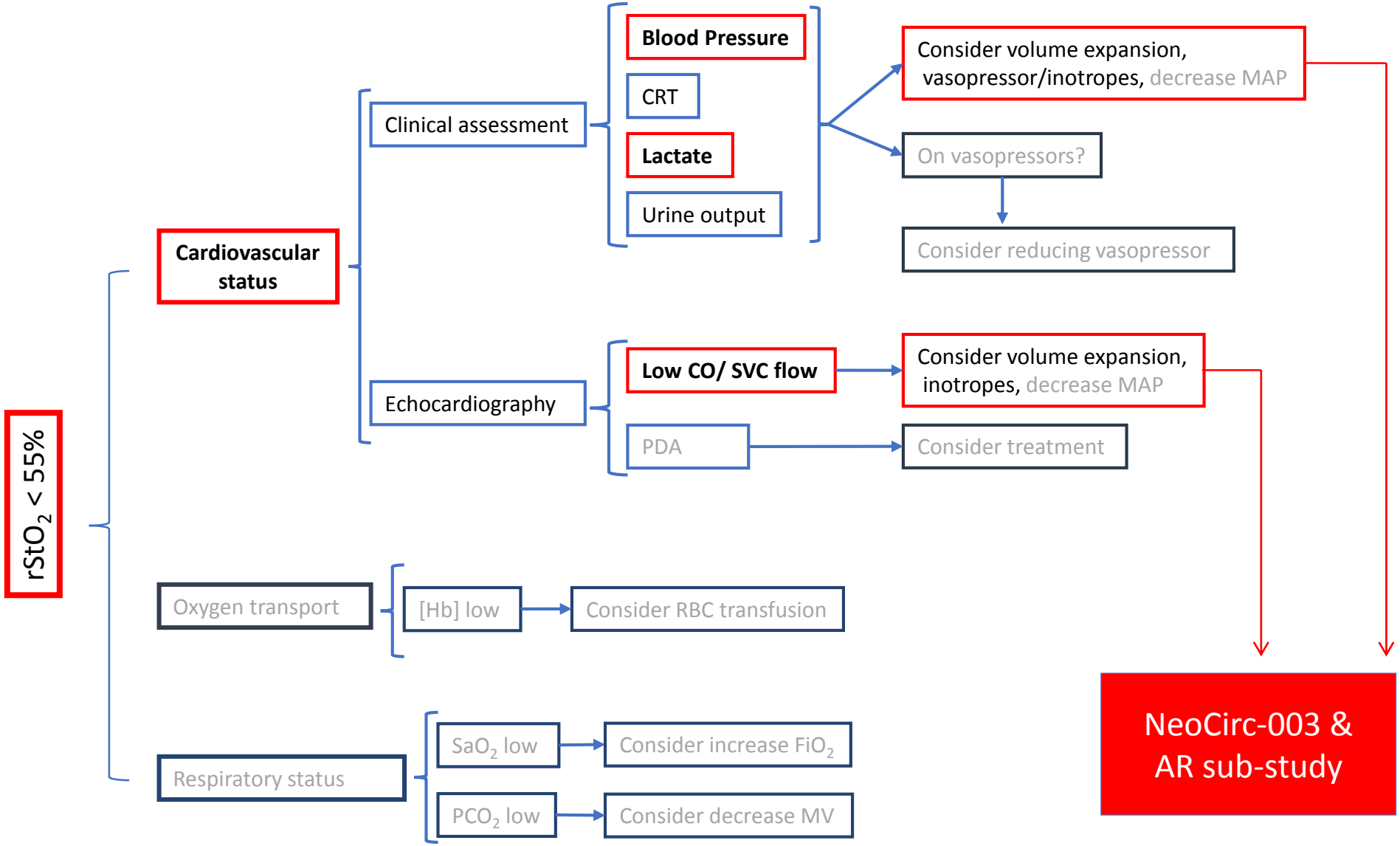
NeoCirc-003



Neonatal circulatory maladaptation



Clinical intervention algorithm in the SafeBoosC phase III trial



NeoCirculation & Advanced biomarker sub-studies

- Additional Echo-D
- aEEG
- NIRS continuous monitoring
  - Continuos data recording
  - AR studies (invasive blood pressure required)
    - BiAR-COH
    - PDC $_{MABP>>>rStO2}$
  - rStO2 is not a criterion for entry or rescue
  - rStO2 may help in decision-making

Procedures

- Antenatal informed consent
  - Specific ICF
    - SafeBoosC-III
    - NeoCirc-003
  - Deferred consent in both trials (approval site-dependent)
- Advanced biomarkers NeoCirc-003 sub-study only if SafeBoosC-III experimental group

Tomasz Szczapa

Ancillary study on renal tissue oxygenation during NICU interventions in the SafeBoosC-III trial

Tomasz Szczapa, MD PhD

Department of Neonatology

Poznań University of Medical Sciences

Renal StO_2 in SafeBoosC-III patients

- Additional, simultaneous monitoring of renal tissue oxygention in the preterm infants enrolled to SafeBoosC-III trial
- Polish centers (10)

Rationale for the study

- measuring renal function in premature neonates is challenging
- validity of biochemical markers such as creatinine during the first few days of life is limited
- association between renal StO_2 and renal perfusion was described in neonates
- hypoxemia may affect kidney oxygenation
- **What are the changes in the renal StO_2 while interventions are guided by cerebral NIRS monitoring?**
- **What are the values of renal StO_2 in extremely premature infants in the first days of life?**

Petrova A, Mehta R. Arch Dis Child Fetal Neonatal Ed. 2010
Terstappen F et al. PLoS One. 2018
Lau PE et al. J Pediatr Surg. 2017 May;52(5):689-692.
Balci C et al. Int Med Res. 2018
Altit G et al. Neonatology. 2018
Chock VY et al. J Pediatr. 2018

Additional measures

- NIRS sensor placement on the lateral posterior flank
- Renal and cerebral StO_2 data collection
- Clinical data regarding renal function