Learning material and quiz on SafeBoosC III treatment guideline
Learning materials

Learning objectives
By the end of this module participants will be able to
1- understand the pathophysiology of transitional circulation
2- understand the causes of low rStO2, relevant clinical assessment, and interventions to restore rStO2 within normal range
3- understand the role of rStO2 in decision making
4- understand the challenges that may appear during the conduct of SafeBoosC-III

1- Pathophysiology of transitional circulation

Soon after an infant is born there is a rise in systemic vascular resistance (SVR), a decrease in pulmonary vascular resistance, and the cardiac output (CO) is distributed in parallel. Progressively, the foetal channels foramen ovale and ductus arteriosus closes.

The immature cardiovascular system frequently fails to adapt to birth. This is due to the limited myocardial contractility of the immature heart, and a potentially compromised preload due to poor diastolic function and lung inflation (Fig. 2). This may lead to decreased CO and abnormal blood flow distribution.

Decreased blood flow to the brain (CBF) and oxygen delivery to the brain may be the consequence.
Blood flow, oxygen transport and cellular metabolism are interdependent. Several aspects should be taken into account when evaluating the haemodynamic condition of an infant (Fig. 3).

At the level of macro-circulation, the perfusion pressure (PP) is the driving force which moves blood through the vasculature. The perfusion pressure (PP), depends on the CO and the SVR. At the level of the micro-circulation, the resistance of small arteries and arterioles, and changes in venous capacity regulates peripheral blood flow. To meet the metabolic demands, tissue blood flow is normally adjusted according to oxygen consumption. When the blood flow is low, however, in comparison to the oxygen need then oxygen extraction is increased with the effect that oxygen saturation in the venous
blood drop. If this reach a certain point, we say that the brain is hypoxic and that there is a risk that brain cells suffer from hypoxia-ischemia.

The regional tissue oxygen saturation (rStO2) is a volume-weighted parameter, representing the oxygenation of arterial, capillary and venous blood, of which the venous contribution is the largest. Therefore, rStO2 can be used as a surrogate measure for venous oxygen saturation (SvO2). From this parameter a continuous estimate of the balance between oxygen delivery (DO2), represented by SpO2 (pulse oximeter), and oxygen consumption can be derived (VO2=SpO2-rStO2). The fractional oxygen extraction (FOE) = (SpO2-rStO2)/SpO2 then represents VO2/DO2.

2- Causes of low rStO2, clinical assessment, and interventions

Low StO2 (cerebral hypoxia) during the first days after a baby is born can be due to suboptimal ventilation, cardio-vascular dysfunction, insufficient oxygen transport capacity, or a combination of these factors. In order for the clinician to identify the most likely cause of cerebral hypoxia in a given clinical situation, it is necessary that he/she is aware of the potential causes and how to assess them. (Fig.4).

![Diagram](image)

*Figure 4. Clinical assessment tools to evaluate potential causes of a low rStO2 during the transitional period in ELGANs.*

In the SafeBoosC-III trial, a clinical treatment guideline is available (Fig. 5). This guideline is a list of possible interventions when cerebral hypoxia is present. It a modified version of the one used in the SafeBoosC II trial.

The interventions proposed are not listed in a pre-established sequence or prioritized. It was not considered possible to make a flow chart, where defined criteria leads to specific actions, or sequences of actions. The relevance of each of possible interventions...
depends on an assessment of the complete picture of the infant’s clinical condition. Sometimes the most reasonable ‘action’ may be watchful waiting.

The proposed interventions are all routinely used in clinical care of the extremely low birth weight neonate (ELGAN), during the first hours and days after birth.

**Figure 5.** Treatment Guideline algorithm for the SafeBoosC-III RCT. In brackets, the level of evidence and recommendation for a given intervention (U.S. Preventive Services Task Force system 2001). Note: The rStO2 value (here 55%), depends on the cerebral oximeter used.

**Respiratory status**

*The effect of low PCO2 on brain oxygenation.* One of the most important determinants of cerebral blood flow and thereby of cerebral oxygenation is partial pressure of carbon dioxide (PCO2). During the acute phase of respiratory distress syndrome, infants on assisted ventilation, even on volume targeted ventilation, may have inadvertent low PCO2 or a fast decrease in normal range. This has an immediate effect on cerebral blood flow that is reflected in rStO2 (Fig.6).
Figure 6. rStO2. In this example a decrease in ventilation (a decrease in minute volume, tidal volume or respiratory frequency, depending on the ventilation mode) should have been made at the arrow, and not as it happened many minutes later.

The effect of low SaO2 on brain oxygenation. Normally there is a direct proportionality between changes in SpO2 and in rStO2, so that for example a 5% increase in SpO2 will lead to a 5% increase in StO2. It is crucial, however, not to exceed the upper target threshold for SpO2 (95% in most NICUs) since this will expose the infant to the risks of retinopathy of prematurity. If SpO2 is low, then the first step may be to increase supplemental oxygen. Of notice, in infants with very sick lungs, insufficient lung recruitment could be the cause. An X-ray may help to judge whether an increase in mean airway pressure could help to increase SpO2. Usually, the positive effect of lung recruitment on SpO2 and rStO2 trends is rather fast. Caution should be taken not to exceed the threshold for SpO2. Caution should also be taken not to over-distend the lungs (Fig. 7), particularly if the infant is on high frequency ventilation, since this may compromise right atrial preload and consequently, reduce cardiac output (see below). Lung over-distension may also cause a raise in pulmonary vascular resistance, decreased pulmonary blood flow, and protracted hypoxemia.
Cardiovascular status

The diagnosis. Failure to drive oxygenated blood to the organs, due to circulatory impairment will usually also lead to decreased cerebral rStO2. Routine clinical assessment of circulation mainly relies on blood pressure (BP) monitoring, either invasive or non-invasive. However, BP alone is a poor surrogate of systemic (and brain) perfusion (Fig. 3). The use of a combination of assessments, in addition to BP, to guide cardiovascular support is recommended. This includes capillary refill time, urine output, or serum blood lactate assessment. Whenever feasible, functional echocardiography is of value, informing about systemic blood flow (superior vena cava flow-SVC flow, right ventricular output-RVO, left ventricular output-LVO), preload (filling of the heart), contractility, and abnormal shunts through the foetal channels.

The treatment. When a physician suspects impaired circulation to be the cause of low rStO2, he/she should consider either volume expansion, vasopressor-inotrope (dopamine and epinephrine) or inotrope (dobutamine) prescription. The effect of these interventions on BP, cardiac output, and cerebral perfusion-oxygenation may be variable. Of note, if CO or SVC flows are low, even if blood pressure is within normal range, it is suggested to start on inotrope treatment (+/-fluid bolus). Impaired myocardial performance is assumed to be the main determinant of circulatory failure in such cases, and therefore, raising muscular tone at the vascular bed (increased afterload) by vasopressors (dopamine, epinephrine, or norepinephrine) can be counterproductive. Low rStO2 may be the sole parameter, indicating that systemic (and cerebral) blood flow is compromised in an infant who otherwise appear rather well (Fig. 8 and Fig. 9). Following the same line of thought, if an infant is already on vasopressor therapy, particularly if using high doses, the main pharmacodynamic effect may be on the α-adrenergic receptors at the vascular bed, causing further myocardial depression and protracted systemic hypoperfusion. Step-down titration of vasopressors should be considered in this situation.
Figure 8. Preterm infant, 23+4 w, <24h after birth. Cerebral rStO2 is maintained between 55% to 60% but SpO2 and BP are within normal ranges according to NICU policies. Echocardiography revealed very low RVO (<150 ml/k/min) and SVC flow (<41 ml/k/min) and pulmonary hypertension (PP, pulmonary pressure >60% of systemic pressure). In such case, interventions to improve cardiac output may used regardless of the SafeBoosC-III trial.

Figure 9. The same infant 3 hours after dobutamine treatment started. No other change in management was implemented.
A haemodynamically significant patent ductus arteriosus (PDA) causing blood flow redistribution towards the lungs, may lead to low systemic and cerebral blood flow and low rStO2. Treatment of PDA may be the most relevant intervention for a low rStO2.

**Oxygen transport**
Routine blood sampling may reveal anemia potentially requiring red blood cell transfusion. Furthermore, during the first hours after birth, hypovolemia may be caused by acute haemorrhage during birth. In contrast, placental-to-foetal transfusion increases rStO2, possibly not only due to increased oxygen carrying capacity but also to improved preload. Infection, coagulopathy, or repeated blood sampling are frequent determinants of early acquired anaemia, often associated with postnatal bleeding, causing insufficient oxygen delivery to the cell, raised serum lactate and acidosis, and low rStO2. Policies regarding transfusion varies among NICUS. In some infants with marginal anaemia and a low rStO2 transfusion may be the most relevant intervention.

**3- The role of rStO2 in decision making**
The use of interventions in situations with alarms for low rStO2 in the SafeBoosC II trial, was assessed by post-hoc analysis of the experimental group data, examining the impact on rStO2 and SpO2.
The responses to low rStO2 alarms were grouped in four groups: treatment guidelines (TG) intervention, other action not included in the TG, sensor repositioning, and no-action.

In 55% of alarms no action was taken. In 25% of alarms a TG-intervention was used, while in 14% another clinical management decision was made, and in 5% the sensor was re-positioned.

![Figure 13. Decisions in response to an alarm in the experimental group in the SafeBoosC-II trial. (Riera et al, Arch Dis Child Fetal Neonatal Ed 2016)](image)

The greatest rise in StO2 occurred after TG interventions (Fig. 10). But significant rises were also seen after non-TG interventions, sensor repositioning and even after no-action (watchful waiting). We do not know the details which led physicians to choose what to do, so it is unlikely that the four groups were similar. Also, the response of SpO2
The greatest change in SpO2 occurred after a TG intervention, which makes pathophysiological sense since most intervention were to change respiratory management. Repositioning the sensor, or not doing anything (watchful waiting) as a response to the alarm, did not cause any changes in SpO2.

It is noteworthy that infants in atmospheric air had high SpO2 without having particularly high rStO2 (Table 1). This supports the notion that other factors than SpO2 are important for rStO2 and that FiO2 adjustments should be use sparingly.

Table 1. rStO2 and SaO2 according to level of inspired supplementary oxygen (FiO2) in the SafeBoosC-II trial

<table>
<thead>
<tr>
<th>FiO2 value</th>
<th>rStO2 % (SD) [n]</th>
<th>SpO2 % (SD) [n]</th>
</tr>
</thead>
<tbody>
<tr>
<td>21%</td>
<td>64.9 (15.9) [580]</td>
<td>94.5 (5.2) [711]§</td>
</tr>
<tr>
<td>22-29%</td>
<td>67.3 (14.8) [376]*</td>
<td>92.8 (4.6) [447]</td>
</tr>
<tr>
<td>≥30%</td>
<td>63.8 (11.8) [149]*</td>
<td>92.0 (4.1) [180]</td>
</tr>
</tbody>
</table>

* differences between 21% and 22-29% FiO2 strata (p=0.001)  
§ differences between 21% and the other two FiO2 strata (p<0.001)

The time needed before rStO2 was back into the target range varied between the groups (Fig. 11). After ‘alarm-prompted re-position’, rStO2 was back into the normal range within 60 min in 95% of cases. However, after an TG or non-TG intervention, this was only 80-85% of cases. This means that even if the intervention chosen may be appropriate, the mechanism involved in improving brain perfusion-oxygenation, may take time. Furthermore, in some very ill infants, it is likely that cerebral hypoxia was resistant to all interventions.
Figure 11. Kaplan-Meier plot diagram representing time needed for the alarm to be resolved according to type of decision taken (no action vs: TG intervention p<0.001; sensor reposition p=0.001; other p=0.009)

4- Challenges during the conduct of SafeBoosC-III RCT

The post-hoc analysis of SafeBoosC-II experimental group demonstrated heterogeneity among the participating centres.

a) **Reliability of rStO2.** Periodical re-positioning of the NIRS sensor, that was prescribed by the SafeBoosC II protocol, varied between NICUs. Repositions per hour ranged from 0.0 to 0.28. Alarm-prompted repositioning also varied among NICUs, ranging from 0% to 23% of alarms. In the SafeBoosC-III trial it is important to keep in mind, that if the rStO2 differs markedly from what can be expected from the infant’s condition, the precision of the measurement should be questioned, and the sensor should be moved to a different site before management decisions are made.

b) **Use of the treatment guideline.** The decisions after rStO2 alarms, also varied among centres. On average, a TG-intervention was used in 25% of alarms but this ranged from 42% to 11% among centres. Some of this difference may be due to differences in the concern about cerebral hypoxia, and some may be due to the fact the clinical management also depend on other monitoring devices and other clinical information. Only the interventions triggered by NIRS alarms were analysed. It is clear, however, that the benefit of extra monitoring, as tested in the SafeBoosC-III trial, depends on effective use of abnormal values for modifying clinical management. This means prompt and adequate reactions to alarms.

c) **How to set and use alarms.** Different cerebral oximeters were used, but due to the blinded nature of the trial, oximeters were hidden in a box and rStO2 with a trend was displayed on a computer screen. The computer program also provided an audible alarm after an accumulated 0.2 %hours (12 %minutes) rStO2 outside the target range – faster when rStO2 was far out (one minute or rStO2 was 12% below the target range, and slower when rStO2 was just outside the range (12 minutes if rStO2 was 1% below the target range (Fig. 12).
In the SafeBoosC-III trial oximeters will be used as they are, usually with simple alarms that go off without delay. This means that decisions will have to be made of where to set the hypoxic alarm limit and how fast to react.

Marginal hypoxia of the brain takes some time to cause injury. In total anoxia, severe brain injury occurs within minutes, but in a situation with marginal hypoxia, the first cellular reactions are to decrease metabolic expenses. The relative resistance of neonates to hypoxia is due to the effectiveness of these processes in the normal immature brain. But it is likely that immature brains influenced by inflammation, growth restriction or other pathology may be more vulnerable, and also likely that marginal hypoxia may set off slow, detrimental processes other than mere cell death.

The realistic aim of the SafeBoosC-III trial is to reduce the risk of unrecognised deep, critical cerebral hypoxia and to reduce the overall burden of graded cerebral hypoxia during the first days after birth. In the SafeBoosC-II trial, the median burden in the experimental group was 16.6 %hours compared to 53.6 %hours in the control group. The purpose of the SafeBoosC-III trial is to try to achieve the same reduction in hypoxic burden and to test if that will result in a better clinical outcome in the experimental group. Therefore the primary outcome is survival without major brain injury at 36 weeks postmenstrual age.
Quiz

Learning objectives
By the end of this module participants will be able to
5- understand the pathophysiology of transitional circulation
6- understand causes of disturbances of brain perfusion, which
   biomarkers/assessments that can be used to evaluate the infant’s clinical
   condition, and suggested interventions to restore rStO2 within normal
   range
7- understand the role of rStO2 in decision making
8- understand the challenges that we can face during the conduct of
   SafeBoosC-III

An example of a quiz case.
Please note that several answers may be appropriate but we ask you to choose the
most - or the least - appropriate answer. This is to mimic the clinical situation
where the cerebral oxygenation is low and several interventions could be relevant.
The challenge of the clinician is to choose the single intervention that is most
reasonable, given all the available information. In all but critical situations, it is
recommended to do one intervention at a time, and wait for the effect on cerebral
oxygenation before prescribing another intervention. In critical situations, it is
important to know what not to do.

Do not give up if your choice of answer is turned down. Try again. We hope that
the explanations we provide, will help you succeed in the end.

Test case
A boy was born after spontaneous contractions since the day before yesterday.
Initially, the contractions were stopped with atosiban. Had one dose of
corticosteroids. Contractions reappeared again and the boy was born, vaginal
delivery with intact membranes, at 25+2 weeks. BW 685 g. No asphyxia. Intubated
in the delivery room and given surfactant. Once in the NICU umbilical catheters
were placed. Now, at 3 hours of age, he is on IPPV, antibiotics and morphine. He
appears vigorous with good skin colour. Temperature is 36.6.

IPPV: pressure 25 / 6, Ti = 0.3, Te = 0.6, FiO2 55%
Hb 7.1 = 11.5 g/dl
SpO2 = 87%, pO2 = 60 mmHg
MABP 24 mmHg
The blood gas shows pCO2 = 37 mmHg, pH = 7.38

The boy looks fine, CRT 2-3 s, but the cerebral oxygenation is 6% below the
hypoxic threshold of your cerebral oximeter. What could be done? (tick the most
appropriate answer - only one):
1. Red blood cell transfusion
2. Increase FiO2
3. Give vasopressor to increase blood pressure
4. Reduce inspiratory pressure or target tidal volume
5. Reduce PEEP
Answers

1. Wrong. It is correct that red blood cell transfusion will lead to increased haemoglobin levels and proportionally increased oxygen carrying capacity. An increase in haemoglobin from 7 to 8 mmol/l will therefore improve oxygen transport by 15%. However, the viscosity of the blood will also increase and may subtract from the effect - and there is a better alternative.

2. Wrong. Increasing FiO2 will increase SpO2, not rStO2 (cerebral tissue oxygenation). Even increasing FiO2 to get SpO2 at the maximal safe level of 95%, will increase oxygen transport by 8%. Furthermore, the risk of hyperoxic complications such as retinopathy of prematurity should be considered, and cerebral hypoxia should never lead to the use of oxygen in excess of what is needed to keep arterial oxygenation within normal range - and there is a better alternative.

3. Wrong. It is correct that vasopressor administration will increase blood pressure, and since autoregulation is unlikely to be perfect in this infant, it is likely that this will lead to an increased cerebral blood flow and oxygenation. But the reactivity usually is in the range of 1-3% change in cerebral blood flow per mmHg change in blood pressure. This corresponds to a 0.5-1.5% change in oxygenation. This means that increasing blood pressure to 35 mmHg will lead to an increase in cerebral oxygenation by 6 to 18 %. And there is a better alternative.

4. Correct. Decreasing ventilation will increase pCO2, which is a strong cerebral vasodilator. Since the pCO2 of this infant, at the time of the blood gas, is likely to be lower than before, a full effect of 4% CBF per mmHg pCO2 can be expected. pCO2 could be allowed to increase to 50 mmHg and this would be expected to increase cerebral oxygenation by 25%. Furthermore, this is likely to reduce the mechanical stress to the lungs.

5. Wrong. It is true that reducing peep, may reduce pressure in the chest and improve the blood flow back to the heart, increase preload, and hence improve cardiac output. However, in this infant with a high oxygen requirement, the lungs are still likely to be non-compliant, and a reduction in PEEP is likely to increase oxygen needs. If still in doubt, a chest X-ray should be done to document overfilling of the lungs.

Quiz cases

1. (Objective 1). Following air entrance into the lungs after birth, the following physiological changes in circulation occurs (tick the most appropriate answer):
   1. Sudden rise in pO2, causes pulmonary vascular bed vasodilation and a rise in systemic vascular resistance
   2. Sudden rise in pO2 causes a drop in pulmonary vascular bed resistance.
   3. The expel of lung fluids during birth, creates room for pulmonary vascular bed filling.
   4. The ductus arteriosus remains open to guarantee blood flow to the organs

Answers
1. Correct. Start of breathing causes the lungs to fill with air (oxygen), which increases pO2. Oxygen is a vasodilator in the vascular bed in the lungs, but in other arteries, increased pO2 causes vasoconstriction, and therefore increased systemic vascular resistance.

2. Wrong. While it is true that air entrance into the lungs causes pO2 to rise, and that pulmonary arteries dilate in response to the increase in pO2, it also has a significant effect in the systemic circulation. In fetal life, SaO2 is only about 70% and during birth it may be even lower. This hypoxia maintains a degree of dilation of the systemic vascular bed.

3. Wrong. While lung fluid is expressed through the trachea during delivery, and more fluid is absorbed from lung tissue when pO2 increase, this room is taken up by air.

4. Wrong. While it is true that the arterial duct typically remains open for some time after birth, and in preterm infants even for many days after birth, an ‘adult’-type circulation is normally established in the first minutes after birth. The resistance of the pulmonary vascular bed decreases sufficiently, for almost all of the output of the right ventricle to pass to the lungs.

2. (Objective 1)
In relation to the circulatory assessment of the very preterm infant, it is true that (tick the least appropriate answer):

1. Blood pressure is not a good estimator of systemic blood flow
2. Cardiac output (CO) depends on preload, myocardial contractility and may be affected by increased afterload
3. The balance between oxygen delivery and consumption can be assessed at cot side
4. Perfusion pressure is the driving force, moving blood through the vessels and depends on systemic vascular resistance and CO
5. You must know SpO2 to interpret rStO2

Answers
1. Correct. Correlation between blood pressure and echocardiography-derived parameters of blood flow (SVC flow and CO) is poor. During compensated shock, systemic vascular resistance is high, and so blood pressure is maintained in normal range, and yet blood flow is low. Clinically the baby will be pale and capillary refill time will be prolonged
2. Correct. Cardiac output is a dependent variable. The immature heart has a poor myocardial reserve when facing increased systemic vascular resistance (causing high afterload). The result is low CO. Increasing preload by volume transfusion may (briefly) improve stroke volume (Frank Starling law).
3. Correct. The balance between oxygen delivery and consumption (VO2/DO2) can be monitored by NIRS oximetry at cot side, using rStO2 as a surrogate measure of venous saturation.
4. Correct. Perfusion pressure is the product of the systemic vascular resistance and CO
5. Wrong. Although rStO2 is a volume-weighted parameter, representing arterial, capillary and venous blood oxygenation, the venous contribution is
the most important (A-V-ratio typically 25-33%). A precise correction for
variations in SaO2 is impossible anyway, due to a variable A-V ratio.

3. (Objective 2)
Baby-G is a 23+4 boy, 17 hours from birth. Two doses of surfactant were
administered at 2 and 14 hours, due to severe respiratory distress
syndrome. After the second dose, air leak was identified, and a pleural tube
was put in place. Now he is stable with FiO2 between 45% and 50%, but
over the last 30 minutes, rStO2 is progressively decreasing, while still just
above the hypoxic threshold. SaO2 has been between 87% and 91% to 87%.
What should you do? (tick the most appropriate action):
1. Wait and see because rStO2 is in normal range
2. Check if air is accumulating in pleural space
3. Check blood pressure, if normal, wait and see
4. Take blood gas to see if lactate is rising
5. Check the arterial blood gases to see if the infant is being
hyperventilated

Answers
1. Wrong. Even if rStO2 (still) and other monitoring parameters are in the
normal range, a progressive decrease in rStO2 should raise the suspicion of
potential problems in this small and sick infant.
2. Correct. This would be a good first consideration. Progressive air
trapping in the pleural space, may cause compression of the mediastinum
and decreased preload. It may take some time until other clinical signs of
low cardiac output appear. An x-ray may be indicated if doubts persist.
3. Wrong. It is correct that blood pressure should be measured, but even if
it is within normal range, it does not exclude a decreasing cardiac output as
the cause of the steadily decreasing rStO2.
4. Wrong. While it is correct that an elevated blood lactate is an indicator
of organ hypoxia, it should not be the first choice in this particular infant,
partly since lactate does take time to increase, and partly since we know
that this infant has an air leak.
5. Wrong. Air leak often leads to increased pCO2, in particular in babies
who are ventilated without volume guarantee. When the air leak is relieved
by drainage, this is usually rapidly reversed and the drop in pCO2 is
followed by an immediate and rapid drop in rStO2. In the case of Baby-G,
the drop in rStO2 came later and slower.

4. (Objective 2)
Baby-F is a twin brother born 25+3 and the recipient of foetal-to-foetal
transfusion. He was intubated after birth due to high oxygen demand and
hypercapnia. He had surfactant and arterial blood pressure dropped to 22
mmHg. Now at 4 hours of age, he is stabilised on vasopressor treatment
(dopamine 7.5 μg/kg/min), invasive mean blood pressure is around 27
mmHg, SpO2 91% and rStO2 a few % below the hypoxic threshold of your
oximeter. Blood gas analysis show PCO2 51 mmHg, Hb 15.3 g/dL, and
lactate 2.7mmol/L. What would your judgement be? (tick the most
appropriate answer):
1. Baby-F is just fine
2. Cerebral oxygenation is indicating that something could be improved. Echocardiography could be informative
3. Baby-F probably needs volume expansion to improve blood flow
4. Wait a couple of hours, in order to evaluate urine output and hereafter re-assess treatment

Answers
1. Wrong. It is possible, that baby-F’s clinical condition is fine, but if the rStO2 values are accurate, one should be worried about the cerebral perfusion, due to the circumstances and history of the infant.
2. Correct. As a twin-to-twin transfusion syndrome recipient, baby-F’s heart has been handling an excessive volume in foetal life, an therefore potentially is hypertrophic. Echocardiography could confirm this, and indicate if dopamine impairs the filling of the heart in diastole and thus, paradoxically, cause a low CO. Step-down of dopamine should be considered.

The figure illustrates a long parasternal view showing hypertrophic cardiomyopathy, the interventricular septum (1) and the left ventricular posterior wall (2) are thick.

3. Wrong. It is normally reasonable to consider volume expansion to (briefly) increase preload. However, based on the infant’s history as the blood recipient, it may be assumed that this infant is either normo- or hypervolemic.
4. Wrong. The pathophysiological background of Baby-F, combined with marginal cerebral hypoxia should call for further evaluation. Two hours of cerebral hypoxia due to over-treatment with vasopressor would be unacceptable.

5. (Objective 2)
Baby-Y is 26+2, born by c-section after acute placental detachment. No antenatal steroids. She was intubated shortly after birth and received early surfactant due to severe hypoxia. At 5 hours from birth, she is on flow-
triggered synchronized mechanical ventilation, with mean airway pressure around 17 cm H2O and FiO2 21%. Mean blood pressure is 26 to 29 mmHg, she moves when touched and she passes urine. Cerebral oxygenation has been slowly, but constantly decreasing during the last 30 min, and has passed the hypoxic threshold of your oximeter. What would you do? (tick the most appropriate answer):

1. Reposition the sensor to see if the oximeter reading is reliable.
2. Wait and see.
3. Check if baby-Y is triggering the ventilator.
4. Check the blood haemoglobin
5. Start vasopressor.

Answers
1. Wrong. There is a gradual decrease in rStO2 over some time. Baby-Y is only 3 hours old, so there is no reason to re-position the sensor yet. Unless there is another reason to doubt the quality of the reading, the baby should not be disturbed by this.
2. Wrong. Although it appears that Baby-Y has recovered quickly and is doing well in most respects, a consistent downward slope of rStO2 for 30 minutes should not be ignored.
3. Correct. Baby-Y's respiratory status has improved due to surfactant therapy. If she does not trigger the respirator, then the back-up frequency is too high and she may now be over-ventilated due to rapidly improved lung function. A blood sample to check for pCO2 should be taken. A decreasing pCO2 may result in iatrogenic cerebral ischemia and brain injury.
4. Wrong. It is true that placental detachment may cause foetal blood loss, and that it may take hours for blood haemoglobin to equalise. But a significant foetal blood loss would be expected to cause low CO due to hypovolaemia immediately after birth, and does not well explain the steady decrease of rStO2 several hours after birth.
5. Wrong. It is true that the blood pressure is marginally low. The diuresis, however, suggests that perfusion pressure to the kidney is adequate. This suggests a specific brain cause, i.e. hypocapnia.

6. (Objective 2)
You are worried because Baby-R, 25 weeks + 5 days at birth and now 62 hours after birth, who is very sick on high frequency oscillatory ventilation, became hypoxemic after tracheal suctioning. You did lung recruitment (increased mean airway pressure from 12-to-15 cmH2O,) which improved SaO2, which is now stable at 87%-92%. Mean blood pressure is stable too (32-to-35 mmHg). However, baby-R is rather pale and although rStO2 did improve, it is still a bit below the hypoxic threshold of your cerebral oximeter, and rStO2 did not improve in spite of better systemic oxygenation. What should you do? (tick the most appropriate answer):

1. Buah! this silly instrument (the cerebral oximeter) is not accurate. You should not do anything.
2. Set the mean airway pressure back to 12 cmH2O
3. Ask for an echocardiography to rule out pulmonary hypertension
4. Order an x-ray to judge the lung gas volume
5. Get a blood sample to check blood haemoglobin because the infant is pale

Answers
1. Wrong. It is true that cerebral oximetry has limited accuracy. If in doubt of the oximeter's reliability, the sensor should be checked and possibly moved. Disregarding rStO2 will not give the SafeBoosC-trial a chance to demonstrate the value of cerebral oximetry.
2. Wrong. Baby-R’s oxygenation improved with lung recruitment. The manoeuvre could also have caused lung over-distension leading to decreased filling of the heart. However, it would be safe to assess this by x-ray at first, before decreasing mean airway pressure again.
3. Wrong. Since the mean airway pressure has been increased, lung over-distension should be the first suspected cause of cerebral hypoxia. If this has been excluded by chest X-ray, other causes should be considered and echocardiography would be a reasonable examination. In the meantime, pre- and post-ductal SpO2 can be monitored, to confirm suspected right-to-left shunt associated to pulmonary hypertension
4. Correct. It is reasonable to check lung volume by x-ray. Lung over-distension may prevent filling of the heart and may cause pulmonary hypertension. Both may decrease systemic and cerebral blood flow and oxygenation.
5. Wrong. While a pale skin and low rStO2 combined with a normal SpO2 could be explained by low blood haemoglobin, is less likely in this case. The problem came rather abruptly, and there are no reasons to suspect an acute blood loss.

7. (Objectives 3)
Baby-A is 2 days of age and still on ≥45% supplementary oxygen and non-invasive mechanical ventilation. She moved to kangaroo care with her mother, for the first time, 2 hours ago. The SpO2 is 86-to-88% and rStO2 is close to the hypoxic threshold of your oximeter. Baby-A does not usually respond very much to small increases in FiO2. What would you do? (tick the most appropriate answer):
1. Wait and see
2. Check NIV tubing and increase airway pressure transiently to improve lung recruitment
3. Check the sensor and, if necessary, move it
4. Return Baby-A to the incubator

Answers
1. Wrong. Skin-to-skin care is not expected to cause low rStO2, so action should be taken
2. Correct. In infants with high supplementary oxygen demand, good lung expansion may be critical for the systemic (SpO2) and cerebral (rStO2) oxygenation. The baby may have been disconnected, when
moved to her mother’s chest and have been unable to re-recruit her pulmonary residual volume.

3. Wrong. rStO2 as well as SpO2 suggests that there is an underlying problem. The likelihood that rStO2 is unreliable is therefore low.

4. Wrong. There is no hurry. Skin-to-skin care is also important and does not usually interfere with ventilatory support, once the baby has been moved. Try to solve the problem by checking the baby’s position and the NIV tubing and, if necessary, increase airway pressures.

8. (Objective 3)
Baby-S was born at 27 weeks + 4 days, birth weight 1150g, is now 2 days of age and did not require ventilation at birth. She has made it on nasalCPAP without surfactant, is now in air and otherwise doing well. She has had some apnoea’s with desaturation, had a blood culture taken and was started on antibiotics and caffeine this morning. She still has some apnoea’s with desaturation and during those, her StO2 drops below the hypoxic threshold of your oximeter. Even when she is breathing well and the SpO2 is in the 90-93% range, the rStO2 is in the low-normal range.
She passes urin and she takes her feeds. Your physical examination is without anything abnormal, capillary refill is 2 sek and she appears well.
Non-invasive blood pressure is stable, about 30 mmHg, and the blood tests this morning showed
- haemoglobin = 12.3 g/dl
- pCO2 = 53 mmHg
- pH 7.30
- Lactate 1.7 mmol/l
What would you do? (tick the most appropriate answer):
1. Wait and see
2. Ask for an echocardiogram to exclude a patent ductus
3. Put an arterial line, since non-invasive blood pressure is unreliable
4. Give dobutamine
5. Give a little oxygen

Answers
1. Correct. This is a relatively mature baby with normal birth weight for age who has had an uneventful birth and now have simple apnoea and has been covered by antibiotics. Her risk of complications at this time is low, and she should be protected from over-ambitious treatment.
2. Wrong. Even if a PDA was diagnosed, it may not lead to an attempt of closure, although it is clear that policies on treatment of PDA is very variable among NICUs
3. Wrong. While it is true that non-invasive blood pressure measurement may overestimate pressure, there is little to suggest that the problem is a low blood pressure.
4. Wrong. It is true that myocardial reserve is low in extremely preterm infants and that cardiac output, and therefore cerebral blood flow,
may be low, even with normal blood pressure. But this infant is relatively mature, large and has had an otherwise uneventful transition. Other organs appear to function well, blood pressure is not high and hence there is no evidence of excessive systemic vasoconstriction to increase afterload. But, if still in doubt, an echocardiogram could be made to get some direct evidence of low cardiac output.

5. Wrong. It is certainly not reasonable to give oxygen to an infant with normal SpO2. Partly, this will carry a risk of oxygen toxicity but most importantly retinopathy of prematurity, partly the effect is expected to be very limited, one% of SpO2 corresponds grossly speaking to one% of rStO2.

9. (Objectives 4)
In relation to the SafeBoosC-III treatment guideline, which of the following statements is true? (tick the most appropriate answer):

1. The treatment guideline consists of a prioritised list of interventions to optimize circulation, ventilation and oxygen transport. 
2. One of the interventions must be done when cerebral hypoxia appears, i.e. the rStO2 drops below the hypoxic threshold of your oximeter 
3. The proposed interventions are all parts of routine clinical care of extremely preterm infants.
4. The interventions in the treatment guideline are based on a high grade of evidence 

Answers
1. Wrong. It is correct that it consists of a pre-established list of interventions that can be used to optimize circulation, ventilation and oxygen transport. However, it is a non-prioritized list. The responsible clinician should evaluate all other clinically relevant information, before choosing the most appropriate action.
2. Wrong. The treatment guideline suggests the use of these interventions. Frequently, it may be safest to check the sensor, and possibly to move it before changing management, and in some situations the best option may be to wait and see – as for other routinely monitored variables such as SpO2 or blood pressure.
3. Correct. The proposed interventions are all routinely used in clinical care of extremely preterm infants during the first days after birth
4. Wrong. Although it is true that many of the proposed interventions are based on good knowledge of the pathophysiology of transitional circulation, their effects on cerebral oxygenation have not always been demonstrated in similar clinically scenarios.

10. (Objectives 4)
In relation to the possibility to demonstrate the added value of rStO2 for the clinical care of extremely preterm infants (the purpose of SafeBoosC-III), what will constitute the greatest risk? (tick the most appropriate answer) :
1. Clinicians who are responsible for the clinical care of the infants randomised in the trial, will pay insufficient attention to rStO2
2. Clinicians will lose equipoise and use cerebral oximetry in the infants in the control group
3. Parents in the experimental group will withdraw their consent due to the inconveniences with the oximeter sensors, alarms and concern
4. Clinicians will not understand the concepts and be unable to use rStO2 to improve clinical care
5. There will be many severe adverse events, which will make the Data Safe Management Committee recommend that the trial is stopped.
6. Recruitment to the trial will be slow because clinicians are busy

Answers
1. Wrong. This is not likely. Clinicians are usually keen to provide good care and the wide expression of interest in SafeBoosC-III suggests that the value of cerebral oxygenation is easy to understand. Also, it is a pragmatic study, so we do not want to know what experts around the clock and highly dedicated staff could do with cerebral oximetry. We want to know if it is realistic to get clinical value in day-to-day practice.
2. Wrong. Although some NICUs use cerebral oximetry routinely, and thus have lost equipoise, we believe that the NICUs who have agreed to participate in the trial see the value in proper testing of the potential harms and benefits, and that this equipoise can be maintained until the results of the trial will be available in 2021.
3. Wrong. It is unlikely. Parents want the best for their infants, and can easily understand the potential benefit. The sensors and oximeters are reasonably user friendly.
4. Wrong. The basic pathophysiology is understandable, and the interventions are part of routine management. One challenge, however, may be to avoid over-use of oxygen.
5. Wrong. While it is not impossible that attention to the oximeter sensor may cause inattention to a tracheal tube or intravascular catheter during handling of the infant and lead to extubation or loss of intravascular access, such events did not happen in SafeBoosC-II and should be rare. Similarly, it is not impossible that cerebral hypoxia may lead to an intervention that was judged clearly inappropriate in retrospect. But this did not happen in SafeBoosC-II and should also be rare. Also, the aims of the trial is to reduce overall mortality and the risk of severe brain injury – very significant patient benefits.
6. Correct. There is no central funding and the clinical work will be done by clinicians. We hope, though, that good teamwork can be established in the participating NICUs.