Introduction module – SafeBoosC-IIIv

Learning objectives

By the end of this module participants will be able to

1. Recall the results of the SafeBoosC-III-trial
2. Understand the rationale behind the SafeBoosC-IIIv trial
3. Recall the hypothesis of the SafeBoosC-IIIv trial
4. Recall the eligibility criteria of the SafeBoosC-IIIv trial
5. Recall the intervention in the experimental group of the SafeBoosC-IIIv trial
6. Recall the intervention in the control group of the SafeBoosC-IIIv trial
7. Recall the primary outcome of the SafeBoosC-IIIv trial
8. Recall the assessment of the primary outcome in the SafeBoosC-IIIv trial

We would like to thank you for participating in the trial 'Safeguarding the Brain Of Our Smallest Children – SafeBoosC-IIIv'. This online training course is meant as a tool for clinical doctors and nurses to easily understand the concept of the trial as well as to demonstrate and train the needed competencies for the execution of the trial.

The course consists of four modules:

1. Introduction
2. NIRS monitoring
3. Treatment guideline
4. Local Data Monitoring

The modules are designed as integrated teaching and test modules with recognition of prior learning, which means that correct answers will get you through the module faster. We expect the modules '2' and '3' to take between 10 and 45 minutes to complete each, depending on your previous knowledge and experience. The first and the last module will take less time.

As this course is an offer to staff members participating in the trial, none of the modules are mandatory. However, we hope that staff members will complete the following modules, depending on their clinical position:

- Nurses: Introduction, NIRS monitoring.
- Neonatologists: Introduction, NIRS monitoring, Treatment guideline.
- Principal Investigator: Introduction, NIRS monitoring, Treatment guideline, Local Data Monitoring.
- Local Monitor: Local Data Monitoring

In this introduction module, the most important aspects of the SafeBoosC project and SafeBoosC-IIIv trial are presented, followed by a short quiz to test your knowledge. In contrast to the quizzes found in the other modules, you do not need to get a specific number of questions right, to pass this quiz. We hope you will enjoy the course!

The SafeBoosC project

SafeBoosC kicked off at a small investigator meeting in Copenhagen in 2009. Here, the research hypothesis was developed based on existing clinical and laboratory research.

Monitoring of cerebral oxygenation by NIRS in extremely preterm infants and modification of cardio-respiratory support trying to normalise out-of-range values leads to…

a reduced burden of cerebral hypoxia and hyperoxia which leads to…

less brain injury, which leads to

less neurodevelopmental impairment

This was tested in a randomised clinical phase-II trial, SafeBoosC-II, enrolling 166 patients from eight European countries. The burden of cerebral hypoxia and hyperoxia was the primary outcome and the results showed that:

1. Cerebral oximetry monitoring combined with a treatment guideline significantly reduced the burden of hypoxia and hyperoxia by more than half.
2. The risk of severe brain injury and the mortality rate tended to be lower in the intervention group.

Based on these findings, the larger phase III clinical trial, SafeBoosC-III, was conducted. In the SafeBoosC-III trial, 1601 extremely preterm infants (gestational age, <28 weeks) were randomised across 70 sites in 17 countries. The primary outcome was a composite of death or severe brain injury. The trial found that treatment guided by cerebral oximetry monitoring for the first 72 hours after birth was not associated with a lower incidence of death or severe brain injury at 36 weeks' postmenstrual age than usual care. The incidence of serious adverse events did not differ between the two groups.

The SafeBoosC-II and -III trials tested the benefits and harms of cerebral oximetry in extremely preterm infants. However, they are not the only group of patients, which could potentially benefit from cerebral oximetry monitoring. Newborns in need of invasive mechanical ventilation are also a high-risk population, not only due to the underlying condition, but also due to complications from the invasive mechanical ventilation itself. Given the instability of the newborn's pulmonary and circulatory physiology and the complexity of invasive mechanical ventilation, it is possible that these patients might benefit from treatment guided by cerebral oximetry monitoring. Therefore, SafeBoosC-IIIv will assess cerebral oximetry monitoring in newborns receiving invasive mechanical ventilation based on the robust trial logistics of SafeBoosC-III.

SafeBoosC-IIIv

Trial design

The SafeBoosC-IIIv trial is an investigator-initiated, randomised, multinational, pragmatic phase-III trial with a two-parallel group design. The trial will be conducted in two steps. In step one, 1,610 newborns will be randomised, and the outcomes will be assessed 90 days after randomisation. Funding has been obtained for step one. If further funding is obtained, we will continue to include newborns until a total of 3,000 newborns are randomised and then follow them up at two years of corrected age (step two). It is expected that newborns will be included from neonatal intensive care units from more than 20 countries across six continents. This training module is focused on step one.

A pragmatic trial

SafeBoosC-IIIv is a pragmatic trial. This means that only the most important work is done for the trial. This is proper randomisation (web-based), blinded assessment of the primary outcome, and local data monitoring (based on GCP principles), check on patient identity, death or survival, and primary outcome data. Other aspects, such as optimising the quality of the intervention, and collection of other interesting data is not done. A pragmatic trial tests an intervention 'in real life'. A pragmatic approach was also chosen due to limitations in funding and the need to involve many hospitals.

Overall objective

The objective of the SafeBoosC-IIIv trial is to evaluate the benefits and harms of cerebral oximetry added to usual care versus usual care in newborns receiving invasive mechanical ventilation. The hypothesis for step one is that the intervention will increase the number of hospital-free days within 90 days of randomisation.

Eligibility:

- Inclusion criteria
  - Newborns with a gestational age more than or equal to 28+0 weeks
  - Postnatal age less than 28 days
  - Expected to receive mechanical ventilation (intubation) for at least 24 hours, as judged by the physician intending to randomise
  - Parental informed consent unless the centre has chosen to use 'opt out' or deferred consent as consent method
  - A cerebral oximeter available so monitoring can be started within six hours after initation of invasive mechanical ventilation
- Exclusion criteria
  - Suspicion of or confirmed brain injury or disorder (e.g., severe hypoxic-ischemic encephalopathy, intraventricular haemorrhage grade 3 or 4, cerebral malformation, genetic or metabolic disease)
  - Suspicion or diagnosis of congenital heart malformations likely to require surgery

Interventions

Participants in the intervention group will be monitored with cerebral oximetry, if possible before or, as soon as possible and within six hours after initiation of invasive mechanical ventilation. Cerebral oximetry will be continued until 1) the cardio-pulmonary function has been

stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, 2) extubation, 3) 28 days after birth, or 4) death. Randomisation will only direct the use of cerebral oximetry during the first invasive mechanical ventilation episode. Cerebral oximetry will be used to minimise cerebral hypoxia by modifying clinical care according to the SafeBoosC treatment guideline. The control group will receive invasive mechanical ventilation without access to cerebral oximetry monitoring and thus, will be treated and monitored as usual.

Outcomes

Primary outcome

The primary outcome will be hospital-free days within 90 days of randomisation. Data will be collected from health care records and contact to the parents. The primary outcome will be assessed by a blinded investigator. The principal investigator from each centre must develop a local blinding procedure, describing how blinding is achieved when assessing the primary outcome.

Secondary outcomes

- One or more Serious Adverse Events within 90 days of randomisation, i.e. one or more of the following:
    - Death from any cause
    - Bronchopulmonary dysplasia (BPD)
    - Any brain injury diagnosed by imaging
    - Seizures treated with antiepileptic medicine
    - Haemodynamic insufficiency that needs cardiovascular support
    - Spontaneous bowel perforation or necrotising enterocolitis (NEC) Bells grade 2 or more
    - Nosocomial infection
    - Extra Corporal Membrane Oxygenation (ECMO)
    - Renal replacement therapy

- Invasive mechanical ventilation-free days within 90 days of randomisation.

On www.safeboosc.eu you will be able to find all relevant trial information, including the protocol, Standard Operating Procedures, local data monitoring plan, and all contact information for investigators.

You will now be presented to a set of questions regarding the trial information that have been presented to you in this introduction module.
If you need to go through the information module again before taking the short test, please do so.

Questions for introduction module – SafeBoosC-IIIv trial

1)
Learning objective: Recall the results of the SafeBoosC-III-trial

Finish the following sentence*: In SafeBoosC-III, extremely preterm infants (gestational age, <28 weeks) were included. The results showed…*

1. *No difference in the incidence of death or severe brain injury at 36 weeks postmenstrual age when infants received treatment guided by cerebral oximetry monitoring compared to usual care*
2. *That infants receiving treatment guided by cerebral oximetry had a lower incidence of serious adverse events, when compared to infants receiving usual care.*
3. *That infants receiving treatment guided by cerebral oximetry had a lower incidence of death or severe brain injury at 36 weeks postmenstrual age, when compared to infants receiving usual care.*

If answering
1. This is correct. No difference in death or severe brain injury was observed between the cerebral oximetry and usual care group. At 36 weeks' postmenstrual age, 272 of 772 extremely preterm infants (35.2%) in the oximetry group and 274 of 807 (34.0%) in the usual-care group had died or survived with a severe brain injury (relative risk with cerebral oximetry, 1.03; 95% confidence interval, 0.90 to 1.18; P = 0.64).
2. This is wrong. No difference in serious adverse events was observed between the cerebral oximetry and usual care group. In the cerebral oximetry group, one or more serious adverse events occurred in 657 of 772 (85.1%) extremely preterm infants, as compared with 698 of 807 (86.5%) infants in the usual-care group (relative risk with oximetry, 0.98; 95% CI, 0.94 to 1.01)
3. This is wrong. No difference in death or severe brain injury was observed between the cerebral oximetry and usual care group. At 36 weeks' postmenstrual age, 272 of 772 extremely preterm infants (35.2%) in the oximetry group and 274 of 807 (34.0%) in the usual-care group had died or survived with a severe brain injury (relative risk with cerebral oximetry, 1.03; 95% confidence interval, 0.90 to 1.18; P = 0.64).

2)
Learning objective: Understand the foundation for SafeBoosC-IIIv.

Answer the following question*: Since the results of SafeBoosC-III showed no difference in the incidence of death or severe brain injury at 36 weeks postmenstrual age when extremely preterm infants received treatment guided by cerebral oximetry monitoring compared to usual care, why is it important to conduct SafeBoosC-IIIv?*

1. *SafeBoosC-IIIv will assess cerebral oximetry monitoring in a different scenario. The included patients will be newborns receiving invasive mechanical ventilation and due to instability of these newborn's pulmonary and circulatory physiology and the complexity of invasive mechanical ventilation, it is possible that this group of critically ill newborns might benefit from undergoing cerebral oximetry monitoring as an extra tool to guide clinical care.*

2. *In SafeBoosC-III the primary outcome was a composite of death or severe brain injury at 36 weeks' postmenstrual age. The trial needs to be repeated with different outcome measures to show the beneficial effects of cerebral oximetry monitoring.*
3. *SafeBoosC-III did not have enough participants (statistical power) to test a difference in clinically relevant outcomes such as death or severe brain injury. Therefore, another trial must be conducted.*

If answering

1. This is correct. Newborns in need of invasive mechanical ventilation are a high-risk population, not only due to the underlying condition, but also due to complications from the invasive mechanical ventilation itself. Given the instability of these newborn's pulmonary and circulatory physiology and the complexity of invasive mechanical ventilation, it is possible that these patients might benefit from treatment guided by cerebral oximetry monitoring. There is good clinical reason to believe, that cerebral oximetry monitoring might benefit these patients, but we do not know for sure. Therefore, it is relevant to conduct SafeBoosC-IIIv.
2. This is wrong. The primary outcome for SafeBoosC-III was chosen as a clinically relevant outcome. Although the primary outcome in SafeBoosC-IIIv is different, this is not the reason for SafeBoosC-IIIv. SafeBoosC-IIIv will assess treatment guided by cerebral oximetry monitoring in a different scenario than SafeBoosC-III. SafeBoosC-III assessed the benefits and harms of cerebral oximetry monitoring in extremely preterm infants during the first days of life where cardiopulmonary system transitions from a fetal to neonatal state. SafeBoosC-IIIv, however, will assess cerebral oximetry monitoring in newborns receiving invasive mechanical ventilation. This is a high-risk population, not only due to the underlying condition that caused the need for invasive mechanical ventilation, but also due to complications from the invasive mechanical ventilation itself. Given the instability of these newborn's pulmonary and circulatory physiology and the complexity of invasive mechanical ventilation, it is possible that these patients might benefit from treatment guided by cerebral oximetry monitoring. There is good clinical reason to believe, that cerebral oximetry monitoring might benefit these patients, but we do not know for sure. Therefore, it is relevant to conduct SafeBoosC-IIIv.
3. This is wrong. SafeBoosC-III enrolled 1601 participants – enough to test a relative risk difference of 22% in death or severe brain injury. One could argue that a smaller difference would be relevant to test as well. However, that would require a much larger sample size. SafeBoosC-IIIv is relevant since it tests the effect of treatment guided by cerebral oximetry monitoring in a different setup and in a different clinical population. SafeBoosC-IIIv will assess cerebral oximetry monitoring in newborns receiving invasive mechanical ventilation. This is a high-risk population, not only due to the underlying condition that caused the need for invasive mechanical ventilation, but also due to complications from the invasive mechanical ventilation itself. Given the instability of these newborn's pulmonary and circulatory physiology and the complexity of invasive mechanical ventilation, it is possible that these patients might benefit from treatment guided by cerebral oximetry monitoring. There is good clinical reason to believe, that cerebral oximetry monitoring might benefit these patients, but we do not know for sure. Therefore, it is relevant to conduct SafeBoosC-IIIv.

3)

Learning objective: Understand the foundation for SafeBoosC-IIIv.

How does the population in SafeBoosC-IIIv differ from the population in SafeBoosC-III?

1. *In SafeBoosC-IIIv all participants will be term infants.*
2. *In SafeBoosC-IIIv participants will be infants with a gestational age more than or equal to 28+0 weeks.*
3. *In SafeBoosC-IIIv all newborns can be enrolled, regardless of gestational age.*

If answering
1. This is wrong. The participants in SafeBoosC-IIIv can be term newborns. However, preterm newborns with a gestational age more than or equal to 28+0 weeks can also be enrolled. In SafeBoosC-III, only extremely preterm infants (gestational age below 28+0 weeks) were included.
2. This is correct. Newborns with a gestational age more than or equal to 28+0 weeks may be included. This is different from SafeBoosC-III, where all participants had a gestational age below 28+0 weeks.
3. This is wrong. The gestational age of newborns enrolled in SafeBoosC-IIIv must be more than or equal to 28+0 weeks. This is different from SafeBoosC-III, where all participants had a gestational age below 28+0 weeks.

4)
Learning objective: Recall the hypothesis of the SafeBoosC-IIIv trial

Please fill-in the blank in the following sentence regarding the hypothesis of SafeBoosC-IIIv: *Treatment based on cerebral oximetry monitoring in newborns receiving invasive mechanical ventilation will _____.*

4. *Increase hospital-free days within 90 days of randomisation*
5. *Reduce the risk of death or severe brain injury at 90 days after randomisation*
6. *Decrease mortality at 90 days after randomisation*

If answering
4. This is correct. The hypothesis is that treatment based on monitoring of cerebral oxygenation for infants receiving invasive mechanical ventilation will result in *an increase in hospital-free days within 90 days of randomisation*
5. This is wrong. Due to the heterogeneity of the population and the pragmatic design of the trial where only routine data will be used, it is not possible to compose and measure a relevant brain injury outcome at 90 days after randomisation. However, at two years of corrected age, we intend to measure neurodevelopmental impairment. This is an outcome for the second step of the trial and therefore, further details will not be covered in this training module.
6. This is wrong. The mortality rate in this population is less than 10% and thus, it would require a much larger sample size to detect a clinically relevant difference on mortality. However, the effect of death is still incorporated in our primary outcome – hospital-free days within 90 days from randomisation – since deceased infants will have less (mostly zero) hospital-free days.

5)
Learning objective: Recall the eligibility criteria of the SafeBoosC-IIIv trial

Choose the correct eligibility criteria for newborns to be enrolled in the trial

1. *Extremely preterm infants*

2. *Gestational age more than or equal to 28+0*
3. *Postnatal age less than 28 days*
4. *Parental informed consent is given (unless 'opt-out' or deferred consent is used)*
5. *Suspected or confirmed brain injury*
6. *Possibility to start monitoring of cerebral oxygenation within six hours of invasive mechanical ventilation*
7. *Receiving CPAP*
8. *Expected to receive invasive mechanical ventilation for at least 24 hours, as judged by the physician intending to randomise*

If answering:
1. This is wrong. This was an inclusion criterium in SafeBoosC-III. In SafeBoosC-IIIv only infants with gestational age more than or equal to 28+0 will be included.
2. Correct. In SafeBoosC-IIIv, preterm (gestational age more than or equal to 28+0) and term infants can be included.
3. Correct. Infants can be included if the postnatal age is less than 28 days.
4. Correct. If parental informed consent is not given, the infant cannot be included (unless 'opt-out' or deferred consent is used).
5. This is wrong. Infants with suspicion of or confirmed brain injury (such as cerebral haemorrhage, cerebral malformation, genetic or metabolic disease) are excluded from the trial.
6. Correct. If the newborn is randomised to the intervention group, cerebral oximetry monitoring must be initiated, if possible before or, as soon as possible and within six hours after initiation of invasive mechanical ventilation.
7. This is wrong. The newborn must receive invasive mechanical ventilation (intubation) to be included in SafeBoosC-IIIv. CPAP is not invasive mechanical ventilation.
8. Correct. If the infant is expected to receive invasive mechanical ventilation for less than 24 hours, the newborn cannot be included.

6)
Learning objective: Recall the intervention in the experimental group of the SafeBoosC-IIIv trial

If the newborn is randomised to the experimental group, what will the intervention be?

1. *Cerebral oximetry monitoring added to usual care. This will be used with the purpose of reducing cerebral hypoxia, by modifying clinical care as suggested in the SafeBoosC treatment guideline.*
2. *Cerebral oximetry monitoring will be added to usual care. Based on the cerebral oximetry monitoring, the physicians must follow the flow-chart in the SafeBoosC treatment guideline.*
3. *Cerebral oximetry monitoring will be used instead of a pulse oximeter.*

If answering
1. This is correct. Participants in the experimental group will undergo cerebral oximetry monitoring which will be used to modify clinical care according to the SafeBoosC treatment guideline. The treatment guideline should not be seen as a 'flow-chart', but rather as a list of possible interventions that can be administered by the treating physician based on an overall assessment of the newborns' clinical status, including the cerebral oximetry monitoring.

2. This is wrong. The treatment guideline should not be seen as a 'flow-chart', but rather as a list of possible interventions that can be administered by the treating physician based on an overall assessment of the newborns' clinical status, including the cerebral oximetry monitoring.
3. This is wrong. Cerebral oximetry monitoring will be added to usual care and therefore, monitoring as part of the usual care protocols in the participating departments, should be used regardless of trial participation.

7)
Learning objective: Recall the intervention in the experimental group of the SafeBoosC-IIIv trial

When should cerebral oximetry monitoring be initiated in experimental group participants?

1. *Always before invasive mechanical ventilation.*
2. *Always after initiation of mechanical ventilation.*
3. *If possible before or, as soon as possible and within six hours after initiation of invasive mechanical ventilation*

If answering:
1. This is wrong. If possible, cerebral oximetry monitoring should begin before initiation of invasive mechanical ventilation. If not possible, cerebral oximetry monitoring must begin as soon as possible and within six hours after initiation of invasive mechanical ventilation.
2. This is wrong. If possible, cerebral oximetry monitoring should begin before initiation of invasive mechanical ventilation. If not possible, cerebral oximetry monitoring must begin as soon as possible and within six hours after initiation of invasive mechanical ventilation.
3. This is correct. If possible, cerebral oximetry monitoring should begin before initiation of invasive mechanical ventilation. If not possible, cerebral oximetry monitoring must begin as soon as possible and within six hours after initiation of invasive mechanical ventilation.

8)
Learning objective: Recall the intervention in the experimental group of the SafeBoosC-IIIv trial

Choose the correct answers below.
In the experimental group, cerebral oximetry monitoring will be continued until…

1. *72 hours after initiation of invasive mechanical ventilation*
2. *The cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician*
3. *7 days after birth*
4. *The infant is extubated*
5. *28 days after birth*
6. *Death*

If answering:
1. This is wrong. The 72 hour 'window' was part of the intervention in SafeBoosC-III, where infants in the experimental group underwent cerebral oximetry monitoring for the first 72 hours after birth. In SafeBoosC-IIIv, infants in the experimental group will undergo cerebral oximetry monitoring until 1) the

cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, 2) extubation, 3) 28 days after birth, or 4) death.

2. This is correct. Stabilisation of the cardio-pulmonary function as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician is one of the four reasons to stop cerebral oximetry monitoring. The other three are: Extubation, 28 days after birth, or death.
3. This is wrong. Cerebral oximetry will be continued until 1) the cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, 2) extubation, 3) 28 days after birth), or 4) death.
4. This is correct. Extubation is one of the four reasons to stop cerebral oximetry monitoring. The other three are: The cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, 28 days after birth, or death.
5. This is correct. Once the newborn period ends (28 days after birth), cerebral oximetry monitoring will be stopped. This is one of the four reasons to stop cerebral oximetry monitoring. The other three are: The cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, extubation, or death.
6. This is correct. Death is one of the four reasons to stop cerebral oximetry monitoring. The other three are: The cardio-pulmonary function has been stabilised as indicated by the need for respiratory and circulatory support and evaluated by the responsible physician, extubation, or 28 days after birth.

9)

Learning objective: Recall the intervention in the experimental group of the SafeBoosC-IIIv trial

A newborn receiving invasive mechanical ventilation was included in SafeBoosC-IIIv and randomised to the experimental group. Cerebral oximetry monitoring was stopped, since the newborn was extubated. The newborn now needs to be reintubated. What do you do?

1. *Since the newborn was randomised to the experimental group and the newborn is intubated, cerebral oximetry monitoring must be reapplied as soon as possible.*
2. *Since the newborn is now in need of invasive mechanical ventilation, the newborn should be randomised once again.*
3. *The newborn should receive usual care as part of the local monitoring and treatment protocols, regardless of participation in the SafeBoosC-IIIv trial.*

If answering:

1. This is wrong. Randomisation will only direct the use of cerebral oximetry during the first invasive mechanical ventilation episode. In case of any subsequent episodes of invasive mechanical ventilation, trial participation and group allocation should not determine or influent clinical care.
2. This is wrong. The newborn has already been included in the trial and cannot be randomised again. The initial randomisation will only direct the use of cerebral oximetry during the first invasive mechanical ventilation episode. In case of any subsequent episodes of invasive mechanical ventilation, trial participation and group allocation should not determine or influent clinical care.
3. This is correct. The initial randomisation will only direct the use of cerebral oximetry during the first invasive mechanical ventilation episode. In case of any subsequent episodes of invasive mechanical ventilation, trial participation and group allocation should not determine or influent clinical care.

10)
Learning objective: Recall the intervention in the usual care group of the SafeBoosC-IIIv trial

Please fill-in the blank in the following sentence: *Participants in the usual care group* _____.

1. *Will undergo cerebral oximetry monitoring, but the monitor will show random values.*
2. *Will not undergo cerebral oximetry monitoring, and they will be monitored and receive treatment as usual, i.e., as per local guidelines.*
3. *Will undergo cerebral oximetry monitoring, but values will be blinded.*

If answering:
1. This is wrong. Newborns randomised to the usual care group will not undergo cerebral oximetry monitoring as part of the trial protocol. Random values may do harm by false reassurance and/or by causing inappropriate interventions. Newborns randomised to the usual care group should receive usual monitoring and treatment as per local guidelines.
2. This is correct. Infants in the usual care group will not under cerebral oximetry monitoring as part of the trial protocol, but receive usual treatment and monitoring according to local guidelines.
3. This is wrong. Infants in the usual care group will not under cerebral oximetry monitoring as part of the trial protocol, but receive usual treatment and monitoring according to local guidelines.

11)
Learning objective: Recall the intervention in the usual care group of the SafeBoosC-IIIv trial

Please fill-in the blank in the following sentence: *Participants in the usual care group will not have the cerebral oxygenation monitored* _____.

1. *but will be treated according to an evidence-based treatment guideline as defined per protocol*
2. *but will receive treatment and monitoring as usual according to local guidelines.*

If answering
1. This is wrong. Newborns randomised to the usual care group should receive usual monitoring and treatment as per local guidelines.
2. This is correct. Newborns randomised to the usual care group should receive usual monitoring and treatment as per local guidelines.

12)
Learning objective: Recall the primary outcome of the SafeBoosC-IIIv trial.

The primary outcome in the SafeBoosC-IIIv trial is

1. *Severe brain injury*
2. *Hospital-free days within 90 days of randomisation.*

If answering

1. This is wrong. Due to the heterogeneity of the population and the pragmatic design of the trial where only routine data will be used, it is not possible to compose and measure a relevant brain injury outcome at 90 days after randomisation. However, at two years of corrected age, we intend to measure neurodevelopmental impairment. This is an outcome for the second step of the trial and therefore, further details will not be covered in this training module.
2. This is correct. Hospital-free days will have value to patients in itself; it must be considered important to patients and their relatives to spend as little time as possible in the hospital. It may also be a valid surrogate outcome for other patient-important outcomes, as a low number of hospital-free days will likely correlate with complications and abilities to breathe and feed. Also, results based on hospital-free days reflect both incidences of deaths, as patients who die in hospital will experience no hospital-free days, and the cumulated hospital burden.

13)
Learning objective: Recall the assessment of the primary outcome in the SafeBoosC-IIIv trial

Choose the correct answer*: Hospital-free days within 90 days of randomisation will be determined through...*

1. *Review of health care records*
2. *Contact with parents*
3. *NICU nursing staff*
4. *Review of health care records and contact with parents.*

If answering
1. This is partly correct. Health care records will be reviewed to assess the index admission. However, the parents will also be contacted, as the newborn may have been admitted to other hospitals after the initial discharge. As this is not necessarily visible in the health care records, the parents will be contacted to obtain this information.
2. This is partly correct. Parents will be contacted as a part of the assessment, as the participant may have been admitted to other hospitals after the initial discharge. As this is not necessarily visible in the health care records, the parents will be contacted to obtain this information. However, the health care records will also be reviewed to assess the index admission.
3. This is wrong. Data on the primary outcome will be collected from health care records and parents will be contacted. Information from health care records will be prioritised regarding the index admission, while information from the parents will be used only as additional information (e.g., readmissions) not visible in the health care records.
4. This is correct. Data on the primary outcome will be collected from health care records and parents will be contacted. Information from health care records will be prioritised regarding the index admission, while information from the parents will be used only as additional information (e.g., readmissions) not visible in the health care records.