Blinding method for cranial ultrasound reading and classification of brain injury

Nation	Department	Investigator	Method	Approved
Austria	Graz University Hospital	Gerhard Pichler	The neonates included into the study will be inborn babies admitted to neonatal intensive care unit I (NICU I) that is located at the Department of Gynecology and Obstetrics. Neonates with less than 29weeks of gestation stay there for at least one week before they are transferred to the NICU II located at the Department of Pediatrics. Therefore, during the study period - the first 72 hours – the team of the NICU I takes care of these neonates and is aware of the allocation in the intervention and control group of the included neonates. The neonatologists at the NICUs in Graz routinely perform ultrasound. Pictures of cranial ultrasound of included neonates will be printed out and anonymized with the patient identification number on it. Prof Friedrich Reiterer a neonatologist, who is experienced in cranial ultrasound and who will retire this year and who is not working any more on the NICU I - thus not knowing the allocation -, will interpret the anonymized cranial ultrasound pictures (and continue with this after his retirement) and document his findings in a printed version of the eCRF on severe brain injury. Gerhard Pichler, PI, will enter data on severe brain injury, completely based on the printed, filled-out version of the eCRF by Prof Reiterer.	Yes

Belgium	All sites	Gunnar Naulaers	In all Belgium sites, Paul Govaert who is an expert in ultrasound, will independently assess all cranial ultrasound images of babies enrolled in the SafeBoosC III trial and diagnose brain injury. He will diagnose severe brain injury according to the criteria outlined in the SOP "diagnosis and classification of brain injury". Since Paul Govaert is not involved in clinical care in any of the participating Belgium sites, he will be unaware of the babies group allocation. 1. Performing cranial ultrasound readings and anonymizing Radiologists or neonatologists who perform the cUS need to anonymize the images by replacing all personal data (such as patient name, date of birth, social security number, …) by the study-specific subject number assigned to the patient. 2. Transfer of the cranial ultrasound readings to Paul Govaert Each Belgium site will be responsible of sending the anonymized images to Paul Govaert. Radiologists or neonatologists who perform the cUS need to transfer the anonymized images to a CD-ROM. The CD-ROM will be sent by courier to: Paul Govaert Wildforkaai 10 bus G 9140 Temse 3. Transfer of the results after diagnosing brain injury by Paul Govaert Paul Govaert will provide the cranial ultrasound reports, with the study-specific subject number assigned to the patient, via secured e-mail to the research nurse of UZ Leuven: Studieteam.neonatologie@uzleuven.be 4. Data entry – OpenClinica (eCRF) The research nurses of UZ Leuven, department neonatology: Julie Messiaen and Isabelle Hermans, will enter the blinded data on severe brain injury into OpenClinica for UZ Leuven and the other participating sites. This was approved by Mathias Lüehr Hansen and the SafeboosC III-team.	Yes

Nation	Department	Investigator	Method	Approved
China	Longgang District Central Hospital of Shenzhen	Shujuan Sheng	Because of the interventional of the SafeBoosC III randomized clinical trial, it is difficult for clinical staff and parents to be blinded. In order to minimize the impact of cranial ultrasound results on the diagnosis of corrected brain injury at 36 weeks of gestational age and the effect of eCRF on the outcome of severe brain injury, it must be performed by a person who has no know the infant grouping. Head ultrasound examination and report blindness are as follows in Longgang Distric Central Hospital of Shenzhen : 1. Ultrasonic examination by the ultrasonic doctor: Dr. Ling SiZhuo, who was not aware of the grouping, conducted the cranial ultrasonic examination, preserved the image (hid the clinical data of the children), and given the report. 2. If the brain oxygen monitoring is still under way during ultrasonic examination, the brain oxygen monitoring probe should be temporarily removed and pushed away from the bedside of the child. 3. All ultrasonic examinations shall be completed by Dr. Ling SiZhuo to avoid differences between the examiners. 4. Dr. He Xuesen reviewed the ultrasonic images and reports. 5. The above can be done to enlarge the diagnostic blindness method, and the subjective error can be reduced by two people 6. Dr. Guo Xiaobin, who had no know the grouping, filled out the eCRF form of severe brain injury strictly accordance with the report, realizing data report blindness.	Yes

Nation	Department	Investigator	Method	Approved
China	Hainan Women and Children's Medical Center, Haikou	Yang Ling	Because of the interventional of the SafeBoosC III randomized clinical trial, it is difficult for clinical staff and parents to be blinded. In order to minimize the impact of cranial ultrasound results on the diagnosis of corrected brain injury at 36 weeks of gestational age and the effect of eCRF on the outcome of severe brain injury, it must be performed by a person who has no know the infant grouping. Head ultrasound examination and report blindness are as follows in Hainan Women and Children's Medical Center: 1. Ultrasonic examination by the ultrasonic doctor: Dr. Lin Shiping, who was not aware of the grouping, conducted the cranial ultrasonic examination, preserved the image (hid the clinical data of the children), and given the report. 2. If the brain oxygen monitoring is still under way during ultrasonic examination, the brain oxygen monitoring probe should be temporarily removed and pushed away from the bedside of the child. 3. All ultrasonic examinations shall be completed by Dr. Lin Shiping to avoid differences between the examiners. 4. Dr. Mo Zelai reviewed the ultrasonic images and reports. 5. The above can be done to enlarge the diagnostic blindness method, and the subjective error can be reduced by two people 6. Dr. Cao Xiang, who had no know the grouping, filled out the eCRF form of severe brain injury strictly accordance with the report, realizing data report blindness.	Yes

Nation	Department	Investigator	Method	Approved
China	The First Affiliated Hospital of Zhengzhou University	Qian Zhang	Because the SafeBoosC III randomized clinical trial is of an intervention nature, it is difficult for clinical staff and parents to achieve blindness. The blind ultrasound has to be operated by a person who has no knowledge of the group in order to minimize the influence of brain injury diagnosis at 36 weeks correction gestational age and eCRF to the severe brain injury outcome. The blind ultrasound method and report of head ultrasound in China are as followed: 1. Ultrasound examination by a radiologist: an ultrasound doctor who has no knowledge of the group performs a head ultrasound examination, saves the image, and writes a report. If the brain oxygen monitoring is still being performed during the ultrasound examination, the brain oxygen monitoring probe should be temporarily removed and pushed away from the patient's bed. All ultrasound examinations should be completed by 1-2 people to avoid differences between the examiners. The eCRF form should be filled out by neonatal doctor knowing nothing about grouping situation to order to achieve the reporting blind. 2. Cranial ultrasound examination by neonatal specialists: Cranial ultrasound examination is made and imaged by neonatal specialists unaware of grouping. Neonatal doctors unaware of grouping read the images, and fill out eCRF form at correction of gestational age at 36 weeks to realize the blind method of diagnosis and report.	Yes

Nation	Department	Investigator	Method	Approved
China	Xiamen Children's Hospital	Xin Xu	In our department, we invited a radiologist (Zeyi Dai) to perform the cUS and diagnose the cerebral affections of the infants, who have finish the train online. Zeyi Dai will describe the cUS according to the SafeBoosC severe brain injury criteria. If a baby is scanned within the first 72 hrs of life and in the experimental group, the sensor and device will be removed from the baby in order to ensure that Zeyi Dai is blinded to group allocation. In order to blind intervention during diagnosis of brain injury, I ask a nurse(Yang Li) to read the radiologists image description and fill in the eCRF data field on severe brain injury and the question regarding achievement of blinding. so,I reassign tasks again.	Yes
China	Guanxi Maternal and Child Healthcare Hospital, Nanning	Xiaoyan Gao	Head ultrasound examination and report blindness are as follows in Maternity and child health care of Guangxi Zhuang Autonomous Region: 1. Radiologists will conduct all cerebral ultrasound scans on babies included in SafeBoosC III. They are not involved in the daily care of babies in the NICU and will therefore be blinded to group allocation. 2.If a baby is scanned within the first 72 hrs and the baby is in the experimental group, the NIRS sensor and montor will be removed during the scan. 3. All ultrasound scans shall be completed by Yanhe Luo to avoid differences between the examiners. 4. Guidan He reviewed the ultrasonic images and reports. 5. Lianying Zhang, who had no know the grouping, filled out the eCRF form of severe brain injury strictly accordance with the report, realizing data report blindness.	Yes

Nation	Department	Investigator	Method	Approved
China	The People's Hospital of Dehong, Autonomous Prefecture	Zaoqin Yin	In order to minimize the effect of cranial ultrasound results on correcting the diagnosis of brain injury at 36 weeks of gestational age and the effect of eCRF on the outcome of severe brain injury, cranial ultrasound examination and report blindness in China must be performed by a person totally unaware of the infant group as follows: **1.** Ultrasound image doctor: by grouping the unwitting cranial ultrasound,ultrasound doctors to save images, issue a report if ultrasound is still on cerebral oxygen monitoring, monitoring cerebral oxygen probe will be temporarily removed, push off with all bedside ultrasound, 1-2 people operation is completed, avoid the difference between inspectors do diagnosis blinded by grouping the unwitting new pediatrician form of severe brain injury eCRF and upload, implement the data report blinded. **2.** Cranial ultrasound examination by neonatal specialists: cranial ultrasound examination was performed by neonatal specialists who were not aware of the grouping, and the images were saved. The images were read by neonatal specialists who were not aware of the grouping, and the wCRF form was filled out at the time of the correction of gestational age at 36 weeks and went to bed to achieve diagnosis and report blindness.	Yes

Nation	Department	Investigator	Method	Approved
China	Chengdu Women's and Children's Central Hospital	Hu Xuhong	Because of the interventional of the SafeBoosC III randomized clinical trial, it is difficult for clinical staff and parents to be blinded. In order to minimize the impact of cranial ultrasound results on the diagnosis of corrected brain injury at 36 weeks of gestational age and the effect of eCRF on the outcome of severe brain injury, it must be performed by a person who has no know the infant grouping. Head ultrasound examination and report blindness are as follows in Chengdu Women's & Children's Central Hospital: 1. Ultrasonic examination by the ultrasonic doctor: Dr. Li Biao, who was not aware of the grouping, conducted the cranial ultrasonic examination, preserved the image (hid the clinical data of the children), and geiven the report. 2. If the brain oxygen monitoring is still under way during ultrasonic examination, the brain oxygen monitoring probe should be temporarily removed and pushed away from the bedside of the child. 3. All ultrasonic examinations shall be completed by Dr. Li Biao to avoid differences between the examiners. 4. Yang Sheng reviewed the ultrasonic images and reports. 5. The above can be done to enlarge the diagnostic blindness method, and the subjective error can be reduced by two people 6. Dr. Ma Jiao, who had no know the grouping, filled out the eCRF form of severe brain injury strictly accordance with the report, realizing data report blindness.	Yes

Nation	Department	Investigator	Method	Approved
China	Children's Hospital Zhejiang, Hangzhou	Luo Fang	Because of the interventional of the SafeBoosC III randomized clinical trial, it is difficult for clinical staff and parents to be blinded. In order to minimize the impact of cranial ultrasound results on the diagnosis of corrected brain injury at 36 weeks of gestational age and the effect of eCRF on the outcome of severe brain injury, it must be performed by a person who has no know the infant grouping. Head ultrasound examination and report blindness are as follows in Children's Hospital , Zhejiang University School of medicine 1. Ultrasonic examination by the ultrasonic doctor: Dr. xubin, who was not aware of the grouping, conducted the cranial ultrasonic examination, preserved the image (hid the clinical data of the children), and geiven the report. 2. If the brain oxygen monitoring is still under way during ultrasonic examination, the brain oxygen monitoring probe should be temporarily removed and pushed away from the bedside of the child. 3. All ultrasonic examinations shall be completed by Dr xubin to avoid differences between the examiners. 4.. Dr. Lin huijia, who had no know the grouping, filled out the eCRF form of severe brain injury strictly accordance with the report, realizing data report blindness.	Yes

Nation	Department	Investigator	Method	Approved
China	Children's Hospital of Fudan University	Guoqiang Cheng	Because of the interventional of the SafeBoosC III randomized clinical trial, it is difficult for clinical staff and parents to be blinded. In order to minimize the impact of cranial ultrasound results on the diagnosis of corrected brain injury at 36 weeks of gestational age and the effect of eCRF on the outcome of severe brain injury, it must be performed by a person who has no know the infant grouping. Head ultrasound examination and report blindness are as follows in Children's Hospital Of Fudan University: 1. Ultrasonic examination by the ultrasonic doctor: Dr. Gao yanyan, who was not aware of the grouping, conducted the cranial ultrasonic examination, preserved the image (hid the clinical data of the children), and geiven the report. 2. If the brain oxygen monitoring is still under way during ultrasonic examination, the brain oxygen monitoring probe should be temporarily removed and pushed away from the bedside of the child. 3. All ultrasonic examinations shall be completed by gao yanyan to avoid differences between the examiners. 4. Sun Yinghua reviewed the ultrasonic images and reports. 5. The above can be done to enlarge the diagnostic blindness method, and the subjective error can be reduced by two people 6. Dr. Wang le, who had no know the grouping, filled out the eCRF form of severe brain injury strictly accordance with the report, realizing data report blindness.	Yes

Nation	Department	Investigator	Method	Approved
China	Nanfang Hospital	Weibin	Because of the interventional of the SafeBoosC III randomized clinical trial, it is difficult for clinical staff and parents to be blinded. In order to minimize the impact of cranial ultrasound results on the diagnosis of corrected brain injury at 36 weeks of gestational age and the effect of eCRF on the outcome of severe brain injury, it must be performed by a person who has no know the infant grouping. Head ultrasound examination and report blindness are as follows in Nanfang Hospital: 1. Ultrasonic examination by the ultrasonic doctor: Dr. Zhang Yanyan, who was not aware of the grouping, conducted the cranial ultrasonic examination, preserved the image (hid the clinical data of the infants), and gave the report. 2. If the brain oxygen monitoring is still under way during ultrasonic examination, the brain oxygen monitoring probe should be temporarily removed and pushed away from the bedside of the child. 3. All ultrasonic examinations shall be completed by Zhang Yanyan to avoid differences between the examiners. 4. Dr. Song Xiaoyan reviewed the ultrasonic images and reports (don't know group). 5. The above can be done to enlarge the diagnostic blindness method, and the subjective error can be reduced by two people 6. Dr. Wu Weibin, who had no know the grouping, filled out the eCRF form of severe brain injury strictly accordance with the report, realizing data report blindness. Done by Dr. Zhang yanyan（dong't know group）	Yes

Nation	Department	Investigator	Method	Approved
China	Guangzhou Women and Children's Medical Center	Jinghua Zhang	Because of the interventional of the SafeBoosC III randomized clinical trial, it is difficult for clinical staff and parents to be blinded. In order to minimize the impact of cranial ultrasound results on the diagnosis of corrected brain injury at 36 weeks of gestational age and the effect of eCRF on the outcome of severe brain injury, it must be performed by a person who has no know the infant grouping. Head ultrasound examination and report blindness are as follows in Guangzhou Women and Children's Medical Center: 1. Ultrasonic examination by the ultrasonic doctor: Dr. Lei wenjia, who was not aware of the grouping, conducted the cranial ultrasonic examination, preserved the image (hid the clinical data of the children), and given the report. 2. If the brain oxygen monitoring is still under way during ultrasonic examination, the brain oxygen monitoring probe should be temporarily removed and pushed away from the bedside of the child. 3. All ultrasonic examinations shall be completed by Lei wenjia to avoid differences between the examiners. 4. Dr. Cai yueju, who had no know the grouping, filled out the eCRF form of severe brain injury strictly accordance with the report, realizing data report blindness.	Yes
Czech Republic	The Institute for the Care of Mother and Child, Prague	Jan Sirc	In Institute for the Care of Mother and Child, the neonatologists themselves perform the cUS. Routine cUS are performed by Jáchym Kučera MD, neonatologist, which is never within the first 72 hours. Dr Kučera is not in charge for routine care of neonates in NICU. In NICU, It is responsibility of attending physicians to perform the cUS. Therefore, Dr Kučera will be unaware of group allocation, will review all images until 36 weeks postmenstrual age and fill-in the eCRF data fields on severe brain injury. Sometimes Dr Kucera is supervising ultrasound exams if there are doubts or questions, and if this is the case, it will be made sure that group allocation is not revealed for Dr Kucera.	Yes

Nation	Department	Investigator	Method	Approved
Czech Republic	Motol Univ. Hospital	Jakub Tkaczky	In the NICU of University Hospotal Motol, neonatologists caring for the newborns perform cranial ultrasounds themselves. Sometimes we require additional reading by radiologists, especially in case of pathology findings that will need long term follow-up. For the purpose of SafebooSC-III trial, I asked our former colleague, Dr. Fišárková, who is BC neonatologist with ultrasound skills. She still keeps a part time teaching job at the department and agreed to be the blindes assessor. Attending neonatologist will do the regular cUS readings and store the images in the ultrasound machine as part of our routine practice. Stored images will then be checked and evaluated by dr. Fišárková, who will also fill the data into the eCRF form. In case of her absence, another neonatologist or radiologist unaware of patients´ group allocation will be asked to do the reading and eCRF form fininishing.	Yes
Denmark	Rigshospitalet, Copenhagen	Gitte Hahn	All cUS is done by neonatologists in the department, saved in electronic file. Gitte will open all relevant cUS scans on computer, hide the personal information and clinical data, Prof Gorm Greisen will evaluate scans and/or image descriptions and type brain injury classifications into eCRF. If he in some way can recognize scans, Gitte will find another consultant to check the images	Yes
Denmark	Odense Univ. Hosp	Svend Mortensen	PI will send cUS scans electronically to GG in CPH. Only study number and age at scan will be included on picture, no personal identifiers. GG will then enter data directly into OpenClinica.	Yes
Denmark	Aalborg University Hospital	Lars Bender	Pediatric radiologists will conduct all cuS scans on babies included in SafeBoosC III. They are not involved in the daily care of babies in the NICU and will therefore be blinded to group allocation. If a baby is scanned within the first 72 hrs and the baby is in the experimental group, the NIRS sensor and montor will be removed during the scan. A neonatologist will use the image descriptions from the radiologists to enter data on severe brain injury in the eCRF. The radiologist will be aware of the SafeBoosC brain injury criteria, and use these in their image descriptions.	Yes

Nation	Department	Investigator	Method	Approved
Denmark	Aarhus University Hospital	Peter Agergaard	Radiologists perform cranial ultrasounds through the anterior fontanelle, save images, and describe the findings with focus on the pre-specified brain injuries (corresponding to usual practice). To ensure radiologist's blinding to the SafeBoosC intervention, the NIRS monitoring device will be removed prior to the radiologist's presence on the ward, if the scan is conducted within the first 72 hours of life. No specific blinding procedure is needed for later scans. Completion of the eCRF data field will be conducted by principal investigator Peter Agergaard. Reading of the cranial ultrasound descriptions will be provided by professor Tine Brink Henriksen, who will be blinded to group allocation due to her position in the team.	Yes
Germany	Freiburg University Hospital	Hans Fuchs	Brain ultrasound is done on a regular base (d3, d7, thereafter weekly or two weekly) by the doctors team of the NICU. Ultrasound scans, but no written reports, are regularly saved in the hospital´s PACS system. At discharge of a study infant all scans saved in the PACS system will be reviewed by the head of the pediatric ultrasound department, not involved in the therapy of preterm infants and unaware of Safe-BoosCIII group assignment. A written report is prepared with emphasis on maximum IVH grading and the other items of severe brain injury. His assessment will be reported as study outcome.	Yes
Greece	Ippokrateion General Hospital of Thessaloniki	Kosmas Sarafidis	A neonatalogist colleague unaware of group allocation will review all cUS images until 36 weeks post-menstrual age and fill-in the eCRF data fields on severe brain injury.and the question regarding achievement of blinding.	Yes

Nation	Department	Investigator	Method	Approved
Greece	Patras University Hospital	Gabriel Dimitriou	Three doctors (two radiologists, one neonatologist) will conduct all cUS scans on babies included in SafeBoosC III. They are not involved in the daily care of babies in the NICU and will therefore be blinded to group allocation. The three doctors performing cUS will be aware of the SafeBoosC brain injury criteria and use these in their image descriptions. If a baby is scanned within the first 72 hrs and the baby is in the experimental group, the NIRS sensor and monitor will be removed during the scan. A neonatologist not conducting the cUS scans will use the image descriptions from the three doctors performing ultrasound scans, to enter data on severe brain injury in the eCRF.	Yes
Greece	Alexandra University Hospital	Stavroula Gavrili	Pediatric radiologists will perform all cranial ultrasound scans on babies included in SafeBoosC III. They are not involved in the daily care of babies in the NICU and will therefore be blinded to group allocation. If a baby is scanned within the first 72 hrs and the baby is in the experimental group, the NIRS sensor and montor will be removed during the scan. A neonatologist will use the image descriptions from the radiologists to enter data on severe brain injury in the eCRF. The radiologist will be aware of the SafeBoosC brain injury criteria and use these in their image descriptions.	Yes
Greece	University Hospital of Heraklion	Eleftheria Hatzidaki	In the Neonatology Department and NICU of the University Hospital of Heraklion radiologists perform the cranial US and diagnose the cerebral affections of the neonates. If a cranial US is conducted within the first 72 hours of life in a baby in the experimental group, the monitor and sensor will be removed from the baby to conceal group allocation. In order for the blinding of the SafeBoosC-III intervention to take place, a colleague unaware of group allocation, and specifically a pediatrician intern not involved in the treatment of premature neonates, will read the radiologists image description and fill in the eCRF data field on severe brain injury and the question regarding achievement of blinding. The radiologists will be aware of the SafeBoosC severe brain injury criteria while they write the image descriptions.	Yes

Nation	Department	Investigator	Method	Approved
India	Bangalore	Saudamini Nesargi	Blinding of the cranial ultrasound. All neonates < 32 weeks or <1500g routinely get cranial ultrasounds on day 3 and then at 36- 40 weeks corrected age. Any additional scans are done if needed. The ultrasound on day 3 is done by a neonatologist **who is not involved in the care of babies in the trial on a daily basis**. To ensure continuous blinding we propose to remove the probe so that the person doing the ultrasound is unaware of the group to which the baby was randomized. The report will be written in the chart, **based on the severe brain injury criteria for SafeBoosC III**, and entered in the e-CRF by one of the investigators. The same procedure will be followed for any other ultrasounds done during NICU stay. The ultrasound at 36 weeks , will be done by the radiologist who will be blinded to the treatment the baby received. This report too, will **be based on the severe brain injury criteria for SafeBoosC III, and** entered in to the e CRF by one of the investigators.	Yes

Nation	Department	Investigator	Method	Approved
Ireland	Cork	Eugene Dempsey	Clinical ultrasounds are performed by one of two paediatric radiologists twice a week at the neonatal intensive care unit at Cork University Maternity Hospital, typically on a Monday and Thursday. When Safeboosc trial is running these two radiologists will be performing the ultrasound scans. There is another prospective observational study being conducted at CUMH at the same time called NOAH. This is evaluating an ICON device and cerebral NIRS is being performed at the same time. This is observational only and the clinican is not observing the values, or interacting with them. We anticipate that any baby enrolled in Safeboosc will also be included in NOAH. The NIRS values will not be available to the bedside clinician if enrolled into the standard arm of Safeboosc. The screen will be blanked out to ensure no data is visible. Therefore every baby will have a NIRS probe in situ and the radiologist performing the scan will be unaware of Safeboosc arm which the baby is randomised to. Data entry will be performed by an administrative staff member who will enter the radiologists report into the eCRF. This process ensures that neither the radiologist performing the scan or the person entering the data is aware of group assignment.	Yes

Nation	Department	Investigator	Method	Approved
Ireland	Coombe Hospital, Dublin	Jan Miletin	Clinical ultrasounds are performed by one of two paediatric radiologists twice a week at the neonatal intensive care unit at Cork University Maternity Hospital, typically on a Monday and Thursday. When Safeboosc trial is running these two radiologists will be performing the ultrasound scans. There is another prospective observational study being conducted at CUMH at the same time called NOAH. This is evaluating an ICON device and cerebral NIRS is being performed at the same time. This is observational only and the clinican is not observing the values, or interacting with them. We anticipate that any baby enrolled in Safeboosc will also be included in NOAH. The NIRS values will not be available to the bedside clinician if enrolled into the standard arm of Safeboosc. The screen will be blanked out to ensure no data is visible. Therefore every baby will have a NIRS probe in situ and the radiologist performing the scan will be unaware of Safeboosc arm which the baby is randomised to. Data entry will be performed by an administrative staff member who will enter the radiologists report into the eCRF. This process ensures that neither the radiologist performing the scan or the person entering the data is aware of group assignment.	Yes

Nation	Department	Investigator	Method	Approved
Ireland	Rotunda	Afif EL-Khuffash	- All infants born under 1500 grams and/or 36 weeks of corrected undergo multiple routine cranial US assessment up until 36 weeks of corrected age. -The individual performing these assessments (Paediatric Radiologist) will be unaware of enrollment into any trial undergoing in the unit or indeed assignment to intervention. If the baby is scanned within the first 72 hrs of age and are in the experimental group, the NIRS monitor will be removed before the scan and reinitiated immediately after. -All cranial US scans are centrally reported by a different radiologist in batches. This radiologist will be unaware of enrollment into the trial or assignment of intervention. This will also apply to the initial US scans obtained over the first week of age. -The individual reading the results of the radiology reports to enter the data to the eCRF will be blinded to the to the treatment allocation. This person will not be involved in the NIRS set up or patient assignment.	Yes
Ireland	NMH Holles st.	Anna Curley	Clinical ultrasounds are performed by a radiographer twice to three times per week at the neonatal intensive care unit in NMH Holles st. After the images are obtained, they are reviewed and reported by one of two radiologists. These radiologists are not in the neonatal intensive care unit and will be unaware of which SafeboosC arm the babies are randomised to. Data entry will be performed by the separate administrative staff member who will enter the radiologists report into the eCRF.	Yes

Nation	Department	Investigator	Method	Approved
Italy	Milan	Monica Fumagalli	In our NICU at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan (Italy), the neonatologists perform the cranial ultrasound (cUS) scans. The following protocol has been developed to ensure effective blinding of cranial ultrasound readings and data entry. Infants enrolled in SafeBoosC-III will undergo routine cUS according to local NICU guidelines. The sonograms will be performed by Laura Bassi (LB) and Ida Sirgiovanni (IS), who are NICU specialists on cUS. They will edit the cUS reports on the corresponding infant's electronic clinical history (eCH). The images will be stored by Tiziana Boggini (TB), who is a research fellow, in an anonymous form that is without exam date, patient name or group allocation. The images will be collected in electronic folders identified with casual numeric codes, which will be recorded in a column in the participant-inclusion-list (PIL) guarded by TB. Every four weeks, Monica Fumagalli (MF), who is the principal investigator and specialist in neonatal neurology, will randomly review all anonymised images until 36 weeks postmenstrual age (PMA), diagnose and enter data on brain injury into the eCRF. If she can recognize the baby's images (if she can remember group allocation), she will consult a third party who cannot recognize the images: Agnese De Carli (ADC), at the moment not involved in clinical care (maternity leave).	Yes

Nation	Department	Investigator	Method	Approved
Italy	Torino	Emmanuele Mastretta	In our NICU at Presidio Ospedaliero Sant'Anna – Città della Salute di Torino (Italy), neonatologists do routinely perform cranial ultrasound (cUS) scans. The following protocol has been developed to ensure effective blinding of cranial ultrasound readings and data entry. Infants enrolled in SafeBoosC-III will undergo routine cUS scans according to local NICU guidelines, which, for preterm less than 28 weeks of gestational age (GA), include the first scan during the 1st day of life (DOL), the second after 72 hours of life, the third at 7-10 DOL and then every second week until discharge, unless the presence of findings needing to be checked earlier. The last cUS assessment is made at 36 weeks GA (during the first follow-up visit, if the baby has already been discharged, or in the ward if still hospitalized). By 40 weeks GA a cerebral magnetic resonance imaging (MRI) is routinely done. Scans are usually performed by Dr Francesca Campagnoli, Dr Giuseppina Bonfante and Dr Emmanuele Mastretta, who are NICU specialists about cUS. They will also edit the cUS reports on the corresponding infant's electronic clinical history (eCH). At follow-up time all cUS scans images will be reviewed by Dr Paolo Galletto, former chief of our NICU until December 2019, who has a long experience on cerebral ultrasound. Dr Galletto has currently a grant dedicated to the out-patient clinic and he is not involved in the routine clinical care of the NICU, therefore he will not be able to know the patient's group allocation. Dr Galletto will then enter data about brain injury into the eCRF.	Yes

Nation	Department	Investigator	Method	Approved
Italy	Fondazione IRCCS Policlinico Gemelli of Rome	Giovanni Vento Francesca Serrao	In our NICU at Fondazione IRCCS Policlinico Gemelli of Rome (Italy), the neonatologists perform the cranial ultrasound (cUS) scans. The following protocol has been developed to ensure effective blinding of cranial ultrasound readings and data entry. Infants enrolled in SafeBoosC-III will undergo routine cUS according to local NICU guidelines. The sonograms will be performed by Francesca Serrao (FS), Alessandra Lio (AL) and Serena Rubortone (SR), who are NICU specialists on cUS. They will edit the cUS reports on the corresponding infant's electronic clinical history (eCH). The images will be stored by Serena Rubortone (SR), who is a research fellow, in an anonymous form that is without exam date, patient name or group allocation. The images will be collected in electronic folders identified with casual numeric codes, which will be recorded in a column in the participant-inclusion-list (PIL) guarded by TB. At the end of study, Rita Luciano (RL), specialist in neonatal neurology not involved in clinical care, will randomly review all anonymised images until 36 weeks postmenstrual age (PMA) and diagnose. Francesca Serrao (FS) will enter data on brain injury into the eCRF.	Yes

Nation	Department	Investigator	Method	Approved
Italy	Ospedalo Fillipo del Ponte, Varese	Massimo Agostino Dario Gallo	In our NICU of 'Ospedale del Ponte- Varese (Italy)', either neonatologists or radiologists routinely perform cranial ultrasound (cUS) scans. The following protocol has been developed to ensure blinding of cranial ultrasound readings and data entry. Infants enrolled in SafeBoosC-III will undergo routine cUS scans according to local NICU guidelines, which, for preterm less than 28 weeks of gestational age (GA), include the first scan during the 1st day of life (DOL), the second after 48-72 hours of life, the third at 7-10 DOL or before in relation to the findings, and thereafter every 1-2 weeks until 36 weeks GA (in the outpatient if the baby is discharged before). By 38-40 weeks GA a cerebral magnetic resonance imaging (MRI) is routinely done. Scans will be performed by Dr Dario Gallo and Dr Valentina Chierici, who are our NICU specialists about cUS. They will also edit the cUS reports on the corresponding infant's electronic clinical history (eCH). At 36 weeks GA all cUS scans images will be reviewed by Dr Alberto Pozzi, Head of Radiology Depai tment, who has a long experience on cerebral ultrasound, and Dr Ida Daniela D'Angelo, radiologist, since they are not involved in neonatal clinical care. Dr Alberto Pozzi will enter data about brain injury into the eCRF.	Yes
Norway	Oslo University Hospital	Siv Fredly	Pediatric radiologists will conduct all cranial ultrasounds on babies included in SafeBoosC III. They are not involved in the daily care of babies in the NICU and will therefore be blinded to group allocation. If a baby is scanned within the first 72 hrs and the baby is in the experimental group, the NIRS sensor and monitor will be removed during the scan. The pediatric radiologists are aware of the SafeBoosC brain injury criteria, and will use these in their image descriptions. A study nurse not involved in the care of the babies will enter data on severe brain injury in the eCRF, based on the image descriptions from the pediatric radiologists.	Yes

Nation	Department	Investigator	Method	Approved
Poland	UJASTEK Krakow	Elzbieta Rafinska Wazny Beata Rzepecka	Piotr Kruczek (PK) will conduct all cuS scans on babies included in SafeBoosC III and also enter data on severe brain injury into the eCRF. PK is not involved in the daily care of babies in the NICU and will therefore be blinded to group allocation. If he scans a baby within the first 72 hrs and the baby is in the experimental group, the NIRS sensor and monitor will be removed during the scan, to ensure that PK is blinded.	Yes
Poland	Jan Biziel Univ. Hospital	Iwona-Sadowska	A neonatologist not involved in the care of trial participants on a daily basis will be provided with anonymized electronic images of trial participants. The neonatologist will then, completely blinded from group allocation, review the images and enter data into the eCRF on brain injury,	Yes
Poland	Specialist Hospital No. 2 in Bytom	Klaudiusz Bober	In Bytom, neonatologists who are involved in the daily care of trial participants routinely perform cUS scans on the participants. Based on these blinded scans, MD Katarzyna Szczepańska and MD Patrycja Gazy will write image reports. These two MDs (fellows during neonatology training who are highly experienced in performing cUS, proven by certificates) are not involved in the daily care of trial participants. The aforementioned fellows work in the neonatal physiology ward on a daily basis, which is located in another part of our hospital. Once a month, MD Katarzyna Szczepańska and MD Patrycja Gazy will enter data on severe brain injury into the eCRF, completely based on the images.	Yes
Poland	Poznan Hospital	Tomasz Szczapa	A neonatologist not involved in the care of trial participants on a daily basis will be provided with anonymized electronic images of trial participants. The neonatologist will then, completely blinded from group allocation, review the images and enter data into the eCRF on brain injury.	Yes

Nation	Department	Investigator	Method	Approved
Poland	Warszaw University of Medical Sciences	Agata Bargiel	In Warszaw (Neonatal Department of Princess Anna Mazowiecka Hospital), dr Robert Pawluch, who is not involved in the care of trial participants on a daily basis will come to the NICU and perform cUS scans on trial participants as usual routine. If a scan is conducted within the first 72 hrs of age, sensor and monitor will be removed to ensure proper blinding. Based on these blinded scans, dr Robert Pawluch will write image reports. Once a month, I (Agata Bargieł) will enter data on severe brain injury into the eCRF, completely based on the image descriptions by Robert Pawluch. Robert Pawluch has been informed of the SafeBoosC severe brain injury diagnosis, and will keep this in mind while writing image descriptions. In some situations, dr Robert Pawluch will not have the possibility to scan the trial participants. In these cases someone else will conduct the scans, show the images to Robert Pawluch, who will then write and image report. Another person, who in some cases will write image reports, is Agata Wójcick-Sęp. She has also been informed of the Safeboosc procedures and severe brain injury diagnosis, and will write the descriptions according to instructions.	Yes
Poland	Wroclaw Medical University	Barbara Krolak-Olejnik	Agnieszka Szafranska, a neonatologist, will conduct all cUS scans on babies included in SafeBoosC III. She is not involved in the daily care of babies in the NICU and will therefore be blinded to group allocation. If she scans a baby within the first 72 hrs and the baby is in the experimental group, the NIRS sensor and monitor will be removed from bedside during the scan. Agnieszka will also be the person evaluating her own cUS scans and enter data on severe brain injury in the eCRF.	Yes

Nation	Department	Investigator	Method	Approved
Poland	St Queen Jadwiga's, Reszow	Witold Blaz	in Rzeszow cUS studies are performed by neonatologists. Two pediatricians with great experience in cranial ultrasound confirmed by appropriate certificates who are not involved in the care of trial participants will be provided with anonymized electronic images of trial participants. Subsequently they will then, being completely blinded from group allocation, review the images and enter data into the eCRF on brain injury.	Yes
Poland	Szpital Uniwersytecki, Kraków	Ryszard Lauterbach	Agata Bocheńska, a neonatologist will perform all cUS scans on patients recruited in trial. She will not be involved in the daily care of premies treated in the NICU 1 and will be blinded to group allocation.If she will scans a baby from the experimental group within the first 72 hours, the Oxyprem monitor will be removed from the bedside during scanning. Then, images will be blindly reviewed by Agnieszka Ochoda, a neonatologist highly experienced in cUS scanning, who did not perform the respective cUS and will update the CRF in regards of brain injury. Agnieszka is not involved in the daily care of NICU patients.	Yes
Poland	Medical Postgraduate Education, Warsaw	Maria Wilinska	The epidural head ultrasound is performed by an external radiologist who does not know the child's group affiliation. He also examines many other children during a visit to the center, which virtually eliminates the risk of identification to the group. If a baby scanned within the first 72 hrs of life and in the experimental group, the sensor and device will be removed from bedside during the scan and initiated again, immediately after. The radiologist will then, based on the SafeBoosC-III severe brain injury criteria, write the image description in the childs medical records. A member of the research team will then fill-out the eCRF based on the radiologist's image descriptions.	Yes
Spain	Hospital Universitarie Puerta Del Mar, Cadiz	Pamela Zafra	Two neonatologists will perform all cUS and save images without any identifiers. Images will be blindly reviewed by the neonatologist who did not perform the respective cUS, and will update the CRF in regards of brain injury. The local department will make sure that the blinded neonatologist will not be able to identify the patient in the images.	Yes

Nation	Department	Investigator	Method	Approved
Spain	Hospital General de Ciudad Real	Miguel Angel Cabezas	Radiologists will conduct all cuS scans on babies included in SafeBoosC III. They are not involved in the daily care of babies in the NICU and will therefore be blinded to group allocation. The radiologist will be aware of the SafeBoosC brain injury criteria, and use these in their image descriptions. If a baby is scanned within the first 72 hrs and the baby is in the experimental group, the NIRS sensor and monitor will be removed during the scan. A neonatologist will use the image descriptions from the radiologists to enter data on severe brain injury in the eCRF.	Yes
Spain	Hospital Miguel Servet	Segundo Rite	1. When a <28 EG is born/about the born the enrollment is made by the doctor who is on duty. This doctor will contact con Dr Rite o Dr Serrano for randomization. 2. After randomitation the doctor on duty will manage the patient with the reference of the protocol guideline. 3. C-US will be performed as it's described in the protocol by the doctors responsible for it. The doctors are neonatologists: Dr Galve, Pinillos and Curto. 4. At 36 EPM, Dr Abenia and García will read cranial ultrasound and fill in the eCRF data field on severe brain injury. *These doctors are blinded. They are neonatologists who are not on duty and that are not in charge of extreme preterm babies.*	Yes

Nation	Department	Investigator	Method	Approved
Spain	La Paz University Hospital	Adelina Pellicer	The following protocol has been developed to ensure effective blinding and data entry. Infants enrolled in SafeBoosC-III will undergo routine CUs as per clinical indication according to NICU policies. The sonograms will be performed by a neonatologist [María Carmen Bravo (MB) or Marta Ybarra (MY)] who will edit the corresponding study report. Both, the report and the images, will be stored in the corresponding infant's electronic clinical history (eCH). At 36 weeks postmenstrual age, Eva Valverde (EV), who is one of the NICU specialists on CUs, and Celia Díaz (CD), who is the neonatologist responsible of the outpatient clinic and is exempted from medical duties, will assess the images and enter data on severe brain injury into the eCRF. Since EV is not exempted from medical duties (however, she will try to avoid being involved in the care of babies in SafeBoosC), she will decide on whether she can recognise the cUS images and whether she can recall the baby's group allocation. If EV can recall group allocation, she will not be involved in diagnosing brain injury in that specific baby, and a third party will be called in to support CD with the diagnosis. Group allocation will be recorded in a column in the participant-inclusion-list (PIL). There will not be specific recording of group allocation in any relevant screen of the eCH, with the exeption of references in the daily notes, if considered relevant for the infant's care. The custodian of the list will be the PI [Adelina Pellicer (AP)].	Yes

Nation	Department	Investigator	Method	Approved
Spain	Hospital Clinico San Carlos	Luis Arruza	Infants enrolled in SafeBoosC-III study will undergo routine cranial ultrasound examinations as per clinical indication. The minimum number of ultrasound studies per patient will be 3: one in the first 24 h of life, one at the end of the first week, and one at 36 weeks postconcepcional age. Standard cranial ultrasound views will be obtained according to SafeeBoosC III trial protocol by a neonatologist (Maria Jose Rodriguez and Luis Arruza). Images will be anonymized and stored. Identification of studies will be done with the study-ID of each patient and the moment of the assessment (e.g.: Patient 1-1st day). A pediatric radiologist (David Llanos and Iñigo Pedraja), unaware of patient´s group allocation, will review the study off-line to determine the severity of brain injury and then fill in the eCRF with the result. Pediatric radiologists will not have access to medical records of the patients participating in the study	Yes

Nation	Department	Investigator	Method	Approved
Spain	C.H. Universitario De Santiago	Olalla Suarez	CUs are performed by two experienced neonatologists at Dept. of Neonatology, Hospital Clínico Universitario de Santiago de Compostela (CHUS). The following protocol has been developed to ensure effective blinding and data entry. Infants enrolled in SafeBoosC-III will undergo routine CUs as per clinical indication according to NICU policies. The sonograms will be performed by Alejandro Pérez Muñuzuri (AP) who will edit the corresponding study report. Both, the report and the images, will be stored in the corresponding infant's electronic clinical history (eCH). At 36 weeks postmenstrual age, a third person (name or initials?) experienced with cranial ultrasound, will review the images and fill-in the eCRF data fields on severe brain injury. Third person will be blinded to group allocation since third person do not take care of trial participants. If somehow, third person can recognise the images, i.e. group allocation of the baby, third person will consult with a third party regarding assessment of those specific images. Group allocation will be recorded in a column in the participant-inclusion-list (PIL). There will not be specific recording of group allocation in any relevant screen of the eCH, with the exeption of references in the daily notes, if considered relevant for the infant's care .	Yes

Nation	Department	Investigator	Method	Approved
Spain	Hospital De Sant Joan De Deu, Barcelona	Ruth Del Rio Florentino	Cranial ultrasounds are usually performed by attending neonatologists in Hospital Sant Joan de Déu. In order to ensure blinding of cranial ultrasound interpretation for SafeBoosC III the following protocol has been developed. Ultrasound scans will be performed by a single neonatologist expert in cranial ultrasound (Nuria Carreras-NC) who will store each study and codify it with consecutive series numbers. An Excel file will be created by NC and Ruth del Río (RR) correlating each of these file numbers with patient identification. At 36 weeks postmenstrual age Thais Agut (TA), senior neonatologist and CU expert, will review the images and will fill in the eCRF data files related to brain injury presence/absence for these patients. TA works daily in the follow up clinic. She is sometimes consulted for “difficult” CUS images obtained in the NICU. For SafeBoos-C III if, when assessing ultrasounds blindly, TA should recognize an image a third senior neonatologist expert in CUS, Ana Alarcon (AA) would finally fill the eCRF data files related to brain injury.	Yes

Nation	Department	Investigator	Method	Approved
Spain	12 de Octubre University Hospital	Salvador Piris	CUs are performed by pediatric radiologists at Dept. of Neonatology, 12 de Octubre University Hospital. The following protocol has been developed to ensure effective blinding and data entry. Infants enrolled in SafeBoosC-III will undergo routine CUs as per clinical indication according to NICU policies. The sonograms will be performed by a pediatric radiologist [Carmen Gallego (CG) or Constanza Liébana de Rojas (CL) or Elisa Aguirre (EA) or David Coca (DC)]. Miguel Rasero (MR) is one of the NICU Radiologist especialists on CUs but he is not in charge of the neonatal patients, so he is blind to the allocation information. MR will review the report of the pediatric radiologists and will fill-in the eCRF the final data at 36 weeks of postmenstrual age. If a scan is conducted on a baby in the experimental group within the first 72 hrs of life, the sensor will be removed during those minutes to ensure that the pediatric radiologist is completely blinded to group allocation. Group allocation will be recorded in a column in the participant-inclusion-list (PIL). There will not be specific recording of group allocation in any relevant screen of the eCH, with the exeption of references in the daily notes, if considered relevant for the infant's care. The custodian of the list will be the PI [Salvador Piris (SP)].	Yes

Nation	Department	Investigator	Method	Approved
Spain	Hospital Universitario de Valdecilla	Isabel de las Cuevas	This Standard Operational Protocol refers to the local procedure for the reading of cranial ultrasound (cUS), the diagnosis of brain injury according to the study protocol and the data entry in the eCRF on brain injury outcomes at 36 weeks PMA. Four pediatric radiologist will participate in the sudy: Alexandra de Diego (AD), Vanesa Gómez-Dermit (VG), Macarena Otero (MO) y Marta Pelaz (MP) Three pediatric radiologists [AD, VG, MO] will be responsible for performing cUS according to NICU policies. The images of the recruited patients will be recorded in the eCH without any identification data about group allocation. A fourth pediatric radiologist [MP] not involved in the performance of cUS in the NICU area where the very preterm newborns are admitted and unaware of group allocation, will review the images in order to make a diagnosis following the criteria of the Study Protocol and fill in the eCRF data field on severe brain injury and the question regarding achievement of blinding at 36 weeks PMA. Group allocation will be recorded in a column in the participant-inclusion-list (PIL). There will not be specific recording of group allocation in any relevant screen of the eCH, with the exception of references in the daily notes, if considered relevant for the infant's care. The custodian of the list will be the IP [Isabel de las Cuevas]	Yes

Nation	Department	Investigator	Method	Approved
Spain	Tarragona	Olalla Otero	For this research project we will follow the following protocol to ensure blind evaluation of the US: • An experienced radiologist of the radiologist staff, who usually do ultrasounds in preterm babies, will perfom all the cranial ultrasonography studies (US) of all recruited patients at 36sem. If a baby is scanned within the first 72 hours of age, the NIRS sensor will be shortly removed to ensure that the radiologist is completely blinded to group allocation. • He or she will not have access to clinical data nor to information regarding which group was the patient randomized to. A pediatric colleague (B.R), who don´t work never at the neonatal unit, unaware of group allocation will read the radiologists image description and fill in the eCRF data field on severe brain injury and the question regarding achievement of blinding.	Yes

Nation	Department	Investigator	Method	Approved
Spain	Hospital de Cruces	Bergona Loureiro	CUs are performed by both neonatologists or radiologist at Neonatal Unit, Cruces University Hospital. The following protocol has been developed to ensure effective blinding and data entry. Infants enrolled in SafeBoosC-III will undergo routine CUs as per clinical indication according to NICU policies. On the first 72 hours of life the sonograms will be performed by a neonatologist [Eneritz Guerra (EG) or Mari Cruz López (ML] who will edit the corresponding study report. Both, the report and the images, will be stored in the corresponding infant's electronic clinical history (eCH). At 36 weeks postmenstrual age, Armando Gozalo (AG) or María Berastegui (MB) who are paediatric radiologist especialists on CUs, will review the images, to ensure consistency of images and reports. AG and MB will fill-in the eCRF data fields on severe brain injury and the question regarding the achievement of blinding. Group allocation will be recorded in a column in the participant-inclusion-list (PIL). There will not be specific recording of group allocation in any relevant screen of the eCH, with the exeption of references in the daily notes, if considered relevant for the infant's care. The custodian of the list will be the PI [Begoña Loureiro (BL).	Yes

Nation	Department	Investigator	Method	Approved
Spain	H. U. Virgen de las Nieves (Granada)	Laura Serrano	Cus are performed by radiologists at Dept. of Radiology Virgen de las Nieves University Hospital. Infants enrolled in SafeBoosC-III will undergo routine cUS as per clinical indication according to NICU policies. The sonograms will be performed by a radiologist who will edit the corresponding study report with consideration to the SafeBoosC III brain injury criteria. Since the radiologists is not involved in the care of trial participants, he/she will not be aware of group allocation. If the baby is scanned within the first 72 hrs of life, NIRS sensor and monitor will be removed during the scanning (if it is a baby in the experimental group). Both the report and the images will be stored in the corresponding infant's electronic clinical history (eCH). Group allocation will be recorded in a column in the participant-inclusion-list (PIL). There will not be specific recording of group allocation in any relevant screen of the eCH, with the exception of references in the daily notes, if considered relevant for the infant's care, and during enrolment into the study, where writing group allocation is necessary for GCP monitoring visits. A neonatologist will enter data on severe brain injury into the blinded eCRF, solely based on the radiologists image descriptions. The custodian of the list will be the PI (Laura Serrano Lopez (LS)). The following protocol has been developed to ensure effective blinding and data entry.	

Nation	Department	Investigator	Method	Approved
Spain	Hospital Casa De Maternitat	Miguel Alsina	CUs are performed by neonatologists and radiologists technicians in Hospital Clinic of Barcelona. The following protocol has been developed to ensure effective blinding and data entry. Infants enrolled in SafeBoosC-III will undergo routine CUs as per clinical indication according to NICU policies. We currently perform the first routine cUS at 72 hours of life in order to preserve the minimal manipulation of preterm infants within this time. The sonograms will be performed by a neonatologist Nuria Carreras (NC), who is exempted from medical duties, or a radiologist technician Pilar Hernández (PH) at 72 to hours of life after removing the NIRS monitor. In this way NC and PC won't be aware of the patient allocation. NC or a radiologist Sebastian Capurro (SC) will edit the corresponding study report. Both, the report and the images, will be stored in the corresponding infant's electronic clinical history (eCH). At 36 weeks postmenstrual age, Nuria Carreras (NC), will review all the images. NC will fill-in the eCRF data fields on severe brain injury and the question regarding the achievement of blinding. Group allocation will be recorded in a column in the participant-inclusion-list (PIL). There will not be specific recording of group allocation in any relevant screen of the eCH, with the exemption of references in the daily notes, if considered relevant for the infant's care. The custodian of the list will be the PI [Miguel Alsina (MA)].	Yes

Nation	Department	Investigator	Method	Approved
Switzerland	Zurich University Hospital, Lucerne, Geneva and Lausanne	Tanja Karen (Zürich)	In the sites of Zurich, Lucerne and Geneva, the neonatologists themselves perform the cUS. In aiming for a 100%-blinding of all patients included in the SafeBoosC study in Switzerland, an extern expert will diagnose the brain injury according to the SOP "diagnosis and classification of brain injury". The National Coordinator of SafeBoosC for Switzerland, PD Dr. med. Cornelia Hagmann, fulfils these criteria. She is unaware of group allocation as she has no access to the medical history of any of these patients and is not on site in the NICU. Furthermore, she is very experienced in rating brain injuries on cUS. She reviews all anonymized images of every patient until 36 weeks postmenstrual age and fills in the diagnosis on the pCRF (print out of the electronic version). All sites transmit data themselves from the paper version into the electronic version.	Yes

Turkey	Gazi University Hospital	Ebru Ergenekon	Routine cranial ultrasound for preterms < 32 weeks gestation are performed and reported by pediatric radiologists according to the following schedule where IVH of all grades, cerebellar hemorrhage, PVL or cerebral atrophy are investigated; 1st ultrasound at 1-3 days of age 2nd ultrasound 7-10 days of age 3rd ultrasound around 15 days of age If the above are abnormal (IVH or PVL) ultrasound is repeated weekly until 36-40 weeks CA or discharge. If the first 3 ultrasounds are normal then a final one is obtained at 36-40 weeks CA or at discharge. For the SafeBoosC III trial the same routine is going to be followed. The pediatric radiologist will know that the patient is in the study but will be blinded to the grouping (control/trial group). If the patient is in the study group for the ultrasound which is going to be done within the first 72 hours NIRS probe and device will be removed from the bedside during ultrasound scanning. The radiologist will electronically report the findings on the hospital's patient data system however will not have access to the information regarding which group the patient is in. The radiologist will be aware of the SafeBoosC III severe brain injury criteria, when writing the image description report. A neonatologist will, based completely on the radiologists reported findings and/or image descriptions, fill-out the blinded eCRF on brain injury. In case the ultrasound scan needs to be performed by the neonatology staff (public holidays, inavailability of the pediatric radiologist for a certain period of time), the images will be examined and reported by the radiologist who is again blinded to the grouping. A neonatologist will, based completely on the radiologists reported findings and/or image descriptions, fill-out the blinded eCRF on brain injury.	Yes

Turkey	Uludag University Hospital	Hilal Ozkan	Routine cranial ultrasound for preterms < 32 weeks gestation are performed and reported by pediatric radiologists according to the following schedule where IVH of all grades, cerebellar hemorrhage, PVL or cerebral atrophy are investigated; 1st ultrasound at 1-3 days of age 2nd ultrasound 7-10 days of age 3rd ultrasound around 15 days of age If the above are abnormal (IVH or PVL) ultrasound is repeated weekly until 36-40 weeks CA or discharge. If the first 3 ultrasounds are normal then a final one is obtained at 36-40 weeks CA or at discharge. For the SafeBoosC III trial the same routine is going to be followed. The pediatric radiologist will know that the patient is in the study but will be blinded to the grouping (control/trial group). If the patient is in the study group for the ultrasound which is going to be done within the first 72 hours NIRS probe and device will be removed from the bedside during ultrasound scanning. The radiologist will electronically report the findings on the hospital's patient data system however will not have access to the information regarding which group the patient is in. The radiologist will be aware of the SafeboosC III severe brain injury criteria, when writing the image description report. A neonatologist will, based completely on the radiologists reported findings and/or image descriptions, fill-out the blinded eCRF on brain injury. In case the ultrasound scan needs to be performed by the neonatology staff (public holidays, inavailability of the pediatric radiologist for a certain period of time), the images will be examined and reported by the radiologist who is again blinded to the grouping. A neonatologist will, based completely on the radiologists reported findings and/or image descriptions, fill-out the blinded eCRF on brain injury.	Yes

Nation	Department	Investigator	Method	Approved
Turkey	Kanuni Sultan Suleyman Hospital	Merih Cetinkaya	Preterm infants with gestational age of < 32 weeks are evaluated by routine cranial ultrasound that investigates all grades of IVH, cerebellar hemorrhage, PVL or cerebral atrophy. Cranial ultrasound are performed and reported by pediatric radiologists according to the following schedule in our NICU; 1 st ultrasound wtihin first 3 days of age 2 nd ultrasound at 7-10 days of age 3 rd ultrasound around 15 days of age If the above are abnormal (IVH or PVL) ultrasound is repeated twice in a week until 36-40 weeks CA or discharge If the first 3 ultrasounds are normal then a final one is obtained at 36-40 weeks CA or at discharge. For the SafeBoosC III trial the same routine schedule is going to be followed. The pediatric radiologist will know that the patient is in the study but will be blinded about the grouping (control/trial group). Even if the patient is in the study group, NIRS probe and device will be removed from the bedside during ultrasound scanning to remain the radiologist being blind. The radiologist will electronically report the findings on the hospital's patient data system however will not have access to the information regarding which group the patient is in. The radiologist will be aware of the SafeBoosC III severe brain injury criteria, when writing the image description report. A neonatologist will fill-out the blinded eCRF on brain injury which is based completely on the radiologist findings and report.	Yes

Turkey	Mamara University Hospital	Asli Memisoglu	Routine cranial ultrasound for preterms < 32 weeks gestation are performed and reported by pediatric radiologists according to the following schedule where IVH of all grades, cerebellar hemorrhage, PVL or cerebral atrophy are investigated; 1st ultrasound at 1-3 days of age 2nd ultrasound 7-10 days of age 3rd ultrasound around 15 days of age If the above are abnormal (IVH or PVL) ultrasound is repeated weekly until 36-40 weeks CA or discharge. If the first 3 ultrasounds are normal then a final one is obtained at 36-40 weeks CA or at discharge. For the SafeBoosC III trial the same routine is going to be followed. The pediatric radiologist will know that the patient is in the study but will be blinded to the grouping (control/trial group). If the patient is in the study group for the ultrasound which is going to be done within the first 72 hours NIRS probe and device will be removed from the bedside during ultrasound scanning. The radiologist will electronically report the findings on the hospital's patient data system however will not have access to the information regarding which group the patient is in. The radiologist will be aware of the SafeBoosC III severe brain injury criteria, when writing the image description report. A neonatologist will, based completely on the radiologists reported findings and/or image descriptions, fill-out the blinded eCRF on brain injury. In case the ultrasound scan needs to be performed by the neonatology staff (public holidays, inavailability of the pediatric radiologist for a certain period of time), the images will be examined and reported by the radiologist who is again blinded to the grouping. A neonatologist will, based completely on the radiologists reported findings and/or image descriptions, fill-out the blinded eCRF on brain injury.	Yes

Nation	Department	Investigator	Method	Approved
Turkey	Bilkent Integrated Health Campus	Serife Suna	In our neonatal intensive care unit (NICU) cranial ultrasound is performed for all preterms infants with gestational age (GA) < 32 weeks gestation and reported by pediatric radiologists according to the following scan schedule where IVH (intraventricular hemorrhage) of all grades, cerebellar hemorrhage, PVL (periventrıcular leukomalasia), post-haemorrhagic ventricular dilatation or cerebral atrophy are investigated; • 1st ultrasound at 1-3 days of age • 2nd ultrasound 7-10 days of age • 3rd ultrasound around 15 days of age If the first 3 head ultrasounds are normal then a final one is obtained at 36-40 weeks CA or at discharge. If the above are abnormal (IVH or PVL) ultrasound is repeated weekly until 36-40 weeks CA or discharge In case the ultrasound scan needs to be performed by the neonatology staff (public holidays, inavailability of the pediatric radiologist for a certain period of time), the images will be examined and reported by the pediatric radiologist who is again blinded to the grouping. A neonatologist will, based completely on the radiologists reported findings and/or image descriptions, fill-out the blinded eCRF on brain injury. For the SafeBoosC III trial the same routine is going to be followed. The pediatric radiologist will know that the patient is in the study but will be blinded to the grouping (control/trial group). If the patient is in the study group for the ultrasound which is going to be done within the first 72 hours NIRS probe and device will be removed from the bedside during ultrasound scanning. The radiologist will electronically report the findings on the hospital's patient data system however will not have access to the information regarding which group the patient is in. The radiologist will be aware of the SafeBoosC III severe brain injury criteria, when writing the image description report. A neonatologist will, based completely on the radiologists reported findings and/or image descriptions, fill-out the blinded eCRF on brain injury.	Yes

Nation	Department	Investigator	Method	Approved
Turkey	Istanbul Basaksehir Cam and Sakura City Hospital	Beril Yasa	Preterm infants with gestational age of < 32 weeks are evaluated by routine cranial ultrasound that investigates all grades of IVH, cerebellar hemorrhage, PVL or cerebral atrophy. Cranial ultrasound are performed and reported by pediatric radiologists according to the following schedule in our NICU; 1st ultrasound wtihin first 3 days of age 2nd ultrasound at 7-10 days of age 3rd ultrasound around 15 days of age If the above are abnormal (IVH or PVL) ultrasound is repeated twice in a week until 36-40 weeks CA or discharge If the first 3 ultrasounds are normal then a final one is obtained at 36-40 weeks CA or at discharge. For the SafeBoosC III trial the same routine schedule is going to be followed. The pediatric radiologist will know that the patient is in the study but will be blinded about the grouping (control/trial group). Even if the patient is in the study group, NIRS probe and device will be removed from the bedside during ultrasound scanning to remain the radiologist being blind. The radiologist will electronically report the findings on the hospital's patient data system however will not have access to the information regarding which group the patient is in. A neonatologist will fill-out the blinded eCRF on brain injury which is based completely on the radiologist findings and reports.	Yes

Nation	Department	Investigator	Method	Approved
United Kingdom	Royal Hospital for Children, Glasgow	Anne-Marie Heuchan	In the neonatal centre at RHC Glasgow the key cranial ultrasounds are performed by radiology department sonographers at the end of the 1st week of life, day 28 and 36 CGA. Additional scans will be taken by sonographers if indicated and by clinicians in an emergency. The radiology department sonographers take high quality sequential images which are loaded onto the national imaging archive. The sonographers are responsible for reports but they do not always define ventriculomegaly, grade of IVH and PVL as required for the eCRF. At WGH the ultrasounds are performed by senior neonatal clinicians or radiologists at days 1, 3, 7, 28 and 36 weeks CGA. For the purpose of SafeBoosC III we will perform the 36 weeks CGA at 35+ weeks to ensure data entry before 36 weeks. Images are loaded onto the national imaging archive. Ultrasounds are reported by consultant neonatologists or radiologists. To avoid reporting bias the images from babies recruited at RHC Glasgow will be viewed on the national archive by the WGH PI (Dr K. McCall), who will report the outcomes for the eCRF at RHC. Likewise the images from babies recruited at WGH will be reviewed on the national archive by the RHC PI (Dr A M. Heuchan) who will report on the outcomes for babies recruited at RHC. Both clinicians will review the key images for maximal grades of PVH, ventriculomegaly, periventricular leukomalacia, cerebral atrophy and cerebellar haemorrhage and enter them onto the eCRF. Where in doubt clinicians will seek a 2nd opinion from a colleague on their site who will also be blinded to the patient allocation.	Yes

Nation	Department	Investigator	Method	Approved
United Kingdom	Wishaw General Hospital	Karen McCall	In the neonatal centre at RHC Glasgow the key cranial ultrasounds are performed by radiology department sonographers at the end of the 1st week of life, day 28 and 36 CGA. Additional scans will be taken by sonographers if indicated and by clinicians in an emergency. The radiology department sonographers take high quality sequential images which are loaded onto the national imaging archive. The sonographers are responsible for reports but they do not always define ventriculomegaly, grade of IVH and PVL as required for the eCRF. At WGH the ultrasounds are performed by senior neonatal clinicians or radiologists at days 1, 3, 7, 28 and 36 weeks CGA. For the purpose of SafeBoosC III we will perform the 36 weeks CGA at 35+ weeks to ensure data entry before 36 weeks. Images are loaded onto the national imaging archive. Ultrasounds are reported by consultant neonatologists or radiologists. To avoid reporting bias the images from babies recruited at RHC Glasgow will be viewed on the national archive by the WGH PI (Dr K. McCall), who will report the outcomes for the eCRF at RHC. Likewise the images from babies recruited at WGH will be reviewed on the national archive by the RHC PI (Dr A M. Heuchan) who will report on the outcomes for babies recruited at RHC. Both clinicians will review the key images for maximal grades of PVH, ventriculomegaly, periventricular leukomalacia, cerebral atrophy and cerebellar haemorrhage and enter them onto the eCRF. Where in doubt clinicians will seek a 2nd opinion from a colleague on their site who will also be blinded to the patient allocation.	Yes

Nation	Department	Investigator	Method	Approved
US	Loma Linda Univ. Hospital	Andrew Hopper	Clinical radiologists will conduct cranial ultrasound scans on babies participating in the trial, as per usual routine protocol. Since the clinical radiologists are not involved in the care of the babies on a daily basis, they will be unaware of group allocation. If a baby is scanned within the first 72 hours of life, the monitor and probe will be removed to hide group allocation. The clinical radiologists will therefore write blinded image descriptions, and they will be aware of the SafeBoosC III severe brain injury criteria, while writing the report. A radiologist recruited for the SafeBoosC III trial, will once a month review all image descriptions of babies in the trial and enter data on severe brain injury into the eCRF. This will be done blinded. The radiologists is not involved in the care of babies in the trial on a daily basis and thus, is completely unaware of group allocation.	Yes
US	Saint Louis Univ. Hospital	Amit Mathur	Radiology technicians will conduct all cuS scans on babies included in SafeBoosC III. The radiologist (Dr. Grace Mitchell), does not do the scanning but reads the scan remotely from an office outside the NICU. The radiologist is not involved in the care of trial participants and will only have access to images, thus she is completely blinded to group allocation. She will fill-out a printed version of the blinded follow-up eCRF (diagnosis of severe brain injury) based on the available scans. The GCP monitor will then fill-out the online blinded follow-up eCRF completely based on the already filled-out paper version.	Yes

Nation	Department	Investigator	Method	Approved
US	University Hospital of Utah	Mariana Baserga	Our Division Chief has confirmed that the radiologists who read the images and write the reports for our NICU infants do not access any clinical information as part of their clinical practice. The UU hospital uses radiology technicians to obtain the cranial ultrasound. The following other practices will be put into place to ensure that the image result reports are not biased: 1. If an infant needs a cranial ultrasound during the time that a NIRS monitor is in place, the probe will be removed prior to the radiology technician arriving in the room to do the imaging. This is to ensure that the technician does not inadvertently make a note of the NIRS probe. 2. The research nurses who are extracting the data will do so directly from the cranial ultrasound reports and, therefore, do not need to be blinded as they can't influence the results. If the research nurse has any questions about the results, she will email the reading radiologist directly and ask for clarification.	Yes
US	UT Southwestern Medical Center	Lina Chalak	Clinical radiologists will conduct cranial ultrasound scans on babies participating in the trial, as per usual routine protocol. Since the clinical radiologists are not involved in the care of the babies on a daily basis, they will be unaware of group allocation. If a baby is scanned within the first 72 hours of life, the monitor and probe will be removed to hide group allocation. A radiologist recruited for the SafeBoosC III trial, will review all image descriptions of babies in the trial and enter data on severe brain injury into the eCRF. This will be done blinded. The radiologist is not involved in the care of babies in the trial on a daily basis and thus, is completely unaware of group allocation.	Yes

Nation	Department	Investigator	Method	Approved
US	Washington Univ. Hospital	Zachary Vesoulis	Maintenance of blinding will be straightforward and will leverage existing Radiology workflows. Standard practice is for all cranial ultrasounds to be performed at the patient bedside by a qualified ultrasound technician and include coronal, sagittal, and mastoid views. These images are interpreted remotely by the radiologist who has not physically seen the patient nor has been notified of the patient's group allocation (thus completely blinded). As the ultrasounds are being done following routine clinical guidelines, the request will not disclose information about group allocation. All imaging results will be entered into a standardized eCRF using categorical definitions of brain injury which align with standard clinical image scoring. These elements including presence and severity of intraventricular hemorrhage (including intraparenchymal extension), cystic white matter injury, ventricular dilation, cerebellar hemorrhage, and cerebral atrophy. A research team member will directly input injury data into the eCRF based on findings in the report.	Yes

Nation	Department	Investigator	Method	Approved
US	Nationwide Children's Hospital, Ohio	Omid Fatih	The primary outcomes of this study are radiographic brain injury and mortality. Radiographic brain injury will be judged on the basis on routine clinical screening cranial ultrasounds that are performed on all infants born before 30 weeks on day of life 3, 10, and 28. Maintenance of blinding will be straightforward and will leverage existing Radiology workflows. Standard practice is for all cranial ultrasounds to be performed at the patient bedside by a qualified ultrasound technician and include coronal, sagittal, and mastoid views. These images are interpreted remotely by the radiologist who has not physically seen the patient nor has been notified of the patient's group allocation (thus completely blinded). As the ultrasounds are being done following routine clinical guidelines, the request will not disclose information about group allocation. At times, Ohio State University standards of care do not include ultrasounds on day of life 3 and 10 (SOC at OSU is for day of life 7 and 30 or when clinically indicated). Therefore, in order to ensure blinding of the radiologist, the medical team will use the following language for indication of the ultrasound when placing the ultrasound order: "Prematurity" or "Rule out intraventricular hemorrhage." These are typical indications for an ultrasound in the OSU NICU and will be used instead of any terms relating to an indication for research. All imaging results will be entered into a standardized eCRF using categorical definitions of brain injury which align with standard clinical image scoring. These elements including presence and severity of intraventricular hemorrhage (including intraparenchymal extension), cystic white matter injury, ventricular dilation, cerebellar hemorrhage, and cerebral atrophy. A research team member will directly input injury data into the eCRF based on findings in the report.	Yes

Nation	Department	Investigator	Method	Approved
US	University of Virginia	Santini Zanelli	Radiology technicians will conduct all cranial ultrasounds on babies included in the SafeBoosC III trial per usual routine protocol. The Pediatrics radiologists do not perform the scanning and are not involved in the care of trial participants. They read the scans remotely from an office outside the NICU will only have access to images, thus are completely blinded to group allocation. The radiologists will therefore write blinded cranial ultrasound reports and they will be aware of the SafeBoosC III severe brain injury criteria, while writing the report. NICU CRC study staff will once a month review all image descriptions of babies in the trial and enter data on severe brain injury into the eCRF. This will be done in a blinded fashion. The NICU CRC staff member is not involved in the care of babies in the trial on a daily basis and thus, is completely unaware of group allocation.	Yes

Nation	Department	Investigator	Method	Approved