SOP: Tasks for principal investigators

Version	Author(s)	Date	Changes	Approved by
1.0	Johanne Juul Petersen Mathias Lühr Hansen Caroline Kamp	13/11-24	Initial version	Steering Committee
1.1	Johanne Juul Petersen	23/4-25	Screening log deleted as this is now included in eCRF	Caroline Kamp

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Obtain support for participation in SafeBoosC-IIIv from clinical leadership

We encourage all principal investigators to obtain support for participation in the trial from clinical leadership. We believe this will heighten the chances of a successful implementation in the unit.

Sign collaboration agreement

For a local NICU to participate, the sponsor (Copenhagen Trial Unit, Rigshospitalet, Copenhagen) and the participating NICUs' hospital must sign a bilateral collaboration agreement. Since there is no economic support from the sponsor to local NICUs, the agreement will primarily focus on publication and data policy.

The signed collaboration agreement should be held by the sponsor, and a copy should be filed in the local department's Investigator Site File (ISF). A version of the collaboration agreement can be found on www.safeboosc.eu under 'SOPs and templates'.

Complete ISF

The principal investigator is responsible for creating and keeping an ISF that is available for all doctors involved in enrolment and care of infants in the trial. The ISF must contain the following documents:

- Sponsor contact list
- Participant inclusion list
- Parental information sheets
- Consent forms
- SOP: Assessment of primary outcome
- SOP: Blinding of primary outcome or approved local procedure
- SOP: NIRS device and sensor handling
- SOP: Treatment guideline
- Copy of delegation log
- Primary outcome log
- Newest protocol version including amendments
- List of data needed for eCRF entry and where to find them
- Approval from the local research ethics committee
- Any other approvals needed according to local regulations/laws
- Copy of local data monitoring plan
- Copies of local data monitoring reports

- Copy of signed collaboration agreement

All documents needed (except the sites own approvals and contracts) can be found and downloaded at www.safeboosc.eu.

Oversee training of staff members

To heighten the quality of data and patient care, all clinical staff will be offered web-based training. If the principal investigator finds it more feasible, he or she may arrange training in groups or individually, based on the learning and quiz material from the web-based training. The material will be available at www.safeboosc.eu under 'Web-based training'. It is the responsibility of the principal investigators to ensure that all staff members involved in the care of trial participants are properly trained. To oversee and document this process, the principal investigator must create a delegation log. The delegation log includes doctors and nurses involved in the care of trial participants (see 'SOP: Delegation log'). The principal investigator must ensure that these staff members document their training on the delegation log and sign it.

When the web-based training is ready, additional information will be sent out.

Local data monitoring

In the SafeBoosC-IIIv trial, there will be central and local data monitoring based on Good Clinical Practice (GCP) principles. Central monitoring will be done by the sponsor.

Principal investigators will be involved in planning and conducting the local monitoring, including the following tasks:

Find a local monitor person

For the local data monitoring, the principal investigator must find a local monitor person (see 'Local Monitoring Plan' at www.safeboosc.eu). Requirements for the local monitor personare 1) formal GCP training (this could be an online course such as https://globalhealthtrainingcentre.tghn.org/ich-good-clinical-practice/ which takes approximately one hour to complete) and 2) no involvement in the trial (i.e. a doctor or nurse caring for infants in the trial cannot serve as the local monitor person). To minimise costs and optimise the work process, we suggest that an internal employee is appointed as the local monitor person.

The local monitor person will do initiation and monitoring visits. See ‘Local Data Monitoring’ under ‘Monitoring’ at www.safeboosc.eu for more information.

Prepare for initiation and monitoring visits

The principal investigator must prepare the following for the local monitor at initiation and monitoring visits: the ISF including the participant inclusion list and primary outcome log, access to clinical records of infants, and access to the eCRF.

Obtain ethics approval

National coordinators will obtain ethics approval for their own site first and coordinate ethics approval processes in their own country. In some countries, one approval will cover all sites involved in the trial, while in other countries, each site must obtain their own ethics approval.

Parental information sheets, consent forms, and protocol versions required to apply for ethics approval can be found at www.safeboosc.eu.

Choose a local procedure for blinded assessment of hospital-free days

In order to minimise bias in the assessment of the primary outcome, the assessment must be performed by a person who is blinded to group allocation. In the SOP ‘Blinding of the primary outcome assessment’ available at safeboosc.eu under ‘SOPs and templates’, a suggested default method on how to conduct blinded outcome assessment is provided. The suggested method requires that the principal investigator appoints a blinded colleague to conduct the primary outcome assessment.

Principal investigators may choose an alternative blinding method. The chosen method (default or alternative) must be described and sent to the trial manager at caroline.kamp@ctu.dk for approval.

During the local data monitoring initiation visit, the principal investigator must demonstrate the chosen blinding procedure’s feasibility to the local monitor. He or she will document the feasibility in the initiation visit report (see ‘Local data monitoring’ on safeboosc.eu).

Develop a local procedure for enrolment and randomisation

Infants must be enrolled at all times to achieve the goals of the SafeBoosC-IIIv. This normally means that all staff involved in the care of critically ill infants must know how to enrol infants in the trial.

At www.safeboosc.eu under 'SOPs and templates' a description of how to enrol an infant in the trial is available ('SOP: Enrolment and randomisation'). However, since sites may differ in logistic setup, and since a key element may be to identify the staff members that will enrol infants, we encourage the principal investigator to adjust it according to local practicalities.

Furthermore, at www.safeboosc.eu under 'SOPs and templates' you can find the 'SOP: Manual for OpenClinica' which gives a more thorough description of the randomisation process within OpenClinica.

It is important that the 'SOP: Enrolment and randomisation' (or preferably the adjusted local procedure description on enrolment and randomisation) is always available in the ISF, and that clinical staff members responsible for enrolling infants are aware of its existence.

Data entry at end of monitoring and 90 days after randomisation

In step one of the SafeBoosC-IIIv trial, there will be three time-points for eCRF data entry: 1) at consent/randomisation, 2) end of monitoring, and 3) at 90 days after randomisation. If funding is obtained for step two, additional data entry must be made at 2 years of age.

Since the end of monitoring date will vary from infant to infant, it is not possible to send out automatic reminder e-mails of data entry for the 'end of monitoring' module. Thus, the principal investigator must ensure themselves that the end of monitoring module is completed as soon as possible after cerebral oximetry monitoring has been stopped following the index period. At 90 days after randomisation, the principal investigator will receive an email with a reminder to enter data at 90 days in the eCRF. If end of monitoring data has not been completed, this must be done as well. All data needed to complete the eCRF can be found in the clinical records and the primary outcome log.