Local data monitoring module – SafeBoosC-IIIv

What is GCP?
Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. GCP is mandatory for all trials on medicinal products, and some trials on medical devices involving humans.

The purpose of GCP is to ensure that 1) the trial participant's rights, safety, and wellbeing are protected, as consistent with the principles that have their origin in the Declaration of Helsinki, and 2) that the data collected is valid, complete, and well documented.

The formal guidelines are described in International Council for Harmonisation's Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP). For a trial to state, that it is being conducted in line with Good Clinical Practice, it must comply with the principles described there.

GCP monitoring
As part of Good Clinical Practice, central and local trial monitoring must be conducted. The purpose of trial monitoring is to verify that: 1) the rights and well-being of human subjects are protected, 2) the reported trial data are accurate, complete, and verifiable from source documents and 3) the conduct of the trial is in compliance with the current protocol version, Good Clinical Practice guidelines, and any regulatory requirements.

It is the sponsor's responsibility to ensure, that the trial is adequately monitored. The extent of the monitoring is defined in a monitoring plan and should take into consideration the objective, design, complexity, blinding, size, and outcomes of the trial.

Data monitoring in the SafeBoosC-IIIv trial based on ICH-GCP principles
To heighten data quality of SafeBoosC-IIIv, central and local monitoring of the trial will be conducted based on ICH-GCP principles.

Central monitoring
Central monitoring will be conducted by Copenhagen Trial Unit, who will monitor 1) patient recruitment, and 2) quality, completeness, and timeliness of data entry. In case of problems, the principal investigator will be contacted.

Local monitoring
Local monitoring will be conducted by a local monitor assigned by the principal investigator at each site (each neonatal unit that takes part in SafeBoosC-IIIv). The local monitor will perform monitoring according to the monitoring plan. The monitor plan is available at www.safeboosc.eu.

In SafeBoosC-IIIv, the requirements for a local monitor are: 1) GCP training, and 2) no involvement in the trial or in the clinical care of trial participants. The local monitor may be a nurse, doctor, or any other person with adequate scientific and/or clinical knowledge needed to monitor the trial. The person does not need any specific knowledge about the intervention (i.e., NIRS). This training module is specific for local monitoring based on ICH-GCP principles in SafeBoosC-IIIv and is not sufficient GCP training. However, multiple online courses are available for GCP training (e.g., https://globalhealthtrainingcentre.tghn.org/ich-good-clinical-practice/). Certification on GCP training does not have to be documented to the sponsor. The principal investigator must ensure that the local monitor is properly trained.

The local monitoring plan entails an initiation visit and multiple monitoring visits.

Initiation visit
The initiation visit must take place before inclusion of trial participants at the site. Since we will use pragmatic monitoring based on ICH-GCP principles, the local monitor will only check for 1) completion of Investigator Site File, 2) check of delegation log, and 3) demonstration of the blinding procedure for assessment of hospital-free days.

Following the visit, the local monitor must fill out the initiation visit report. A copy must be sent to the sponsor and the original must be kept in the Investigator Site File. Templates can be found on www.safeboosc.eu.

Monitoring visit
The first visit should take place as soon as possible after the first participant has reached 90 days follow-up, in order to ensure that trial procedures were successfully implemented. Further visits should take place after every fifth participant has reached 90-days follow-up or every third month, whichever occurs first, and also after the last participant has completed 90-day follow-up.

The local monitor must have access to the infant's clinical records, the eCRF, the delegation log, primary outcome log, and the participant inclusion list. The monitoring visit includes the following:

Existence of the participants clinical records and consent:

- Existence of each participant's clinical file and documentation of trial inclusion in the participant's clinical file (unless this is not allowed by local regulations).
- Existence of signed and dated consent form (single or both parents as required by local regulations), or if 'opt-out' method is used, documentation in the clinical records of trial participation, that parents have been informed and the parents' response (continuing in the trial or withdrawal). If prior consent is used, the date must not be later than the date of enrollment.

Source verification overall;
The following data entries in the eCRF must be verified against the infant's clinical records and the primary outcome log:

- Group allocation (experimental or control group)
- GA > 28 weeks gestational age at birth
- Survival status at 90 days after randomisation.
- Number of hospital-free days within 90 days of randomisation

In the primary outcome log, data on hospital-free days and survival status are collected through review of clinical records and contact to parents. Information from clinical records will be prioritised for source verification when available, while information from the parents will be used as supporting information, e.g., readmissions at other hospitals, as this information might not be registered in the clinical records. Details on source verification for survival status and hospital-free days will follow on the next pages.

Source verification on survival status:

If clinical records include up-to-date information on survival status (e.g., in countries where clinical records are linked directly to national registries and automatically updated), the local monitor person must verify survival status in the eCRF against mortality status in the clinical records.

If clinical records do not include up-to-date information about survival status, the local monitor person must verify survival status in the eCRF against survival status in the primary outcome log.

It is the principal investigators responsibility to determine whether clinical records include up-to-date information on survival status or not and inform the local monitor person accordingly.

Source verification on hospital-free days:
Data on hospital-free days within 90 days from randomisation are split into three data entry points:

- 'Hospital-free days according to clinical records': Must be verified against the clinical records.
- 'Information from parents on additional hospitalisation not reported in clinical records': Must be verified against the primary outcome log.
- 'Total number of hospital-free days': Must be verified against the primary outcome log.

Check of delegation log:
The local monitor must check the delegation log, i.e. register 1) the total number of clinical staff members on the delegation log, and 2) the number of clinical staff members that have signed the delegation log, documenting that they have been informed on the trial and the web-based training program.

Check of participant inclusion list:
The local monitor must check that all participants on the participant inclusion list are registered with a personal identifier and a study ID, and that study IDs on the patient inclusion list match the study IDs in the eCRF.

Issues for follow-up:
Last, the local monitor must check if issues for follow-up from previous monitoring visits have been resolved and register if there are new issues for follow-up that must be resolved before next monitoring visit.

Monitoring reports:
After each monitoring visit, the local monitor must fill-out a monitoring report. Original reports must be kept in the Investigator Site File and a copy must be sent to the Sponsor.

Local monitoring module
You have now finished the introduction material for local monitoring based on ICH-GCP principles in the SafeBoosC-IIIv trial and are ready for the quiz! The quiz will focus on the specific requirements for local monitoring based on ICH-GCP principles in the SafeBoosC-IIIv trial. We recommend that the principal investigator (PI) and local monitor also take this module. The questions are directed at either the PI or local monitor, but relevant for both.

Learning objectives for the local monitoring module

- Learning objective 1: Decide on required qualifications of a local monitor in the SafeBoosC-IIIv trial
- Learning objective 2: Explain the local monitor's tasks at the initiation visit
- Learning objective 3: Decide when the initiation visit must be conducted
- Learning objective 4: Apply knowledge on the local monitor's tasks at monitoring visits
- Learning objective 5: Apply knowledge on what needs to be prepared for the monitoring visits
- Learning objective 6: Explain why the initiation visit is important
- Learning objective 7: Give reasons why source data verification is important

Questions for the local monitoring module

1. (objective 1)
As PI, you must find a local monitor for the SafeBoosC-IIIv trial in your department. You know three persons interested in this position. Who will be qualified?

1. A nurse working in your department not caring for neonates receiving invasive mechanical ventilation. He is willing to take an online GCP course but is otherwise not involved in SafeBoosC-IIIv.
2. A biologist that you know from tennis practice, who is also working at your hospital. She has previous experience with clinical trials and GCP, but no formal GCP training. However, she is keen to complete this local monitoring module, if this is necessary to function as local monitor.
3. A neonatologist working in a smaller hospital close to yours. He has no experience with NIRS but is familiar with the concept and has read all previous SafeBoosC publications. He has previously been involved in randomised clinical trials as principal investigator but he has no experience with GCP.

Answers

1. Correct. If he is not involved in the trial and is willing to take an online GCP course, he can function as your local monitor.
2. Wrong. Despite being clinically competent and not involved in the trial per se, she does not have the necessary GCP training. This local monitoring module is not considered relevant GCP training.
3. Wrong. This person cannot function as a monitor unless he has formal GCP training.

2. (objective 1)
As principal investigator, you contact a neonatal colleague from the neighbor hospital to find a local monitor. The neighbor hospital is not participating in the trial. What do you tell him?

1. I am looking for a local monitor to perform local monitoring on the SafeBoosC-IIIv trial in my department, but since the local monitor has to be someone with previous experience on NIRS but no involvement in the trial, I am keen to know if a staff member from your department could be interested in this?
2. I need to find a local monitor to perform local monitoring on the SafeBoosC-IIIv trial in my department. The person needs to be trained in GCP and cannot be involved in the trial. Since your department does not participate in the trial, could you think of a colleague that could be interested?
3. I need to find a local monitor to perform local monitoring on the SafeBoosC-IIIv trial in my department, and I am calling you since this person cannot be involved in the trial in any way. Furthermore, there is a requirement of previous GCP training, but this can be solved if the person completes this online training module on local monitoring, developed for the purpose of certifying staff members in GCP.

Answers

1. Wrong. The local monitor does not need to have previous experience with NIRS monitoring, nor does he/she have to be a neonatologist or experienced in neonatology. However, it is correct that the person cannot be involved in the trial. Furthermore, it is also a requirement that the local monitor has GCP training.
2. Correct! The two requirements for a local monitor are 1) prior GCP training and 2) no involvement in the trial
3. Wrong. It is correct that the local monitor cannot be involved in the trial. However, this local monitoring training module developed for SafeBoosC-IIIv is not sufficient GCP training. This module is made for principal investigators and local monitors to inform them on the local monitoring requirements for SafeBoosC-IIIv – not GCP in general. If the person is willing to take an official GCP course (e.g., online), the person could become local monitor in the trial.

3. (objective 2)

At the initiation visit, the local monitor asks you to show her the documents needed to conduct the initiation visit. Which documents do you hand her?

1. The Investigator Site File, including the delegation log and the approved blinding procedure for assessment of hospital-free days.
2. The Investigator Site File, including the delegation log, the approved blinding procedure for assessment of hospital-free days, and curriculum vitaes on all staff members involved in the trial
3. The Investigator Site File is the only document needed. Furthermore, the local monitor must check that you know how to use a NIRS device. You need to demonstrate this for the local monitor.

Answers

1. Correct! The Investigator Site File includes all the relevant information.
2. Wrong. The local monitor should check the Investigator Site File, which includes all the relevant information. Check of curriculum vitae are not part of the local monitoring.
3. Wrong. The local monitor should check the Investigator Site File, which includes all the relevant information. However, the local monitor should not check if the PI knows how to use a NIRS device.

4. (objective 3)

As PI, you have found a local monitor, and you plan to start enrolling patients the 30th of June 2025. The local monitor calls you three months before and asks, when she should come visit you the first time. What do you tell her?

1. She has to conduct an initiation visit before enrolling the first trial participant
2. It is important that she conduct an initiation visit as soon as possible. Without an initiation visit, ethics approval of the trial protocol cannot be granted.
3. She does not need to come until after the first participant have been enrolled and reached 90 days after randomisation. Until then, there is nothing to check and control.

Answers

1. Correct! Participants should not be enrolled before an initiation visit has checked that all the essential preparations have been made.
2. Wrong. Ethics approval of the trial protocol is an essential condition for enrollment and must be documented in the Investigator Site File before the initiation visit. Completion of the initiation visit is not necessary for ethical approval.

3. Wrong. Initiation visit must be conducted before enrollment of the first patient. However, the first monitoring visit should be conducted when the first participant has reached 90 days after randomisation.

5. (objective 4)
At the first monitoring visit, the local monitor asks you as PI which data entries that should be source checked. What is your answer?

1. Group allocation, gestational age, survival status at 90 days after randomisation, and hospital-free days within 90 days of randomisation
2. All data entries in the eCRF must undergo source data verification
3. Death or alive at 90 days after randomisation, serious adverse events, late-onset sepsis, and invasive mechanical ventilation-related infection

Answers

1. Correct! We consider these the most important data points for quality measure.
2. Wrong. Although source data verification is a requirement when following the ICH-GCP guidelines, the coverage is not specified. For the SafeBoosC-IIIv trial, we believe group allocation, gestational age (inclusion criteria), survival status, and hospital-free days are key data, and therefore they will undergo source data verification.
3. Wrong. Although source data verification is a requirement when following the ICH-GCP guidelines, the coverage is not specified. We will perform pragmatic monitoring based on ICH-GCP principles and only source check the most important data.

6. (objective 4)
You are the PI. At the first monitoring visit, the local monitor starts to leave after having checked for existence of clinical file, signed consent and source data verification on all included participants. Has she forgotten anything?

1. She still needs to check the delegation log, patient inclusion list, and document if there are any issues for follow-up.
2. She still needs to check that an approval from ethics committee, local procedure descriptions and Standard Operation Procedures are updated and available from the Investigator Site File.
3. She still needs to check the delegation log and patient inclusion list before leaving.

Answers

1. Correct! Check of delegation log, consistency between patient inclusion list and eCRF, and documentation of issues for follow-up is obligatory at monitoring visits. This is also described in the monitoring plan.
2. Wrong. Check of existence and placement of these documents in the Investigator Site File, is done at the initiation visit and not monitoring visits. No participant can be enrolled before an ethics approval have been seen at the initiation visit.
3. Wrong. It is correct that the delegation log and patient inclusion list must be checked as written in the monitoring plan. However, it is also important to document any issues for follow-up.

7. (objective 5)
The first monitoring visit is tomorrow at noon. Since you will be on call tomorrow from early morning, you need to prepare for the visit now. What should you prepare before the local monitor shows up?

1. Ensure that the local monitor has access to the enrolled infant's clinical records, eCRF, and delegation log.
2. Ensure that the local monitor has access to the enrolled infant's clinical records, eCRFs, and Investigator Site File including the primary outcome log, delegation log and signed consent forms.
3. Ensure that the local monitor has access to the eCRF and Investigator Site File, including the primary outcome log, delegation log and signed consent forms.

Answers

1. Wrong. He/she will also need access to the Investigator Site File, including the primary outcome and the signed consent forms.
2. Correct! The local monitor must have access to the enrolled infant's clinical records, eCRFs, and primary outcome log in order to perform source data verification. Furthermore, the local monitor must also have access to the Investigator Site File to check clinical staff members that have signed the delegation log for being informed on the trial and the web-based training program, and to check for signed consent forms for all enrolled patients.
3. Wrong. He/she will also need access the source of eCRF data – the infants clinical records and primary outcome log, in order to conduct source data verification. It is therefore essential, that the local monitor has access to both the clinical records, eCRF, and primary outcome log.

Question 8 (objective 6)

As part of setting up the trial in your department, you have arranged a meeting with a younger colleague who potentially could assist you. When you present the local data monitoring plan, he asks why an initiation visit is important in a pragmatic trial like the SafeBoosC-IIIv trial. What is you answer?

1. The initiation visit is important, since it ensures that the site investigator has prepared the study well, that the site's operational procedure documents are in place, that all required permissions have been obtained, and that trial-specific training has been made available to staff that will be involved
2. The initiation visit is important, since it ensures that the first participants have been included correctly and that data is accurate.
3. The initiation visit is important, since this is a large multicenter trial with enhanced need to ensure unified trial practice across all units

Answers

1. Correct. By checking the Investigator Site File for existence of all essential documents such as the delegation log, SOP's and procedure descriptions, it helps ensuring that the organisation is in place and thereby enabling accurate data as well as safe and ethical conduct of the trial.
2. Wrong. No participants are allowed to be enrolled before the initiation visit has been conducted. It is during the monitoring visits, that data is checked against the sources. The initiation visit is important to ensure that the site investigator has prepared the study well, that the site's operational procedure documents are in place, that all required documents have been obtained, and that training has been made available to staff that will be involved
3. Wrong. Initiation visits are important to ensure that each department complies with the predefined trial practice as defined by the Sponsor, and the importance is not dependent on the number of departments participating.

Question 9 (objective 7)

As part of setting up the trial in your department, you have arranged a meeting with a younger colleague who potentially could assist you. When you present the local monitoring plan, he asks why source data verification is important in a pragmatic trial like the SafeBoosC-IIIv trial. What is you answer?

1. Source data verification is important to ensure that the data collected are reliable and ensures the possibility of reconstructing the trial later on (it entails that an independent observer reconfirms data)
2. Source data verification is important to ensure that all required approvals for performing the trial in the respective department is obtained
3. Source data verification is only important, if multiple persons enter data into the eCRF during the trial

Answers

1. Correct. The main objective of source data verification is to confirm, that the information collected during the trial is complete, reliable and verifiable. It is essential to provide confidence when reporting the results of the trial.
2. Wrong. Source data verification checks data entries into the eCRF compared to what is documented in the source – for SafeBoosc-IIIv, that is the clinical records and primary outcome log. Approvals are checked at the initiation visit.
3. Wrong. Source data verification checks for errors and inconsistencies between what is documented in the eCRF, in the clinical records, and primary outcome log. Errors can happen, even when a few people fill the eCRF.

Question 10 (objective 4)

As local monitor, you are at the first monitoring visit. How should you handle source data verification of the primary outcome 'Number of hospital-free days within 90 days of randomisation'?

1. You call the parents and check the clinical records to verify the data entered in the eCRF.
2. You solely use the primary outcome log to verify the data entered in the eCRF.
3. You use the clinical records to verify the 'hospital-free days according to clinical records' entered in the primary outcome log. You then use the 'information from parents on additional hospitalisation not reported in clinical records' and 'total number of hospital-free days' in the primary outcome log to verify the data entered in the eCRF. You use clinical records to verify survival status if these include up-to-date information—otherwise, you use the primary outcome log.

Answers

4. Wrong. You should not call the parents to verify the primary outcome data. Instead, you should use the primary outcome log and clinical records to verify data in the eCRF.
5. Wrong. You should use both the primary outcome log and clinical records to verify the primary outcome data entered in the eCRF.
6. Correct. You should use the primary outcome log and clinical records to verify the data entered in the eCRF.