Central monitoring plan - SafeBoosC III

Version	Author(s)	Date	Changes	Approved by
1.0	Mathias Lühr Hansen Gorm Greisen Janus Christian Jakobsen Christian Gluud	25-nov 2019	Initial version	SafeBoosC III Steering Committee
2.0	Mathias Lühr Hansen Markus Harboe Olsen Gorm Greisen Janus Christian Jakobsen Christian Gluud	26-aug 2020	• Description of missing data part • Addition of quality deficiencies, noteworthy data deviation and Mahalanobis analysis	SafeBoosC III Steering Committee

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Table of content

Purpose

The purpose of the central monitoring plan is to identify centres with 1) missing data, and 2) centres with predefined quality deficiencies or noteworthy data deviations. We will identify data which are worth inquiring through visual inspection of the data. Then we will use the Mahalanobis distance (a measure of the distance between a data point P and a distribution D, introduced by P. C. Mahalanobis in 1936. It is a multi-dimensional generalisation of the idea of measuring how many standard deviations away P is from the mean of D) as an exploratory analysis to identify the most statistical outlying centres, when comparing data from each centre to data from all centres. The purpose of the central monitoring is not safety monitoring, as this is a task for the Data Safety and Monitoring Committee.

As monitoring of missing data will be done once a month, while the additional monitoring will be done every third month, this central monitoring plan will be divided into two parts; 1) missing data monitoring, and 2) monitoring of quality deficiencies, noteworthy data deviations as well as exploratory analysis using Mahalanobis distance.

A step-by-step overview of the central monitoring process can be found in **Appendix 1.**

Part 1

Missing data

The first part of the central monitoring will focus on identifying centres with missing data entries.

For each centre we will calculate 'data form completion', meaning the proportion of each type of data form that are timely completed. 'Data form completion' will be defined as all data forms completed before the relative data entry deadline (a) over all data forms that should have been completed (b) and reported in percentage

$$\text{Data form completion} = a/b * 100\%$$

Each participant included in the trial has five data forms:

1. Randomisation form (data entry deadline at six hours from birth)
2. End-of-monitoring form (data entry deadline at 72 hrs of age + 7 days)
3. Severe adverse reactions form (data entry deadline at 72 hrs of age + 7 days)
4. Follow-up form (data entry deadline at 36 weeks PMA + four weeks)
5. Blinded follow-up form (data entry deadline at 36 weeks PMA + four weeks)

The randomisation form will always be completed, since it is not possible to randomise a participant without a completed randomisation form. Thus, the randomisation form is not relevant in terms of monitoring missing data.

We will therefore only calculate 'data form completion' for the following forms: 1) End-of-monitoring form, 2) Severe adverse reactions form, 3) Follow-up form, 4) blinded follow-up form

To complete a data form, the investigator must 1) perform all data entries and 2) press "submit". If a data form has *not* been completed within the data entry deadline, it will be classified as missing data.

An *example of how* 'data form completion' may be calculated can be found in the supplementary material (**Supplemental figure 1**).

We will also identify the study ID for participants with missing data including which data forms that are incomplete and have exceeded the data entry deadline.

Course of action regarding missing data

Once a month, data extraction on missing data entries will be generated from the eCRF. Data form completion will be calculated and reported for each centre in a 'data completion report'. The report will be assessed and approved by the monitoring group. Following approval, the report will be circulated to all investigators and uploaded to 'safeboosc.eu'. The identified study IDs for participants with missing data will not be included in the report. However, the trial manager will use this information to contact investigators from centres with missing data and inform them of the study IDs of participants with missing data, including the specific data form that have missing data. As there will be zero tolerance to missing data entries, the investigators will be requested to fill-out the missing data entries as soon as possible. Missing data monitoring will start after 100 babies have been randomised. An example of how these data are presented in the data completion report, can be found in the supplementary material (**Supplemental figure 2**).

Part 2

Quality deficiencies

We will aim at identifying centres with prespecified quality deficiencies as defined below:

1. Proportion of participants without an early and a late cranial ultrasound scan (including only participants alive after 35 days of life)
2. Late initiation of cerebral oximetry monitoring (0-6 hours from birth)
3. Proportion of participants where cerebral oximetry was stopped prematurely (including only participants alive after 72 hours of life)
4. Proportion of participants where consent was withdrawn or declined by the parents
5. Proportion of participants with a severe brain injury but no cranial ultrasound scan
6. Proportion of participants with post-haemorrhagic ventricular dilatation or cerebral atrophy but no late cranial ultrasound scan
7. Proportion of participants in the control group that underwent unblinded cerebral oximetry monitoring

Noteworthy data deviations

We will aim at identifying centres with noteworthy data deviations. Any noteworthy data deviations will be defined as 1) outliers due to suspected random errors in data entries or insufficient validation ranges in the eCRF (suspected outliers); 2) suspected systematic errors in data entries due to misunderstandings (suspected misunderstandings); or 3) potentially fabricated data (suspected fabricated data).

Suspected outliers

Suspected outliers of the eCRF are defined as outlying observations for continuous data points in the monitoring data report, identified by visual inspection. An example of this could be a high randomisation age in minutes, e.g. 1200 minutes. This should be impossible since all babies must be randomised within six hours of life (360 minutes). If such a data entry was identified in the data monitoring report, it would be marked as a suspected outlier.

Suspected misunderstandings

Suspected misunderstandings will be defined as any unexpected differences in the distribution of data among centres, that may represent differences in coding practice or misinterpretation of the eCRF or even the overall study design. An example of this could be a local misunderstanding of the definition of a trial outcome, e.g. diagnosing the outcome by different criteria than described in the study protocol. In such a situation, we would expect an abnormally high or low frequency of the event for binary data, or a shift/abnormally large variability in the data distribution for a continuous outcome, in the centre where the misunderstanding occurred (1).

Suspected fabricated data

Suspected fabricated data will be defined as an unexpected distribution or variance in data of each centre, that may represent fabricated data. For continuous data, we would expect to see a different shape or distribution of data when data is graphically illustrated, since natural variance is difficult to fabricate (2). An example of this could be a unexpected narrow or wide distribution of birth weights in a specific centreAn unexpectedly large or small prevalence of a binary data point can also be a sign of data fabrication, but it is also likely that this could be due a misunderstanding (see suspected misunderstandings below).

Course of action regarding quality deficiencies and noteworthy data deviations

Every third month, a data report focusing on quality deficiencies and noteworthy data deviations, will be generated automatically after extraction of data from the eCRF (**Appendix 2**). We will only include data from centres with more than ten included participants, and for every variable a minimum of five participants must be added to be presented. This is to ensure some degree of anonymisation and due to the fact that data assessment is difficult in very small samples. Centre IDs will be blinded under a new name in the report, based on a seed generated by the absolute time of the computer.

The data report will be assessed and results from the monitoring will be logged in a ‘central monitoring log’ by the monitoring group.

Quality deficiencies

If a centre is having a high number or proportion of the prespecified quality deficiencies, this will be reported in the central monitoring log as illustrated in the supplementary material (**Supplemental figure 3)**. The local principal investigator will be contacted for an elaboration and to discuss how to improve, which will also be reported in the log (**Supplemental figure 3**).

Noteworthy data deviations

Every variable will be assessed by the central monitoring group and the following course of action will be used:

1. Is there a centre with noteworthy data as per the previous definitions? [Yes] / [No]
2. If yes, which suspicion has been raised? [Describe]
3. Will any course of action be taken? [Yes] / [No]
4. If yes, the trial manager will contact the principal investigator and take the relevant course of action
5. Results of the course of action will be noted

All decisions, including course of action, will be reported in the central monitoring log as depicted in the supplementary material (**Supplemental figure 4)**.

Exploratory analysis using Mahalanobis distance

A Mahalanobis distance is a parameter of a statistical model which allows for identification of statistical outliers in a multivariate space (3). The distance is a measure (in the unit of standard deviations) of how far a single point is from the multivariate average in the multidimensional space (3). The definition of an outlier varies, depending on the purpose of the analysis. Some define an absolute distance (e.g. 2 SD) before a measurement is an outlier, while some work with other cut-offs depending on the sample size. We will calculate the Mahalanobis distance for each site from the global average. Sites with data from less than 10 participants are not included for this analysis (2)(4). For every site, participants will be randomly re-sampled (Monte Carlo procedure) and the mean for continuous values and proportion for binary features will be calculated. Every centre will then be compared using a multivariable Mahalanobis analysis. This re-sampling and calculation will be repeated 10,000 times to provide robust standard deviations.

Course of action regarding the exploratory analysis using Mahalanobis distance

Outlying centres, defined as a Mahalanobis distance +/- 2 SD, will be identified and registered in the central monitoring log. The centre IDs will then be unblinded and the monitor group will review the data report in order to try an identify the reasons as to why these centres are statistically outlying. Once the potential reasons have been identified, it will be written in the central monitoring log. For an example of this, see the

supplementary material (**Supplemental figure 5**). It will also be written whether these findings have already been identified and written in the log and whether any course of action will be taken, as illustrated in the supplementary material (**Supplemental figure 5)**.

Final report

Once the central monitoring log has been approved and a summary has been written, a conversion key will be sent to the trial manager for re-identification of centres, in order to contact relevant principal investigators. Once the trial manager has been in touch with all relevant investigators, the report will be revised, and the central monitoring log will be updated as needed.

A short version of the final report will be uploaded to safeboosc.eu.

Supplementary material

Figure 1.

Example of centre data completion calculation

Centre ID01 started randomising 1/10 2019, and the first included participant (IB01001) was born 2/10 2019, gestational age 27+0 and randomised to the experimental group. The date is now 14/10 2019 and the status in OpenClinica is this:

As for now, only one participant (ID01001) has been randomised at site ID01.

Green means that data entry is completed, yellow that it has begun (but not completed), and blue that it has not begun yet. Let us do a manual data form completion calculation for each type of data forms: first we need to establish which dates the different forms should be completed, based on the above information on data entry deadlines. As stated above, the randomisation form is not relevant.

- End-of-monitoring form: 12/10 2019 (completed)
- Severe adverse reaction form:12/10 2019 (not begun, data entry deadline has been exceeded)
- Follow-up form: 1/1 2020 (begun, data entry deadline has not been exceeded)
- Blinded follow-up form: 1/10 2020 (not begun, data entry deadline has not been exceeded)

This means that, when calculating data form completions on the 14/10 2019 for this centre, only the end-of monitoring form and severe adverse reaction form should be taken into consideration. Thus, data form completion is 100% for the End-of-monitoring form (one form expected completed and one completed) and 0% for the Serious Adverse reaction form (one form expected completed and none completed).

If there had been more participants included at centre ID01, they should also have been included in the calculation.

Example

If four participants have been randomised to the experimental group and three of them have completed all four data forms within the data entry deadline, but the fourth participant has exceeded data entry deadline for all four data forms, the data form completion would be 75% for all four data forms:

- End-of-monitoring form: 3/4 = 75% (three forms completed out of four forms)
- Serious Adverse Reactions form: 3/4 = 75% (three forms completed out of four forms)
- Follow-up form: 3/4 = 75% (three forms completed out of four forms)
- Blinded follow-up form: 3/4 = 75% (three forms completed out of four forms)

Figure 2.

Example of data completion report

Completion of data entries

Below you will find an overview of data entries across all centres.

Site	Randomisations up until 19-May	End-of-monitoring (72 hrs) % completed	Follow-up (36 weeks) % completed	Blinded follow-up (brain ultrasound) % completed
CH01 University Hospital Zürich	7	100%	100%	100%
CH 03 Univ. Hospital Lucern	8	80%	n/a	n/a
CN02 Children's Hospital, Fudan	4	100%	n/a	n/a
CZ01 The Institute for the Care of Mother and Child	15	100%	100%	92%
DK01 Rigshospitalet	44	100%	100%	100%
DK30 Odense Univ. Hosp.	1	0%	n/a	n/a
Total	247	97%	98%	93%

Figure 3.

Example of quality deficiency assessment in the central monitoring report

Quality deficiency	Blinded site ID	Comment on the issue	Will any course of action be taken?	Unblinded site ID	Summary of course of action
Age in full hours when cerebral oximetry was started	SC	High median time to initiate NIRS monitoring as compared to additional sites	Yes	DK01	Investigator was contacted and elaborated that the process of getting signatures from parents often delayed randomisation and initiation of NIRS. This will be discussed among staff in DK01 in order to optimise this process

Figure 4.

Example of noteworthy data deviation assessment in the central monitoring report.

Variable	Blinded site ID	Which suspicion has been raised?	Will any course of action be taken?	Unblinded site ID	Summary of course of action
Retinopathy of prematurity	PA	Suspected misunderstanding due to high incidence as compared to additional sites	Yes	ES01	Investigator elaborates that data entries are correct and according to local guidelines, no corrections
Rand age in minutes	iG	Suspected outlier since randomisation age for TR04002 was 800 minutes	Yes	TR04	Investigator elaborates that this is a typing error due to insufficient validation. Now corrected in eCRF

Figure 5.

Central monitoring log for statistical outlier identification by Mahalanobis distance

Blinded site ID	Mahalanobis standard deviation	Identified outliers	Already mentioned in the central monitoring log?	Will any course of action be taken?	Unblinded site ID	Summary of course of action
PW	+2.31	1. High gestational age 2. High birthweight 3. High rate of exploratory outcomes	Yes	No	ES01	n/a

Appendix 1

Step-by-step overview of the central monitoring process

Once a month

1. Missing data identification, reporting and contact to principal investigators

Every third month

2. Quality deficiencies identification, reporting and decision on contacting principal investigators
3. Noteworthy data deviation identification, reporting and decision on contacting principal investigators
    a. Suspected outliers
    b. Suspected misunderstandings
    c. Suspected fabrications
4. Exploratory Mahalanobis distance analysis
    a. Identification and reporting of the most statistical outlying centres (if any)
    b. Comparison of statistical outlying centres with the central monitoring log where centres are identified by visual inspection
5. Decision on contacting principal investigators of outlying centres (identified by Mahalanobis)

Appendix 2

List of data points from the eCRF used in the central monitoring report

- Time for cranial ultrasound early/late/both/none
- Age when cerebral oximetry was started
- Premature stop of NIRS monitoring
- Continued or declined consent
- Intraventricular haemorrhage grade 3 or 4 yes/no
- Cystic periventricular leukomalacia yes/no
- Post-haemorrhagic ventricular dilatation yes/no
- Cerebellar haemorrhage yes/no
- Cerebral atrophy yes/no
- Randomisation age in minutes
- Singleton compared to multiple births
- Gestational age at randomisation (above or below 26 weeks PMA)
- Gestational age in weeks
- Birthweight in grams
- Apgar score after one minute 0-10
- Apgar score after five minutes 0-10
- Sex male/female
- Management change due to cerebral hypoxia yes/no
- NIRS in the control group yes/no
- NIRS data available for clinical staff yes/no
- Cardiovascular support within 72 hours yes/no
- Surfactant administration yes/no
- Days of mechanical ventilation
- Last registered weight of the infant
- Mechanical ventilation yes/no
- Death before discharge or 36 weeks PMA yes/no
- Treatment for patent ductus arteriosus yes/no
- Necrotising enterocolitis yes/no
- Late onset sepsis yes/no
- Bronchopulmonary dysplasia yes/no
- Major congenital anomaly yes/no
- Retinopathy of prematurity yes/no

References

1. Venet D, Doffagne E, Burzykowski T, Beckers F, Tellier Y, Genevois-Marlin E, et al. A statistical approach to central monitoring of data quality in clinical trials. Clin Trials. 2012;9:705–13.
2. Kirkwood AA, Cox T, Hackshaw A. Application of methods for central statistical monitoring in clinical trials. Clin Trials J Soc Clin Trials. 2013;10:783–806.
3. De Maesschalck R, Jouan-Rimbaud D, Massart DL. The Mahalanobis distance. Chemom Intell Lab Syst. 2000;50:1–18.
4. Mason RL, Young JC. Multivariate Statistical Process Control with Industrial Applications. ASA-SIAM Series on Statistics and Applied Mathematics. Society for Industrial and Applied Mathematics; 2002. 281 p.