

Monitoring plan

Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU)
A randomised, blinded, placebo-controlled trial.

The trial's EudraCT-number: 2017-003829-15

The monitoring plan's requisite

This monitoring plan is constructed on the grounds of protocol version 4.0, 4th of March 2018 and risk assessment of the trial cf. the GCP units' SOP I02 Monitoring plan.

The monitoring plan's extent

This monitoring plan describes the monitoring that is performed by the external monitor (GCP unit or other authorized party).

It may be necessary to perform further quality assurance/quality control, which ought to be described and documented by sponsor.

Monitoring visit

Initiation is done in every centre. When the prerequisites for inclusion of subjects in the centre is met, it will be documented by the monitor through a written approval to start the trial.

First monitoring visit in every centre is planned immediately after inclusion of the first subject.

The monitor will hereafter perform monitoring visits in every centre taking into account the agreed extent of the monitoring, inclusion speed and the need of the centre. The monitoring frequency is expected to be higher during the inclusion period. As a minimum, the monitor will be in contact with every centre yearly.

The monitoring is finished on the centres when every subject has gone through 90 days follow up and data is registered in the eCRF.

Final monitoring visit at sponsor is performed when completion of the trial is reported to the authorities.

Monitoring of Trial Master File

Relevant documents in the Trial Master file will be checked continuously, however at least yearly.

It is continuously checked that the data is kept out of reach of unauthorized persons and without risk of change or loss.

Monitoring of general protocol compliance and data quality

To verify that the centre has implemented procedures that ensure good compliance with the protocol, it is checked that protocol-specific investigations, analyses and procedures are performed as specified in the protocol.

To verify that the centre has implemented procedures that ensure good data quality, it is checked that all data is properly registered in the CRF. In addition, it is checked that the CRF is fully completed and that corrections are correctly performed according to GCP.

The above is done for the first 3 included subjects at each centre and after this for randomly selected subjects totalling approx. 10% checked.

Since there is no quality related value in monitoring all "Day forms" for patients with a long-term ITA admission, data is only monitored for the first 4 days of inclusion in "Day forms" (however, SARs will be checked in all day forms). Remaining CRF pages are fully monitored for the first 3 patients and randomly selected totalling 10% checked.

Monitoring of informed consent

For all subjects it is checked

- That consent of all necessary parties has been obtained according to national guidelines
- That attempt to obtain possible missing consent is properly recorded in patient file or otherwise documented e.g. in consent log
- That there is not performed protocol-specific actions before informed consent is available
- That informed consent is obtained from persons delegated and trained for this
- That the submission of oral and written information and consent is properly recorded in the patient file

Monitoring of selected trial data

Based on the risk assessment of the trial, the following monitoring strategy has been chosen.

See also Appendix 1, *Data Verification Plan*.

Inclusion, exit and end

For all subjects it is checked

- That the inclusion of subjects is done by persons delegated and trained to do so
- That inclusion and termination of the trial are correctly recorded
- All inclusion and exclusion criteria
- That the patients withdrawn from the trial meet one of the withdrawal criteria and that it is properly recorded and correctly registered in the eCRF.

For the first 3 subjects included in each centre and then randomly selected subjects totalling approx. 10% it is checked

- That meeting withdrawal criteria during admission in the ICU (patient consent is withdrawn, unacceptable side effects to trial medication, SAR/ SUSAR, QTc prolongation, comatose due to trial medicine) has resulted in the withdrawal from the trial. This is done by reviewing the patient file.

Primary efficacy parameters

For all subjects the following is checked

- The primary efficacy parameter (90-day survival and hospitalization) by consulting the electronic patient file

Examinations

No protocol-specific examinations are performed in this trial.

Safety management

Events and side effects

- SDV and checking whether the trial medication has been paused are performed in patients with 'yes' to SAR in the CRF. Thereafter only data collection may be made if permission has been given. This is done for all day forms from inclusion to 24 hours after the last administration or discharge from ICU, in order to check whether registration and reporting of SAR is complete and timely

transferred to the CRF.

- For sponsor's centre: It is checked that all SAR's and SUSAR's have been reported timely to the Danish Medicines Agency and the Scientific Ethics Committee and subsequently to investigators.

Sponsor's monitoring

The coordinating GCP coordinator will check at the sponsor's centre, that sponsor documents the following monitoring:

Queries from monitor

Monitor creates queries if potential errors are found in data in the eCRF. Queries from monitor are handled by the centres in question. Sponsors must ensure that the centres correct relevant queries themselves.

Delirium score

An overview is created in eCRF (site overview) where sponsor will monitor whether there are day forms with incomplete delirium scores, either morning or evening (D3a and D4a). Each site is reviewed by the sponsor's centre, who will contact the centre in question if the delirium score is not filled in.

Trial medication

Ensuring proper use of trial medicine: If the patient is delirium positive (yes in D3a or D4a) and the trial medicine has not been delivered (no in D6), an email will be sent to the coordinating team who will react within a week.

Ensuring proper use of escape medicine: If the patient has not received a trial medicine (no in D6) but has received escape medicine (yes in D7), an email will be sent to the coordinating team who will react within a week.

Ensuring the correct dosage of trial medicine: If the patient has received trial medicine (yes in D6) but has not received any of the fixed doses (D6b, c and d), an email will be sent to the coordinating team who will react within a week.

Monitoring in the department

Trial medication

- It is checked at the initiation visit that the storage of the trial medicine is correct.
- It is checked at the initiation visit as well as continuously that the delivery is properly documented and handled by persons delegated to do so.

Entry into force

This monitoring plan will take effect from the date of sponsor's acceptance of the monitoring plan.

Evaluation of the monitor log

The monitoring plan will be evaluated on a continuous basis and also in case of observed need.

If it by the GCP monitoring, central monitoring or audit is observed, that the prerequisites for this monitoring plan have changed, it will result in evaluation and possible revision of the monitoring plan. This may be conditions such as change in the protocol, significant non-compliance, insufficient data quality and significant changes in project staff composition.

All changes of the monitoring plan will be in writing

19-06-2018



Date

Sponsor, Lone Musaeus Poulsen