Supplemental file 5: Audit frequency and procedures

Monitoring frequency

Visit no.	Selected Sites	Planning*
Initiation Visit	All	Before enrolment of the first subject, but after Ethics Committee and Board of Deans approval has been obtained.
First Monitoring Visit A	All participating sites	After 2 - 3 randomised subjects, irrespective of (e)CRF completion.
First Monitoring Visit B	All 10 NICUs	Only if not including subjects so when Visit A has not been performed. After 5 - 6 randomised subjects have completed the 6 month visit, irrespective of (e)CRF completion.
Remote Visit	All sites	Contact via telephone or email approximately 12 weeks after the First Monitoring Visit A or B
Second Monitoring Visit	5 high recruiting sites	After all subjects have been randomised, the 5 sites who have randomised the most subjects
Remote Visit	All 5 high recruiting sites	Contact via telephone or email approximately 12 weeks after the Second Monitoring Visit
Remote Close Out	All sites	After database lock
TMF check in combinations with check on 6 months FU data if possible	Sponsor site	In 2019 and 2022

*The frequency may be changed based on the total enrolment period, the inclusion rate, quality issues and/ or site performance, but only after consultation with the Coordinating PI.

Monitoring procedures
The follow items will be discussed/ verified by the Clinical Research Associate (CRA) during the different visits.

First Monitoring Visit
- Who is/ are the contact person(s) at site

- Is the entire investigators' study staff adequately informed about the study e.g. randomisation procedure, sample collection, procedures in case of protocol deviations/ serious breaches, SAE notification procedures etc.
- Is the entire investigators' study staff WMO/GCP trained and authorized (site signature and delegation log)
- Has the study staff sufficient time to perform the study?
- How and by whom is the subject informed about the study?
- By whom is consent obtained and is it properly documented?
- Who will examine the subject every visit?
- Who performs the screening, baseline and other visits/ how is this arranged?
- Which source documents are available?
- Source Data Review
- Source Data Verification
- Where is the source data stored?
- Who will maintain the subject identification code list/ screening log/ enrolment log?
- Who is completing the (e)CRF?
- When/ how/ where and by who are questionnaires filled in?
- Which facilities are used (any changes)?
- Which equipment is used (any changes)?
- Have any Serious Adverse Events (SAEs) occurred?
- Reporting of SAE's
- Are there any known protocol deviations and/ or serious breaches of ICH-GCP and/ or protocol?
- Is the Trial Master File/ Investigator Site File up to date (AMC SOP CTR 006/ ICH-GCP guideline 8.1 – 8.3)?
- What is the expected recruitment rate?
- Competitive studies running?
- Informed consent process, use of Patient Information Form and Informed Consent form
- In- and exclusion criteria

Remote Visits

- Discuss progress of follow-up of action items
- Is the enrolment overview up to date (amount screened subjects, amount of screen failures/withdrawn subjects, amount of randomised/enrolled subjects, amount of active subjects, amount of subjects in follow-up and amount of subjects that have completed the trial)?.
- Are there any changes in the investigators' study staff (trained and authorized)?
- Are there any changes in facilities or equipment?
- Have any SAEs been reported since previous on-site monitor visit?
- Are there any known protocol deviations and/or serious breaches of ICH-GCP and/or protocol?

Ongoing Monitoring Visits

- Is the entire investigators' study staff adequately informed about the study?

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- Is the entire investigators' study staff WMO/GCP trained and authorized (site signature and delegation log)
- Are there any changes in the investigators' study staff (trained and authorized)?
- Are there any changes in facilities or equipment?
- Is the investigational medicinal product accountability properly documented?
- Have any SAEs occurred?
- Are there any known protocol deviations and/or serious breaches of ICH-GCP and/or protocol?
- Is the Trial Master File/ Investigator Site File up to date (AMC SOP CTR 006/ICH-GCP guideline 8.1 – 8.3)?
- Are there any new amendments in place?

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