MACE-ICH – Working Practice Document

Title: Site Monitoring, No. 004

1. Introduction

The Nottingham Coordinating Centre is responsible for monitoring MACE-ICH trial sites. The monitoring requirements for this trial are set out in this working practice document, as well as in the sponsor monitoring plan document (template TAFR00202), entitled 22SR001 Monitoring Plan.

The Trial Manager, or where required, a nominated designee of the Sponsor, (referred to as the monitor throughout the WPD) shall carry out monitoring of trial data at site at least once during the period of the study, unless issues are highlighted warranting a further visit (see section 10). It is the responsibility of the monitor to check and report on the trial conduct, the trial documentation, and ensure that procedures have been followed in accordance with the protocol, GCP and with the applicable regulatory requirements.

The monitor will not be visiting sites for the majority of site monitoring visits (SMV), monitoring will be conducted remotely (the details of which are explained in this WPD). The expectation is that sites will complete the monitoring documents, which will be signed off by the PI and returned to the coordinating centre for review. A face-to-face visit may be triggered if there are ongoing concerns about a site despite remedies being suggested to resolve issues.

Evidence of monitoring will be made available for inspection by the regulatory authority as required.

2. Aims

The purpose of the SMV is to assess each recruiting site by examining the source data in order to:

- Verify that the site has all necessary approvals in place in order to conduct the trial and that no participants were recruited before these were in place.
- Ensure that valid consent has been obtained in line with the protocol and a copy of the correct version of the form is present in the patient file and medical records.
- Ensure compliance with the trial protocol and the EU Clinical Trials Directive.
- Check version control of all master documents held in the Investigator Site File (ISF).
- Confirm key eligibility criteria for a selection of recruited patients.
- Confirm that clinical data matches source documentation and electronic data.
- Confirm administration of the trial intervention.
- Check that the IMP is stored appropriately and accounted for.
- Ensure that the site is meeting its responsibility for the maintenance of the ISF.
- Confirm all records have been entered correctly on the trial database.
- Check the responsibility (delegation) log, training records, CVs and GCPs of all investigators and ensure that these are kept up-to-date.

- Determine whether serious adverse events have been appropriately reported and verified within the applicable regulatory requirements.

3. Prior to arranging the SMV

The monitor will check whether any of the following are outstanding prior to the SMV:

- Data – the monitor will check that data entry is complete and up-to-date, and any data queries have been resolved
- Randomisation paperwork – the monitor will review the uploaded documentation for each participant and ensure that all the necessary documentation has been uploaded to the secure vault (e.g., consent form, contact details, device accountability logs).

If any of the above is missing, the monitor will include this in the email to site when arranging the SMV for it to be resolved before the return of the monitoring documentation.

4. Arranging the SMV

An SMV will be triggered once the site has recruited its first two patients or once 2 months have elapsed since the site is issued greenlight, whichever is sooner; with data complete up to and including the discharge/death CRF. There is no fixed frequency for additional monitoring, this will depend on factors such as recruitment and data entry, and will be reviewed on a site-by-site basis. An additional monitoring visit will however be conducted after every 5 participants recruited or after 12 months, whichever is sooner.

Sites will be notified of the remote SMV via an email sent to the main research contact and principle investigator. This correspondence will inform the site about what they need to do to undertake the remote SMV.

The first two recruited participants will be monitored at the initial SMV. For any further visits, a random subset of trial participants will be created from the trial database, and these participants will be monitored during the SMV.

5. Monitoring of Investigator Site File (ISF)

The ISF should contain the necessary essential documentation for the conduct of the trial. These documents serve to demonstrate that the investigator and the sponsor are compliant with the standards of ICH-GCP and other regulatory requirements. When the SMV is arranged, sites will be provided with an ISF checklist (see appendix 1 for an example checklist – the most up to date version will be sent to sites in advance of the SMV) which contains all the necessary documentation that should be filed in the ISF.

Any trial documentation not stored in the ISF must be referenced using a file note explaining its location and stored in the relevant area of the ISF. This should be documented when sites complete the ISF checklist.

6. Monitoring of Patient Notes

When the SMV is arranged, sites will be provided with a patient file checklist (see appendix 2 for an example checklist – the most up to date version will be sent to sites in advance of the SMV) for each patient that is selected to be monitored. The purpose of this is to validate the information provided in the eCRFs with the source data from the medical notes. Examples of documents to be checked are outlined below:

Participant Trial File

- Participant/relative information sheet (PIS/RIS)
- Scan reports
- Blood test results
- All documents stored in the participant trial file must be correctly anonymised; with trial ID (e.g. C01 / 001)

Medical Records

- Written entry of participant/relative's consent and version of consent used
- Written entry of patient being recruited into the MACE-ICH trial including an alert in the medical record detailing the R&I reference of the trial, the IRAS number, the abbreviated title, and the Chief Investigator (CI) and PI contact details
- Presence of sticker requiring retention of medical notes until 25 years post date of issue of the final study report (or digital records similarly 'flagged' for retention)
- Presence of the relevant information sheets, signed consent form(s) and trial-specific GP letter

7. After the SMV

Once the site has completed the ISF and patient file checklists, they should be signed and dated by the site representative who undertook the monitoring and the principle investigator. The documents should then be returned to the coordinating centre (mace-ich@nottingham.ac.uk) where they will be reviewed by the monitor. The monitor will issue a monitoring letter and action list to the site's principle investigator and site representative.

Once the actions have been marked as resolved by the site team, the completed action list should be returned to the coordinating centre. The site monitoring visit log should also be completed by the site and monitor. The monitor should confirm the SMV is complete by sending an email to the site attaching the fully signed and completed documentation, which should be filed in the ISF.

The sponsor should be notified of the outcome of the SMV.

8. Ongoing Trial Monitoring

As part of the ongoing monitoring throughout the duration of the trial, the following paperwork should be uploaded to the secure vault when a patient is recruited to the trial, to be reviewed by the coordinating centre:

- Consent form/s

- Participant contact details (for follow-up)
- Drug chart/s
- Blood test results
- Baseline scan report
- Follow-up scan report (day 5±2)
- Participant-specific file notes as required

For more information on the secure vault upload process and the scan data upload process, please see WPD 001 Secure Vault Uploads.

The following should be uploaded to the trial database:

- Scans: baseline and day 5±2

For more information on uploading scans to the database, please see WPD 002 Uploading Scans.

Sites should also send anonymised participant screening logs (TAFR01501) to the coordinating centre on a monthly basis. See WPD 005 Screening and Enrolment Logs for more information.

Ongoing monitoring also includes the reporting of adverse events – the details of what qualifies as different types of adverse events can be found in the trial protocol.

Central monitoring of the trial database is also carried out by the coordinating centre, with checks of the data for unusual patterns, irregularities and anomalies.

9. Triggered Monitoring Visits

The coordinating centre will conduct a monitoring visit at least once during the period of the study unless issues are highlighted warranting a further visit. A triggered monitoring visit may be performed on request by the Trial Management Group (TMG), or where concerns have been raised during a central monitoring review or following a routine monitoring visit that has identified specific concerns requiring further investigation.

On-site monitoring visit triggers include (but are not limited to):

- A high frequency of protocol queries from site staff
- A high level of findings through central monitoring oversight
- A high level of findings during a previous monitoring visit
- A high number of protocol deviations
- Poor conversion rate from screening to randomisation (low recruiting/no recruitment)
- Low or high SAE reporting rate compared with other sites
- Poor data quality (long data entry delays, high query rate and high percentage of missing data)
- Poor adherence to the trial interventions
- High staff turnover

NB: High denotes a higher frequency than would be expected.

10. Conclusion

The SMV is an essential part to any trial. It is important that all sites follow the protocol and that the trial data collected is of the highest quality in accordance with ICH-GCP guidelines.

Appendix 1

MACE-ICH Site Monitoring Visit– Investigator Site File Checklist (EXAMPLE)

Site No: Site Name:
Date of Completion: Principle Investigator:

	Yes (please initial)	No	N/A	Comments
Is there an Investigator Site File?				
Does it contain the following: a. Trial office contact sheet b. Investigator site file index c. Trial identifier front sheet				
Section A Pre-Trial Opening				
A.1 Trial Development Documentation Coordinating centre file note: MACE-ICH File Note A1 - Trial Development Documents				
A.2 Study protocol and associated documents – final versions a. Signed Protocol Current: Superseded: b. Information Sheets, Consent Forms and GP letters on **local headed paper**: Current: (i) Participant Information Sheet (ii) Participant Pictorial Information Sheet (iii) Consent Form (iv) Legal Representative Information Sheet (v) Legal Representative Pictorial Information Sheet (vi) Legal Representative Consent Form (vi) GP Letter Superseded: c. Case report forms (CRFs) Current:				

(i) Randomisation (ii) Day 1 follow-up at 24 hours (iii) Day 2 follow-up at 48 hours (iv) Day 5 follow-up (v) Day 28 follow-up (vi) Discharge or death in hospital (vii) Serious adverse event or outcome (viii) Protocol violation (ix) Site-to-site transfer (x) Data correction request <u>Superseded:</u>				
A.3 Approval and Agreements a. Initial REC approval letter (dated 10/05/2023) b. Initial HRA Approval letter dated (10/05/2023) c. Initial MHRA approval letter dated (15/05/2023) d. EudraCT email (dated 19/01/2022) e. Site-specific approvals • R&D/R&I approval and confirmation of C&C • Signed non-commercial research agreement • Local site-specific assessment (SSI Form - where applicable) g. Sponsorship letter • Coordinating centre file note: MACE-ICH File Note A3 – Sponsorship letter h. Funding letter • Coordinating centre file note: MACE-ICH File Note A3 – Funding letter i. Trial insurance document (dated 11/08/2022)				
A.4 Staff Participation a. Site delegation log • Coordinating centre file note: MACE-ICH File Note A4 Site File Delegation Log b. Signed and dated CVs and GCP (in date) updated as per site's policies and procedures for all staff on the delegation log c. Attendance at Investigator Training (TAFR01204) signed by all staff on the delegation log				

d. Training slides (current and superseded) e. Evidence of site initiation f. Regulatory green light email from the sponsor				
A.5 Medical Testing and Pharmacy (where applicable) file notes where held in pharmacy a. Laboratory accreditation certificate b. Normal lab ranges c. Investigational product handling (where applicable) – local procedures where not in the study protocol d. Investigational product control (where applicable) – local procedures where not in the study protocol e. Clinical trials transfer request form f. Site Inventory Log g. IMP Accountability Log h. Return of clinical trial supplies i. Record of IMP destruction j. Summary of Product Characteristics (SmPC)				
A.6 Randomisation and Blinding • Coordinating file note: MACE-ICH File Note A6 Randomisation and blinding				
A.7 Database Build • Coordinating file note: MACE-ICH File Note A7 Database Build				
Section B: Ongoing Trial				
B.1 Study Protocol Amendments and Approvals a. TAFR02404 Amendment Log b. Locked amendment tool and regulatory approvals for each amendment				
B.2 Staff Participation (ongoing trial) Updates where applicable a. MACE-ICH File Note B2 Site File Delegation Log b. Updated CVs and training records (GCP) c. Updated attendance at investigator training, TAFR01204				
B.3 Informed Consent a. Signed informed consent forms (master copies) b. Signed GP letters (master copies) c. Participant screening and enrolment logs (TAFR01501 and TAFR01502)				
B.4 Medical Testing and Pharmacy Updates where applicable a. Updated accreditation/certification of supporting laboratories and pharmacies b. Updated 'normal ranges' issued by local laboratories				

c. Documented evidence of any changes and their implementation to investigational product handling (where applicable) – local procedures where not in the study protocol d. Documented evidence of any changes and their implementation to investigational product control (where applicable) – local procedures where not in the study protocol e. Updated investigational medicinal product records – certificate of analyses, shipping records, amended labelling to be used (if any)				
B.5 CRFs and Source Documents a. Completed CRFs or file note explaining where they are stored b. Source documents related to the trial or file note explaining where they are stored				
B.6 Serious Adverse Events a. SAE report forms signed and dated by PI (where applicable) (Check all SAEs on website have been printed and signed by PI, report as all seen or otherwise report those missing which need adding). b. Completed TAFR01912 Serious Adverse Event Reporting Form (CTIMP and Other) (where applicable) c. Completed TAFR01911 SAE Follow-up Form (where applicable) d. SUSAR notifications (where applicable) e. Protocol violation report forms signed and dated by PI (where applicable) f. Completed NUH Non-Compliance Reporting Form TAFR01705 (where applicable) g. GCP breach report, correspondence with the MHRA and REC and subsequent corrective action documentations and evidence (where applicable)				
B.7 Biological Materials a. List and location of retained samples b. Transfer agreements to other institutions • Coordinating Centre file note: MACE-ICH File Note B7 - Biological Materials				
B.8 Audit and Reporting a. Site Visit Log				

b. Monitoring reports for previous visits (if applicable) c. Completed monitoring visit action lists (if applicable) d. Internal monitoring/audit reports e. Local annual reports, e.g. R&D				
B.9 Miscellaneous a. Relevant, important correspondence b. File note template c. Medical notes label d. Eligibility checklist e. WPDs: i. 001 Secure Vault Uploads ii. 002 Uploading Scans iii. 003 Manual Randomisation iv. 004 Site Monitoring v. 005 Screening and Enrolment Logs vi. 006 Entry of Missing Data vii. 007 Protocol Deviations & Violations viii. 008 SAE Reporting ix. 009 CRF Completion Guidelines x. 010 Site Closedown f. Newsletters				
Section C: Closure				
C.1 Closure a. Notification of study closure to the ethics committee, competent authority, HTA, sponsor b. Documentation of IMP return and/or destruction and pharmacy records				
C.2 Audit and publication a. Final study report **b.** Final close-out document (as applicable)				
C.1 IMP management a. IMP accountability logs b. Evidence of destruction of surplus stocks				

Any further comments:

ISF checklist completed by:

Signed:
Date:

Principle Investigator:

Signed:
Date:

To be completed by monitor on receipt:

Name:

Signed:

Date:

Appendix 2

MACE-ICH Site Monitoring Visit – Patient File Checklist (EXAMPLE)

Site No: **Site Name:**
Date of Completion: **Principle Investigator:**

Patient number:

	Present in medical Records? (please initial)		Discrepancies/ Comments:
	Yes:	**No:**	
Consent			
Patient/Legal Representative consent (circle)			Consent form complete?
Verbal/written consent (circle)			If verbal, followed up with written consent?
Randomisation result			
Confirmation of eligibility by medic on delegation log			**Name of Medic:**
Consented by medic on delegation log			**Name of Medic:**
Sticker for retention of medical records for 25 years			
Date of consent/randomisation match?			**Enter date:**
Correct version of information sheet used?			
Correct version of consent form/s used?			
Alert detailing the R&I reference of the trial, IRAS number, abbreviated title, and the CI and PI contact details?			
Secure Vault Uploads			
Scan reports uploaded?			
Consent form/s uploaded?			
Drug chart/s uploaded?			
Blood test results uploaded?			
Patient details uploaded			
Database Uploads			
Scans uploaded?			
Version Control			
	Version:		
	Number:	**Date:**	
GP letter			
Copy of information sheet used			
Copy of signed consent form/s			

1. Does the ELIGIBILITY data correspond with the hospital notes?			
Inclusion criteria:	**Yes**	**No**	**Comments**

Age ≥ 18 years			
Spontaneous ICH confirmed by CT scan with estimated largest diameter >2cm			
≤72 hours of ictus (or from last seen healthy)			
Cerebral oedema with or without evidence of mass effect			
At risk of developing oedema (limited GCS <9 [eye opening and motor only] and NIHSS ≥8)			
Exclusion criteria:			
GCS<5			
Pre-morbid mRS >3			
Isolated subarachnoid haemorrhage			
Haemorrhage known to be from: trauma or venous thrombosis or arteriovenous malformation or brain tumour or transformation of cerebral infarct or cerebral aneurysm or thrombolytic drug			
Known hypersensitivity to mannitol			
Severe renal failure (e-GFR<30ml/ min or dialysis)			
Severe pulmonary oedema/ cardiac failure			
Hypotension at baseline (SBP <90 mmHg)			
Anuria			
~~Patient unwilling to participate~~			
Geographical or other factors which prohibit follow-up			
Pre-existing comorbidity with pre-ictal life expectancy <6 months			
Severe dementia			
Planned for palliative care			
Severe hypernatremia (sodium >160 mmol)			
Severe hyponatremia (sodium <125 mmol)			
Women of child-bearing potential with a positive pregnancy test at the time of admission, or lactating			
Patients in whom peripheral intravenous cannula cannot be placed			
Planned neurosurgery			

2. Does the participant's eCRF data correspond with the hospital notes (please check all data)?			
eCRF	**Yes:**	**No:**	**Comments**
Randomisation			
Day 1 follow up form at 24 hours			
Day 2 follow up at 48 hours			

Day 5 follow up			
Day 28 follow up			

3. Are all CRF forms signed and dated?			
eCRF	**Yes:**	**No:**	**Comments**
Randomisation			
Day 1 follow up form at 24 hours			
Day 2 follow up at 48 hours			
Day 5 follow up			
Day 28 follow up			

4. Does the following SAE/OUTCOME data correspond between the eCRF, Sponsor forms (TAFR01912 [and TAFR01911 if SAE updates were made]) and source hospital data?				
SAE No:		**Yes:**	**No:**	**Comments:**
	Date/Time:			
	Event details:			
SAE No:		**Yes:**	**No:**	**Comments:**
	Date/Time:			
	Event details:			

- Are all SAE reports filed in the ISF and signed by PI? YES /NO /N/A
- Are all TAFR01912 forms fully completed and filed in the ISF? YES /NO /N/A
- Are all TAFR01911 forms fully completed and filed in the ISF? YES /NO /N/A
- Have there been any unreported SAEs or safety outcome events? YES/NO
  If yes, please report the SAE/s to the site team, PI, coordinating centre and Sponsor:

Details of SAE:	**Date/Time:**	**Causality:**

Ensure details of SAEs are added to the database and reported to sponsor using form TAFR01912

5. Does the following protocol violation data correspond between the eCRF, Sponsor form (TAFR01705) and source hospital data?					
Date/time submitted	**Type of protocol violation**	**Explanation/comments**	**Yes:**	**No:**	**Comments**

- **Are all protocol violation reports filed in ISF and signed by PI?** YES/NO/N/A
- **Are all TAFR01705 forms fully completed and filed in the ISF?** YES /NO /N/A
- **Have there been any unreported protocol violations?** YES/NO
  If yes, please report protocol violations to the site team, PI, coordinating centre and Sponsor:

Date/time	Type of protocol violation	Explanation/comments

Ensure details of protocol violations are added to the database and reported to Sponsor using form TAFR01705

Have all database corrections been discussed with the PI? YES/NO/N/A

Additional queries/ comments:

Patient file checklist completed by: Signed:
Date:

Principle Investigator: Signed:
Date:

To be completed by monitor on receipt:

Name: Signed:

Date: