MACE-ICH – Working Practice Document
Title: Protocol Deviations and Violations, No. 008

Protocol deviations

A protocol deviation is a change/divergence/departure from the protocol, which is unplanned, and does not result in significant consequences. This includes any deviation from the trial protocol that is not listed as a protocol violation.

Examples:

Follow-up assessments are performed (as opposed to submitted) outside the specified time as shown below:

- 5±2 day follow-up: 3-6 days past the due date
- 28±2 day follow-up: 3-29 days before/after the due date
- 180±2 day follow-up: 7-29 days before/after the due date

Protocol deviations to inclusion/exclusion criteria are NOT permitted and may be considered a serious breach.

Protocol violations

A protocol violation is a divergence from the protocol which is unplanned, and results in significant consequences, for example, by reducing the quality/completeness of the data, or impacts on the safety/rights/welfare of participants.

Examples

- Participant <18 years of age
- Randomisation >72 hours from onset of symptoms
- No haemorrhagic stroke at time of randomisation
- No brain imaging during index stroke
- Participant enrolled with mRS>4
- Known hypersensitivity to mannitol at the time of randomisation
- Participant enrolled with known severe concomitant illness
- Participant enrolled with known intracranial disease or pathology other than stroke
- Severe coma (GCS<5) at time of randomisation
- Decision already taken for palliative care at time of randomisation
- Female patient pregnant or lactating
- Participant enrolled when not meeting any other inclusion/exclusion criteria
- Failure to obtain consent
- Individual taking consent not authorised to take consent on delegation log
- Failure to comply with the treatment protocol for no particular reason
- Not completing SAE's when appropriate
- Failure to complete outcome assessments as appropriate
- Day 5+ 2 days follow-up over 7 days past due date
- Day 28 follow-up over 30 days after due date
- Day 180 follow-up over 30 days before/after due date

Serious breach of GCP

A serious breach of GCP effects to a significant degree the safety of the participant and/ or the scientific value of the trial. A significant breach requires an investigation to find out what happened, why and what will be done to prevent a further occurrence. Sites should adhere to local Trust policy (such as Datix). A serious breach is rare and would trigger escalation by the Sponsor, to the MHRA & REC.

Reporting protocol deviations and violations

1. Complete the 'protocol deviation' eCRF on the MACE-ICH database.
    - Once submitted, this will send an email notification through to the Principal Investigator, Coordinating Centre and Chief Investigator
2. Complete the ***TAFR01705 NUH Non-Compliance Reporting Form***
    - Available on the MACE-ICH documents page or https://www.nuh.nhs.uk/guidance-researchers
    - Submit to Sponsor immediately via email to R&IQATeam@nuh.nhs.uk (cc in MACE-ICH@nottingham.ac.uk)
3. Review process
    - The CI and Sponsor will review the non-compliance and will advise on appropriate measures to address this.
    - All protocol deviations and violations will be reviewed on a monthly basis by the Trial Management Group.
    - All protocol violations will be reviewed 6 monthly by the DMC (unblinded) and TSC (blinded).