MACE-ICH – Working Practice Document
Title: Adverse Event Reporting, No. 009

Serious adverse events occurring within the first **28 days** after treatment must be reported to the Chief Investigator and Sponsor immediately (within 24 hours).

Fatal SAE's and safety outcome events (thrombophlebitis; hyper/hyponatremia; pulmonary oedema; hypotension; renal impairment) will be reported until **day 180**.

Adverse event definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

Expected events not subject to expedited reporting

Serious adverse events are common in haemorrhagic stroke. For a list of expected events not subject to expedited reporting, please refer to Appendix 2 of the protocol (provided at the end of this WPD as Appendix 1).

Causality assessments

Treating investigators are responsible for all causality and seriousness evaluations of adverse events. The Chief Investigator is responsible for expectedness for seriousness evaluations for serious adverse events (SAEs), and may upgrade, but not downgrade, causality assessments:

Unrelated: a clinical event including, for example, laboratory result will be considered 'not related' to the trial treatment drug if it is not a reasonable possibility that the event has been caused by the treatment drugs. Factors which point to this assessment include but are not limited to the lack of a temporal relationship to the IMP administration or for which other drugs, chemicals, treatment, or disease provide a plausible explanation.

Possible: a clinical event including, for example, laboratory result with a temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals, or concurrent disease.

Probable: a clinical event, for example, including laboratory result with a temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but unlikely to be explained by other drugs, chemicals, or concurrent disease.

Definite: a clinical event, for example, including laboratory result with a temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but definitely not explained by other drugs, chemicals, or concurrent disease.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as 'possible', 'probable', or 'definite' is an Adverse Drug Reaction. All SAE's will be adjudicated independently for causality. With regards to the above criteria, medical

and scientific judgement shall be used in deciding whether prompt reporting is appropriate in that situation.

Process for reporting an adverse event

The following steps should be taken immediately (within 24 hours) after an SAE or safety outcome event has been identified:

1. Complete the 'Serious Adverse Event or outcome' eCRF on the MACE-ICH database

- SAEs and safety outcomes are all reported using the same SAE form on the trial database. Once submitted, this will send an email notification through to the Principal Investigator, who will need to review the information online and sign the online form to say whether they agree. The Chief Investigator will also receive an email to review seriousness and causality of the SAE in conjunction with any treating medical practitioners.
- Review by the Principal Investigator should take place within 24 hours of the SAE being reported. They should review the entire form, and also assess causality and severity of the SAE. It is good practice to have a sub-PI on the delegation log who can assess these events in case of annual leave, sickness etc.

2. Complete the 'TAFR01912 Serious Adverse Event Reporting Form (CTIMP and Other)'

- After completing the eCRF on the database (see point 1 above), a link will be available at the top right-hand side of the screen to click and download the TAFR01912 form which will be partially auto-populated.
- Please download, print and complete all remaining items on the form, then email to: RDSAE@nuh.nhs.uk (cc in mace-ich@nottingham.ac.uk) immediately.

3. Report updates

- Sites should record and monitor all adverse events until resolution, stabilisation or until it has been shown that the study treatment is not the cause.
- Where event outcome is unknown at the time of the initial SAE report, please complete 'TAFR01911 SAE Follow-up Form' (available on the MACE-ICH documents page or https://www.nuh.nhs.uk/guidance-researchers) with updates, until resolution of the SAE. This form should be emailed to: RDSAE@nuh.nhs.uk (cc in mace-ich@nottingham.ac.uk)
- Any updates also need to be submitted on the database by completing a 'Data correction request' (the link to do this will be displayed at the top of the screen after selecting the participant's SAE that needs to be updated).
- It is important that the information on the database and forms sent to Sponsor match.

4. Documentation

- SAE forms (completed CRFs downloaded from the database, TAFR01911 and TAFR01912 forms) must be signed off by the PI and filed in the site file

Appendix 1 – Expected events not subject to expedited reporting

After intravenous infusion of mannitol, the following events are expected and would be indistinguishable from the clinical manifestation of severe haemorrhagic stroke. These events are not subject to expedited reporting:

- hypersensitivity
- Other hypersensitivity infusion reactions, including:
- hypertension
- pyrexia
- chills
- sweating
- cough
- musculoskeletal stiffness and myalgia
- pruritis
- generalised pain
- nausea
- vomiting
- headache
- CNS disorders: headache, dizziness, rebound intracranial pressure
- CNS toxicity manifested by: coma, confusion, lethargy
- Eye disorders: blurred vision
- Respiratory, thoracic, and mediastinal disorders: rhinitis
- Gastrointestinal disorders: dry mouth, thirst, nausea, vomiting
- Skin and subcutaneous disorders
- Musculoskeletal and connective tissue disorders: cramps
- Renal and urinary disorders: excessive diuresis, osmotic nephrosis, urinary retention, azotemia, polyuria
- General disorders and administration site conditions: chills, chest pain (angina-like chest pain), fever, asthenia, malaise, infusion site reactions

All of these events above are listed in the Mannitol summary of product characteristics. Occurrence of these events under other circumstances would not be considered expected and would be subject to expedited reporting.