Managing and Reporting Adverse Events

Standard operating procedure

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v1.0	29/10/2024	This is a first edition

COMET

Cooling in Mild Encephalopathy Trial

IRAS ID: 326176 | REC: 23/LO/0853

1. Purpose

The purpose of the SOP is to provide the necessary definitions, policies, principles, and guidance to staff involved in reporting and managing adverse events relating to the COMET study. This document was developed considering the relevant SOPs on managing and reporting adverse events by Imperial College London and NHS Trusts.

2. Introduction

The COMET Managing and Reporting Adverse events SOP is essential to ensure that all adverse events which occur during participants' involvement in the trial are appropriately recorded and reported to ensure their continuing safety. These regulations, including subsequent amendments, and the UK Policy Framework for Health and Social Care Research (2020) set out specific requirements for the safeguarding of participants involved in clinical research and the management of Adverse Events (AEs).

3. Definitions

Adverse Event (AE) is any untoward medical occurrence in a subject taking part in research study, including occurrences which do not necessarily have a causal relationship with the research. An AE event can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of the investigational intervention, whether or not considered to be related to the intervention.

Serious Adverse Event (SAE) is any untoward response that: (a) results in death, (b) is life-threatening, (c) requires hospitalisation or prolongation or existing hospitalisation, (d) results in persistent or significant disability or incapacity, (e) consists of a congenital anomaly or birth defect or (f) is otherwise considered medically significant by the investigator.

Suspected Unexpected Serious Adverse Reaction (SUSAR) are SAEs that are related and unexpected. Related means it resulted from administration of any of the research procedures. Unexpected is when the type of event is not listed in the protocol as 'expected outcome'. The COMET team is required to report any SAE that occur, and which is deemed related to research procedures and unexpected to the main Research Ethics Committee (REC). The COMET team would report to the main REC if the SAE occurred AND the opinion of the Chief Investigator the event was: (a) 'related' – that is, resulted from administration of any of the research procedures; (b) 'unexpected' – that is, the type of event is listed in the protocol as an expected occurrence.

Study sites (Principal investigator) will complete the COMET SAE Report form v1.0 and send it to the Trial Manager within one working day of becoming aware of a SAE. The form will then be forwarded to the Chief Investigator for assessment (COMET CI SAE Review Form v1.0) and reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator

4. Responsibilities

Principal Investigator (PI)

The Principal Investigator (PI) reports to the Chief Investigator and has responsibility for the research at a local site. The PI's responsibilities:

1) Keep detailed record of all AEs.
2) Reporting all Serious Adverse Events immediately to the Trial manager within one working day. The immediate report shall be followed by detailed written reports.
3) Supplying the Sponsor, REC and relevant Trust R&D with any supplementary information they request.
4) Ensuring that all staff listed and signed off on a delegation log are trained and fully equipped to perform their role.
5) Ensure clinical follow-up is ongoing until the event is resolved.

Chief Investigator (CI)

The Chief Investigator (CI) has overall responsibility for the conduct of the study. In a multi-site study, the CI has co-ordinating responsibility for reporting adverse events to the Research Ethics Committee (REC). These are SAEs which are unexpected and related to treatment or trial procedure. The CI is responsible for reviewing the SAEs for seriousness, causality and expectedness (classifying the SAE) and signing off the SAE form and reporting all SAEs and SUSARs within agreed timelines to the Sponsor.
Only reports of Serious Adverse Events (SAEs) that are: (1) related to the study (i.e. they resulted from administration of any of the research procedures) and (2) unexpected (i.e. not listed in the protocol as an expected occurrence)

Should be emailed to the REC using the Non-CTIMP safety report to REC form.

These should be sent within 15 days of the CI becoming aware of the event.

Trial management group (TMG) is responsible for:

1) Discussing all SAEs that have been received in between TMG meetings.
2) When required – giving consensus to a SAE classification.

Trial Manager is responsible for:

1) Coordinating received SAEs forms and obtaining the sign offs.
2) Scanning/typing and verifying SAEs on the Study database and chasing missing information.
3) Sending relevant reports to the main REC (and Sponsor) within the specified guidelines

5. Procedures

Managing SAEs

Adverse events will be described in the Adverse Events Log, unless they are classified as serious, in which case, these will be reported on a specific SAE form. If an AE is assessed as serious, the PI must report the event to the CI immediately or within 24 hours of being made aware of the event. The initial report can be made verbally but must be promptly followed with a detailed, written report. The PI must record the event with an assessment of severity, causality and expectedness on a trial SAE form provided. When a SAE form is received, the Trial Manager logs receipt of the form. The form is checked for any missing information needed to determine whether a SAE is related or unexpected. If any information is missing, additional information will be requested from a local PI.

Flowchart in Appendix 1 was designed to enable Investigators/research staff to assess AEs and SAEs should they occur during the trial and decide if an event requires further expedited reporting by the CI.

Classifying the SAE

The responsibilities for classifying the events will be shared between CI and PIs. All SAEs are however referred to the CI for the (final) review. The CI assesses the SAE (whether related and unexpected) based on the information provided and completes the relevant section of the SAE form. This should be done as soon as possible (ideally within 24 hours) and returned to the Trial Manager. SAEs will include mortality, major cerebral haemorrhages identified on MRI, pulmonary bleeds, persistent pulmonary hypertension of the newborn (PPHN) requiring inhaled nitric oxide or extracorporeal membrane oxygenation (ECMO), or any other clinical event deemed life-threatening by the investigators. Safety will be evaluated based on the frequency of SAEs and the total number of events per infant.

Assessing Causality

SAEs should be assessed for causality. The definitions below will be used.

- Not related: There is no evidence of any causal relationship.
- Remote: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
- Possible*: There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
- Probable*: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- Definitely*: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

*If a SAE is unexpected, the possible, probable and definitely related will be reported to the relevant REC and the Sponsor as SUSARs.

Documenting the SAE

The trial manager scans/types and verifies the SAE form onto the database and files the SAE form in TMF.

- If event not resolved or there is missing data, the trial manager must chase until the form is complete.
- The Trial Manager updates the log will all new information received.
- Complete SAE is the filed in the TMF and local ISF

Reporting related and unexpected SAEs

The Chief Investigator (CI) should report any SAE that is both related to the research procedures and is unexpected. The report should be emailed within 15 days of the CI becoming aware of the event to the Research Ethics Committee that gave a favourable opinion of the research.

All other PIs within the trial concerned must be informed of the SUSARs. All PIs should be sent a summary of SUSARs approximately every 3 months. The Trial Manager sends anonymised reports of all SAEs to the members of the TSC within the specified timelines.

Appendix 1

Flowchart – Adverse events reporting