
SOP TITLE: ADVERSE EVENTS & SERIOUS ADVERSE EVENTS

1. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to outline the necessary procedures for recording, managing and reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) for the COPCOV study in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.

This SOP outlines the responsibilities of the Investigators and Sponsor. Site staff should be familiar with the study protocol for all further requirements for study conduct.

2.1 DEFINITIONS**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.

AEs can be:

- A new disease or symptom that was not present at baseline (enrolment)
- A symptom that was present at baseline but subsequently worsened
- Abnormal laboratory test results (not routinely checked during COPCOV)
- Signs or symptoms due to the administered drug

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 i.e. the relationship is definitely, probably, possibly or unlikely to be related (see below).

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

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- is life-threatening¹
- requires inpatient hospitalisation² 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.

Serious Adverse Reaction (SAR)

This is an adverse event that is both serious and is considered a drug reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a SAR that is:

- not listed in the summary of product characteristics (SmPC) for that product or
- has not been described in the published literature before

Expectedness

An expected AR or SAR is a drug reaction that is listed in the SmPC and or has been described in the published literature before.

Responsible Personnel

The Sponsor has overall responsibility for the conduct of the study. The site Principal Investigator (PI) has responsibility for the research at a local site where the study involves specified procedures requiring site-specific assessment. There should be one site PI for each research site. The site PI is responsible for informing the organising research team, of all adverse events that occur at their site following the guidelines below.

Site PI Responsibilities

- Ensure trial staff are trained on this SOP and the SOP is readily available

¹ 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.

² Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. The participant must be admitted overnight and/or stay > 1 day for medical reasons, a short stay of several hours to receive treatment is not considered hospitalisation. If a patient is admitted overnight or longer for social/economic reason and is otherwise medically stable, this does not constitute a SAE. Other examples of visits to a hospital facility that are not considered hospitalisation are: Emergency room visits, outpatient surgery and pre-planned or elective procedures for a pre-existing condition (as long as that condition has not deteriorated while on trial treatment or brought forward because of worsening symptoms).

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- Collect and assess each AE for Causality, Severity and Seriousness and record in AE/SAE form
- Ensure AEs and SAEs related to trial medication are followed either until resolution, or the event is considered stable
- Report all SAEs according to the local/ national ethics committee and regulatory requirements
- Report all SAEs to the COPCOV safety team according to the protocol (timelines and frequency noted below)
- Report all pregnancies that occur in female participants to the COPCOV safety team according to the protocol
- Supply additional information to the COPCOV safety team if requested by the DSMB or other relevant parties. Submit the written DSMB reports with recommendations as applicable to local/ national ethics committees and other applicable groups

2. PROCEDURE

2.1 RECORDING AND REPORTING ADVERSE EVENTS

- AEs occurring in participants from enrolment and during trial participation (up until Day 150 for a sub-set of participants with extended follow up) that are observed by the study team or reported by the participant with severity grade of 2 (moderate) or higher will be recorded on the CRF, whether or not attributed to trial medication. AEs will be recorded following the first dose of trial medication. Any symptoms occurring after enrolment but prior to the first dose of trial medication will be recorded as a baseline symptom.
- All adverse events that meet the definition of a serious adverse event (SAE) will be reported. An AE will be considered serious if the following criteria are met:
 - results in death
 - is life-threatening
 - requires inpatient hospitalisation³ or prolongation of existing hospitalisation
 - results in persistent or significant disability/incapacity
 - consists of a congenital anomaly or birth defect.

³ Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. The participant must be admitted overnight and/or stay > 1 day for medical reasons, a short stay of several hours to receive treatment is not considered hospitalisation. If a patient is admitted overnight or longer for social/economic reason and is otherwise medically stable, this does not constitute a SAE. Other examples of visits to a hospital facility that are not considered hospitalisation are: Emergency room visits, outpatient surgery and pre-planned or elective procedures for a pre-existing condition (as long as that condition has not deteriorated while on trial treatment or brought forward because of worsening symptoms).

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- 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.

2.2 AE SEVERITY ASSESSMENT

- To avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.
- The severity of adverse events will be assessed following the Common Terminology Criteria for Adverse Events (CTCAE) v5.0:

1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = fatal

2.3 AE CAUSALITY ASSESSMENT

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Definitely related: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Probably related: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

Possibly related: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

Unlikely to be related: There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication), or there is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

Not related: There is no evidence of any causal relationship.

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2.4 IDENTIFYING AEs FROM THE EPRO APP

- Data entered on the ePRO App by the participant will be used to identify those participants in whom an adverse event (Grade 2 and above) may have occurred.
- Participants should be contacted for the purpose of assessing a possible AE if data from the ePRO App meets **any** of the criteria below:
 - Difficulty performing daily tasks
 - Only able to leave chair/bed for short periods due to severe symptoms
 - Going to hospital for treatment
 - Admitted to hospital
 - Not taking study drug
- The above are indicators for contacting the participant to assess for a possible AE.

| ePRO indicators | Grade - Severity | Description |
|--|----------------------|---|
| | 1 - Mild | Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| Difficulty performing daily tasks | 2 - Moderate | Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL* |
| Only able to leave chair/bed for short periods of time due to severe symptoms, going to hospital for treatment, admitted to hospital | 3 - Severe | Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL** |
| | 4 - Life-threatening | Urgent intervention indicated |
| | 5 - Death | Death related to AE |

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- If the site team believe that in their clinical judgement a symptom is of grade 2 severity or above but it does not meet the above criteria, they can still report it as an AE.
- It is recognised that at some sites contact may be made to check on a participant's well-being if the ePRO App indicated they were unwell despite no indicator of severity. This would remain at the discretion of the site PI for that particular site.

NOTE: Data on the ePRO app is also used to identify those needing a nose/throat swab but the procedures detailed here relate only to the identification of AEs.

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- Unwell symptoms and indicators reported by the participant are recorded in Fusion (ePRO database). This information is generated and viewed through Fusion's Unwell Report and are assessed by the site staff to identify the symptom/s responsible for the AE (i.e. which symptom/s are linked to the severity indicator) which are then graded according to CTCAE v5.0. For the purpose of this study, AEs will be reported as individual signs and symptoms.
- The following information will be recorded in the AE CRF: description, date of onset (when of grade 2 severity or above) and end date (the last date the severity grade was higher than 1), severity, assessment of relatedness to trial medication, and action taken.

| COPCOV | ADVERSE EVENTS | Subject Number: <input type="text"/> | Initials: <input type="text"/> | | | | |
|--|---|--------------------------------------|--------------------------------|---|---|---|---|
| ADVERSE EVENTS (Record only AEs that are grade 2 or higher) | | | | | | | |
| AE Number | Event Description (select one, if other describe) 1= Itching 2= Headache 3= Dizziness 4= Visual Disturbance 5= Abdominal pain 6= Poor appetite 7= Nausea 8= Vomiting 9= Diarrhoea 10= Skin rash 99= Other | Start date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Relationship to drug (select one) 1=Not Related, 2=Unlikely Related, 3=Possibly Related, 4= Probably Related, 5=Definitely Related | Severity (select one) 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening 5=Fatal | Action Taken (list all that apply) 1= No Action Taken, 2= Study drug discontinued, 3= Concomitant therapy | Outcome (select one) 1=Resolved, 2=Ongoing, 3=Unknown, 4=Death |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |

- AEs considered related to the trial medication as judged by a medically qualified investigator will be followed either until resolution, or the event is considered stable.
- It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.
- If an adverse event meets the definition of a serious adverse event (SAE) then an SAE form will be completed and reported as below.

2.5 SAEs RELATED TO AN ACUTE RESPIRATORY ILLNESS/ COVID-19

- Participants who are hospitalised (see criteria for hospitalisation) meet the definition of a SAE and therefore must have a SAE form completed. Those participants who are hospitalised as a result of an acute respiratory illness (ARI)/ COVID-19 (but not for

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isolation or quarantine purposes) additionally must have the COVID/ARI Admissions Form (CRF) completed.

- This should be completed on a daily basis; were this is not feasible data can be added retrospectively from the patient's medical notes or following discussion with the treating physician.

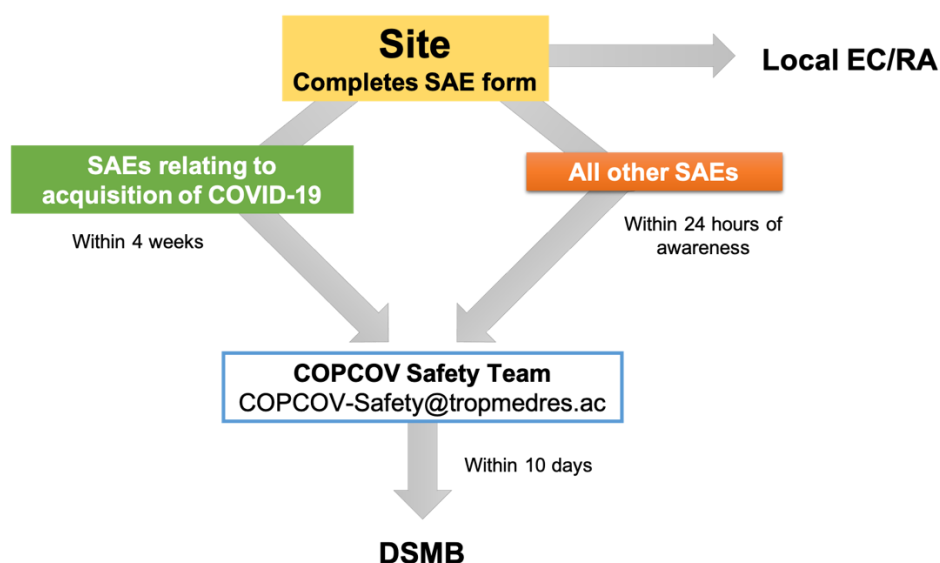
2.6 GUIDELINES FOR REPORTING

AEs

- AEs that are of grade 2 and above (see definition above) should be recorded in the AE CRF.

SAEs

- If an AE is assessed as meeting the criteria for an SAE, the site PI must report the event to the COPCOV safety team within **24 hours of awareness** through completion of an SAE form and submission to: [**COPCOV-Safety@tropmedres.ac**](mailto:COPCOV-Safety@tropmedres.ac). If an ECG is undertaken as part of the clinical management of an SAE then this should be affixed to the initial SAE report. Additional information should be reported to the COPCOV safety team by the site PI on a subsequent SAE form (indicating follow up/final report) when it becomes available. The COPCOV safety team will inform the DSMB within 10 days of initial notification of the SAE and keep the DSMB updated as needed.
- SAEs relating to acquisition of COVID-19, and morbidity and mortality associated with this, do not need to be reported to the COPCOV safety team immediately, but should be reported no less than monthly in order to be included in scheduled Safety Monitoring Committee meetings.
- The site PI must report all SAEs according to the local/ national ethics committee and regulatory requirements.
- If required, treatment codes will be unblinded for specific participants after discussion with the study co-PI (for the unblinding procedure, see Randomisation SOP).

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- If a female participant becomes pregnant after enrolment she will be instructed to discontinue study drug. The site study team must notify the COPCOV safety team within 24 hours of site awareness through completion of the pregnancy notification form and submission to: COPCOV-Safety@tropmedres.ac.

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eDiary

1. Is this report for today? ☒ Yes ☐ No If No, Date: 13 Jun 20 Time: []:[]:[]

2. How do you feel? ☒ Well ☐ Unwell If unwell,

☐ Sore throat

☒ Running nose

☐ Cough

☒ Difficulty performing daily tasks

☐ Shortness of breath if yes, ☐ at rest ☐ on exertion

☐ Mild Muscle aches

☐ Only able to leave chair/bed for short periods due to severe symptoms

☐ Going to hospital for treatment

☐ Admitted to hospital

☒ Other

☐ Itching

☐ Skin rash

☐ Headache

☒ Dizziness

☒ Visual Disturbance

☐ Abdominal pain

☐ Vomiting

☒ Nausea

☐ Diarrhoea

☒ Swollen left eye

Fusion – Unwell Report

COPCOV

Axiom Fusion - Unwell Subjects Report

Generated By: Marja Dondorp Date: 19 Jun 2020 Time: 10:18 PM EST/EDT

| Site | Site Number | Subject Number | Subject is: | Date | Reason for Unwell | Shortness of breath | Other Unwell Reason | Other Symptom |
|--|-------------|----------------|-------------|-------------|---|---------------------|---------------------------------------|------------------|
| Thailand - TH001 - Hospital of Tropical Diseases | TH001 | A001-014 | Unwell | 13 Jun 2020 | Running Nose, Difficulty performing daily tasks, Shortness of breath, Other | on exertion | Dizziness, Visual Disturbance, Nausea | Swollen left eye |

Fusion – Unwell Report

COPCOV

Axiom Fusion - Unwell Subjects Report

Generated By: Marja Dondorp Date: 19 Jun 2020 Time: 10:18 PM EST/EDT

| Site | Site Number | Subject Number | Subject is: | Date | Reason for Unwell | Shortness of breath | Other Unwell Reason | Other Symptom |
|--|-------------|----------------|-------------|-------------|---|---------------------|---------------------------------------|------------------|
| Thailand - TH001 - Hospital of Tropical Diseases | TH001 | A001-014 | Unwell | 13 Jun 2020 | Running Nose; Difficulty performing daily tasks; Shortness of breath; Other | on exertion | Dizziness; Visual Disturbance; Nausea | Swollen left eye |

- Indicators
- Side effect symptoms – potentially related to study drug
- Possible ARI symptoms
- Any other symptoms not listed in the eDiary

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Worksheet AE Symptoms

[illegible][illegible]

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COPCOV

Worksheet AE symptoms

Site: XXXXX

Click on the column headers for more info

| Subject Number | Date (ePRO) | Severity indication (ePRO) | Symptom (ePRO) | Grade (1,2,3,4) | AE number | Concom required? (Yes/No) | Initials (DE completion) | Date (DE completion) |
|----------------|-------------|-----------------------------------|---------------------------|-----------------|-----------|---------------------------|--------------------------|----------------------|
| A001-014 | 13-Jun-20 | Difficulty performing daily tasks | Running Nose | 1 | | N | AB | 14-Jun-20 |
| A001-014 | 13-Jun-20 | Difficulty performing daily tasks | Shortness of breath | 1 | | N | AB | 14-Jun-20 |
| A001-014 | 13-Jun-20 | Difficulty performing daily tasks | Dizziness | 1 | | N | AB | 14-Jun-20 |
| A001-014 | 13-Jun-20 | Difficulty performing daily tasks | Visual disturbance | 1 | | N | AB | 14-Jun-20 |
| A001-014 | 13-Jun-20 | Difficulty performing daily tasks | Nausea | 2 | 1 | Y | AB | 14-Jun-20 |
| A001-014 | 13-Jun-20 | Difficulty performing daily tasks | Swollen left index finger | 2 | 2 | Y | AB | 14-Jun-20 |

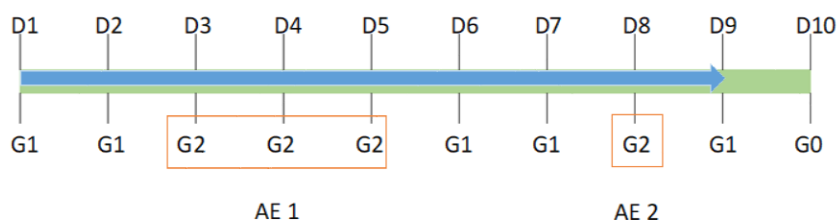
COPCOV ADVERSE EVENTS Subject Number: A001-014 Initials: X|Y|Z

| AE Number | Event Description (select one, if other describe) | Start date (dd/mm/yyyy) | End Date (dd/mm/yyyy) | Relationship to drug (select one) | Severity (select one) | Action Taken (list all that apply) | Outcome (select one) |
|-----------|---|-------------------------|-----------------------|-----------------------------------|-----------------------|------------------------------------|----------------------|
| 01 | 7 | 13 JUN 2020 | 13 JUN 2020 | 3 | 2 | 3 | 1 |
| 02 | 99 Swollen left eye | 13 JUN 2020 | | 1 | 2 | 3 | |

AE Start Date and End Date

- Start Date = First date of grade 2 (or higher)
- End Date = Last date of grade 2 (before grade 1 or completely resolved)

Example: Nausea from D1 to D9

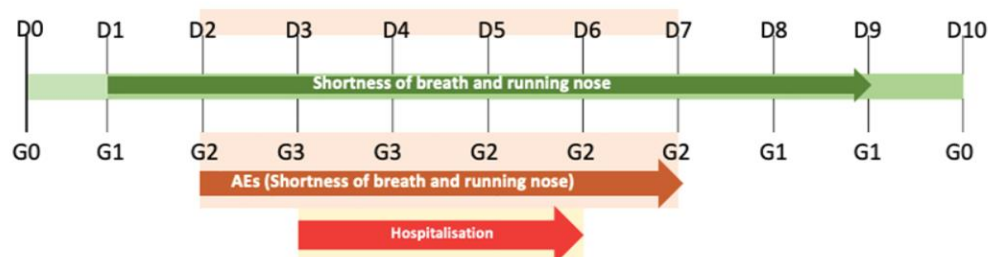


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SAE - hospitalisation

- SAE start date = date of hospitalisation
- SAE end date = discharge date



- AE (shortness of breath and running nose) = D2 → D7
- SAE (ARI?) = D3 → D6

Related Documentation

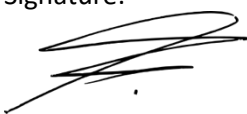

- Adverse Event (AE) Form
- Serious Adverse Event (SAE) Form
- COVID-19/ ARI Admissions Form
- Pregnancy Notification Form
- ePRO App/Fusion platform
- Case Record Form (CRF)
- CTCAE v5.0

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3. SOP VERSION HISTORY

| Version number/date | Major revisions |
|---------------------|--|
| 1/ 16 Sep 2020 | Initial version |
| 2/ 24 Feb 2021 | 1. The definitions of life-threatening and inpatient hospitalisation were updated. 2. "If an ECG is undertaken as part of the clinical management of an SAE then this should be affixed to the initial SAE report" was added in guideline for SAE reporting section. 3. "AE/SAE worked example" section was added. |

4. SOP SIGNOFF

| | | |
|---------------------------------------|---|------------------|
| Authored by: James Callery | Signature:  | Date: 09/03/21 |
| Approved by: William Schilling | Signature:  | Date: 09/03/2021 |

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