

PRINCIPLE: Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

1. Definition:

AEs for unlicensed drugs only will be collected. The description of the Adverse Events (AEs) that require reporting are given in the PRINCIPLE protocol and Intervention Specific Appendices (ISA) for each IMP.

The description of Serious Adverse Events (SAEs) that require reporting are given in the PRINCIPLE protocol. Hospitalisation and/or death due to confirmed or possible SARS-Cov-2 infection is a primary outcome, we will collect this data using a risk-adapted approach and will not report such SAEs. **Any SAEs other than hospitalisation or death due to COVID-19 must be reported for all treatments and Usual Care.** SAEs must be reported by the person who has discovered the SAE or nominated delegate within 24 hours of becoming aware of the event.

Hospitalisations will be defined as at least a one night admission to hospital. Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute an SAE, and standard supportive care for the disease under study are not SAEs and do not require SAE reporting.

This WI refers to processes specific for the PRINCIPLE trial, the 'PC-CTU_SOP_TM119 5.0 Pharmacovigilance' provides full details of the SAE reporting process and timelines for reporting.

In summary AEs will be assessed by a clinician for unlicensed drugs only (as detailed in the ISA), SAEs will be reported and assessed for all treatments.

Trial Resources:

- **PRINCIPLE Protocol**
- **TMF A16.1: AE/SAE log** (excel spreadsheet) – to log all reported S(AEs).
- **PRINCIPLE_Randomised_Patient_tracker (Excel Sharepoint)** – contains details of all (S)AE's reported from day 3 or incoming calls and logs all GP contact on the "GP call tracker (unlicensed)" tab
- **Principle-safety@phc.ox.ac.uk email** account – automatic (S)AE alerts will be sent to this email account.
- **AE form** in OpenClinica
- **SAE report form** (paper/electronic)
- **SAE assessment form** (paper/electronic)
- **24 hour safety phone line (0800 9150045)**
- **OpenClinica and Sentry** databases

2. Process:

Flow diagrams of the flow for AE reporting and SAE reporting are given in Appendix A and B respectively.

2.1 Notification of (S)AE:

1. (S)AEs are reported in the following ways:

I. In CRFs:

AEs: Daily Diary, Call on Day 7, 14 and 28

SAEs: Daily Diary, Call on Day 7, 14 and 28, Notes Review, Hospitalisation/Death Form

- II.** A member of the clinical team may be notified of an (S)AE when a participant calls the PRINCIPLE 24 hour safety telephone line
- III.** A member of the on-site trial team may be notified of an (S)AE during the day 3 call or from an unscheduled incoming call from a participant
- IV.** SAEs: SUS/HES/CHES data reports/RSC data extracts

2. (S)AEs are monitored in the following ways:

- I.** (S)AE alerts are set-up to automatically email the PRINCIPLE Safety inbox (principle-safety@phc.ox.ac.uk), these alerts are sent when a participant indicates an (S)AE in their daily diary (SENTRY) or on the Day 7/14/28 Call CRF (OpenClinica). The safety inbox will be checked daily by a member of the trial team for any (S)AE alerts.
or
- II.** The data team will download a daily list of non-COVID hospitalisations and required moderate/major symptoms as indicated in the IMP ISA from OpenClinica for trial team to review for SAEs (see Working Instructions Daily Safety Reports, v1.1, 23.04.2021).

For unlicensed IMP if there has been no contact from the participant or study partner since randomisation after the day 7 call (including no diary entries), a member of the trial team will contact the participants GP to check for any (S)AE's since starting the trial (this information will be recorded in the day 7 call CRF in OpenClinica).

- III.** To avoid multiple calls within short time, unsuccessful Sentry safety calls will be performed by the clinical safety monitor. Sentry safety calls are triggered by a participant being randomised to an unlicensed IMP and takes place on Day 1 of randomisation. The nurse making the initial day 1 call will be responsible for attempting to make the day 1 call 2nd attempt. If they are unable to do this they are responsible for handing this over to the clinical safety monitor. The clinical safety monitor will do the third attempt, address any safety concerns and take action accordingly. If safety monitor is unable to reach participant, safety monitor will hand over to the Senior Research Nurse and GP will be contacted.

2.3 (Serious) Adverse Event Log:

- 1.** The Clinical Safety Monitor or a delegated member of the trial team will review the Safety Report/(S)AE alert emails (contain the same information) daily to check that the

event is a true (S)AE (for example, the reported AE is within the timeframe of reportable AE's according the IMP ISA in the protocol). If the event is considered a true (S)AE, the (S)AE will be logged on the SAE or AE log in the PRINCIPLE TMF (section A16.1). All safety alerts must be recorded on the 'Safety Alerts' tabs and confirmed AEs to be listed on the 'AE Log' tab, of the AE log. **All participants who have been admitted but where the hospitalisation is not thought to be related to suspected COVID-19 will be reviewed by two independent clinicians, blinded to trial treatment, to ensure there are no overt omissions of clear COVID-19 related hospitalisations. See appendix C for determination of hospitalisation as primary outcome, or an SAE.**

2. For (S)AE alerts via the 24 hour safety phone line the clinical safety monitor will record the details of the discussion on the Call Tracker safety line (K:ID\PRINCIPLE\TM\TMF\PART A\A16 SAFETY) and if necessary log the (S)AE details in the SAE/AE log. SAE forms will be completed for all participants enrolled on the trial as required. If required, an AE form will be entered directly into OpenClinica for those participants randomised to unlicensed medications only.
3. All (S)AE's reported from day 3 or incoming calls will be logged on the comments box of the PRINCIPLE_Randomised_Patient_tracker (Excel Sharepoint) and emailed to principle-safety@phc.ox.ac.uk or indicated as a reported hospitalisation or death in OpenClinica. The tracker will be reviewed daily by the trial manager or delegate for any (S)AE's. Any AE's listed will be followed up with the participant and if it is confirmed as a reportable AE, the AE will be logged on the AE log. An AE form will be completed for those participants randomised to unlicensed medications only.
4. If during the telephone call to the participants GP an (S)AE is discovered, the trial team member will complete an (S)AE form while the GP is on the call. Once complete the (S)AE will be added to the SAE/AE log and followed up with the clinical team where necessary. An AE form is required for those participants randomised to unlicensed medications only.

There is a Whatsapp group 'PRINCIPLE Safety Group' for the clinical safety monitor and trial team members to discuss any issue with (S)AE's.

2.4 Participant Follow-Up for Moderate/Major Symptoms/AE's:

On a daily basis the trial team member/clinical safety monitor will review the AE reports generated from the Open Clinica Database/email alerts sent to the PRINCIPLE safety mailbox. The clinical safety assessor will review any AEs to confirm if follow-up is necessary. The clinical safety monitor will review the list of moderate/major AEs daily and use their clinical judgement to determine whether they need to contact the participant for further information or to advise the participant on the appropriate clinical care. The AE will be logged and an AE form will be completed by the clinician for participants randomised to unlicensed IMP only.

If the same AE continues to be reported as a moderate/major problem the clinical safety assessor will review the AE and continue to follow up with the participant as deemed necessary.

Any follow-up and resolution of the AE will logged on the AE log.

2.5 Serious Adverse Event Form (Paper/electronic):

On a daily basis the trial team member will review the SAE reports generated from the Open Clinica Database. They will complete the SAE form on paper. If any further information is required the trial team member will follow up with the participant to enable full completion of the SAE form. Once complete the SAE form will be reviewed and the causality (and expectedness for SAEs) assessed by a delegated clinically qualified member of the team. See appendix D for a guide to interpreting the causality.

2.6 Participants Follow-up for SAE's:

If the SAE has not resolved at the 28 day time point the SAE will be reviewed again to see if resolution has occurred. If the event is considered 'resolved' or 'resolving' no further follow up is required. If not, the event must be followed up until such a time point, even if the participant has chosen to withdraw from the trial. If participant has withdrawn from further calls and contact, the trial team should contact their GP for further details.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the participant's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilises
- The event returns to "baseline", if a "baseline" value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

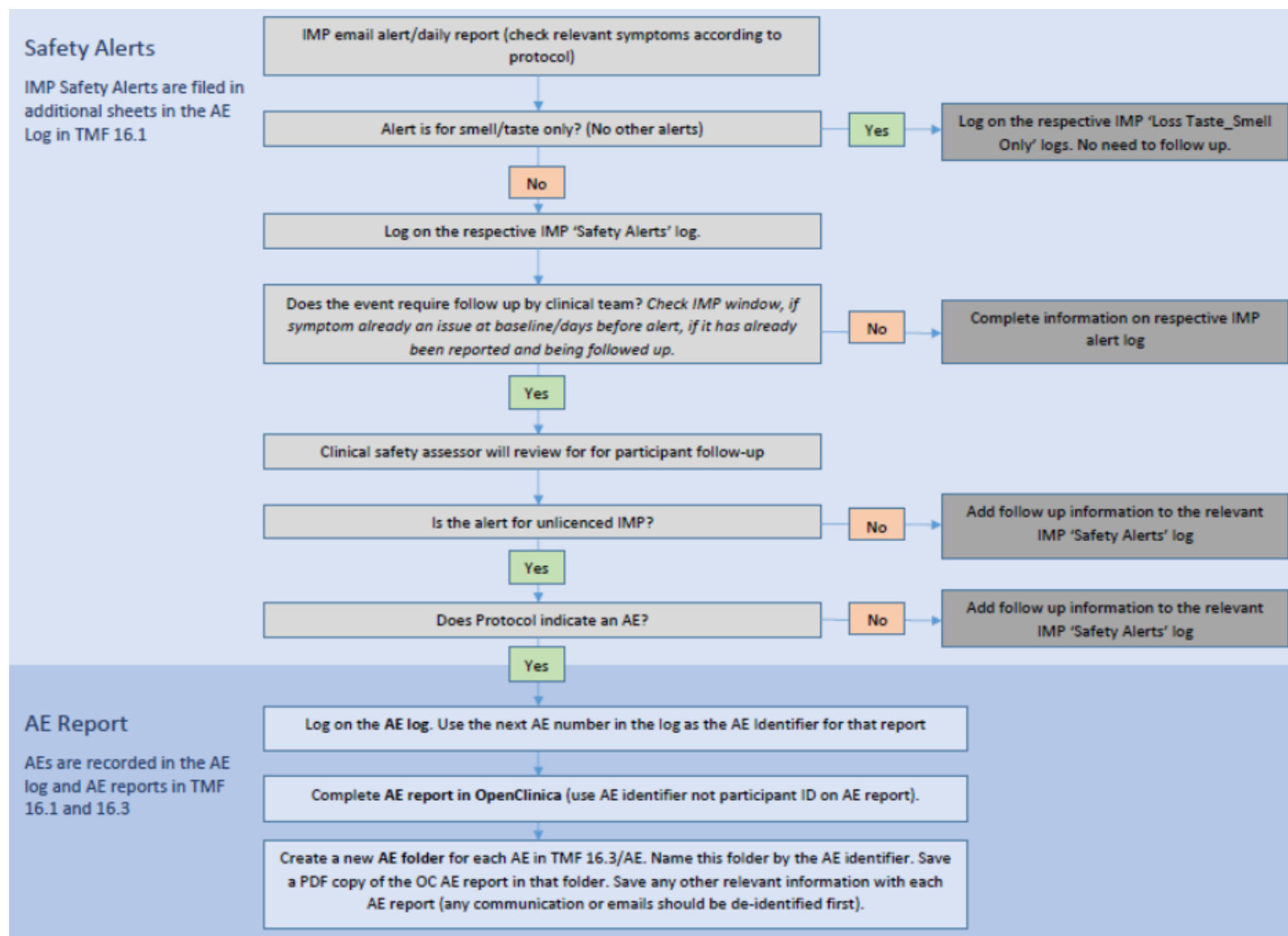
2.7 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any SAE that is considered definitely, probably or possibly related to the IMP (recorded as a Serious Adverse Reaction (SAR)) after clinical causality review, but the event isn't listed in the IMP ISA section of the protocol or in the IMP's Investigator Brochure (therefore 'unexpected') should be considered a SUSAR. The Chief Investigator or delegate completing the CI SAE Assessment Form (TM119_G) should alert the trial team to the outcome of SUSAR immediately. The trial team will process the SUSAR according to the PC-CTU_SOP_TM119 5.0 Pharmacovigilance SOP with the help of the clinical team and Chief Investigator.

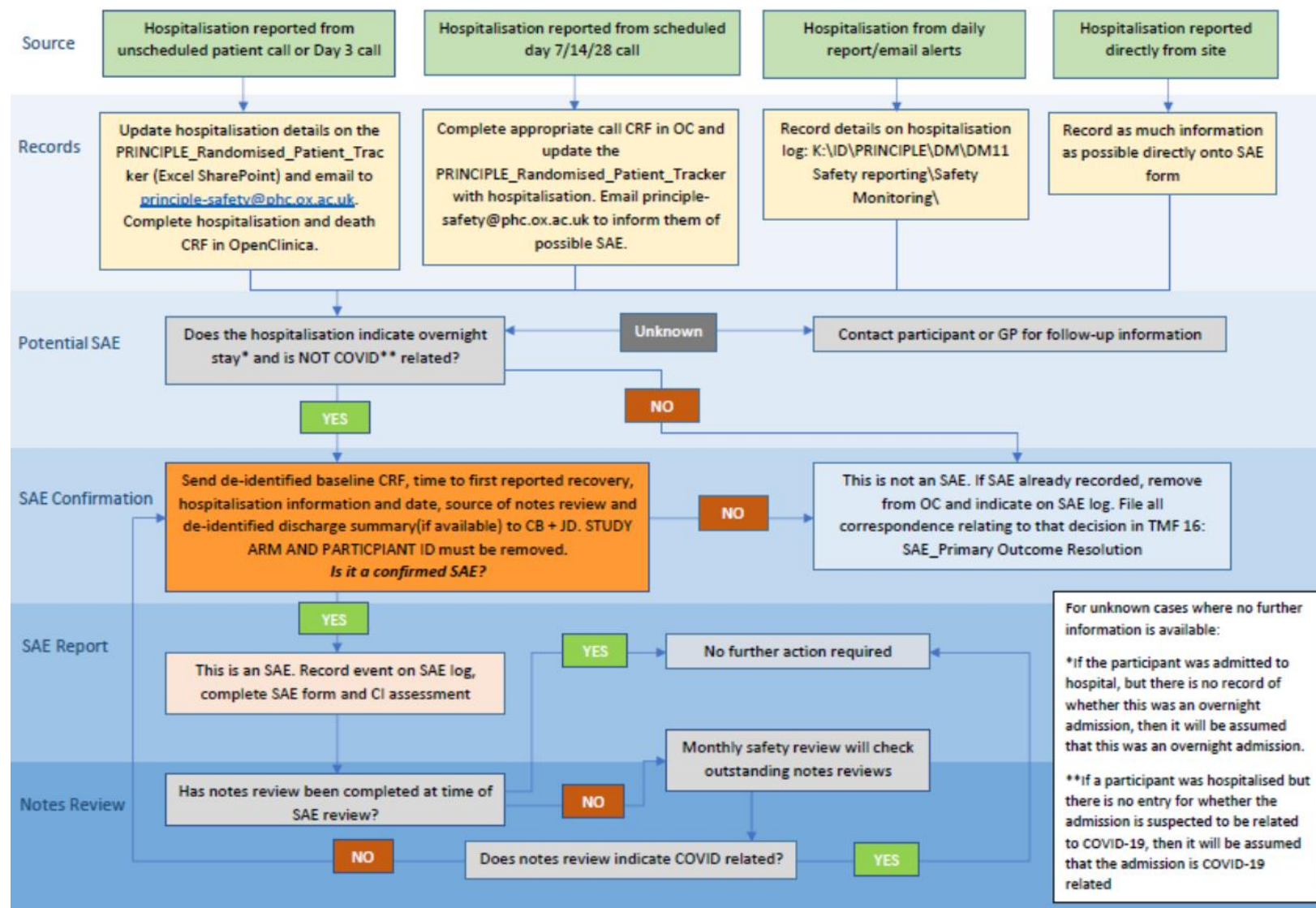
2.8 Monthly Safety Review

As part of the safety oversight a member of the PRINCIPLE trial team will conduct a safety review of the reported safety alerts, hospitalisations and reported (S)AE's. Appendix E outlines the safety review form to be completed, template and completed forms are saved here: K:\ID\PRINCIPLE\TM\TM recruitment\Safety Review. The review will include following up any ongoing (S)AE's and checking for new notes reviews that need to be checked against reported SAE's. The safety review report and actions will be discussed with the trial team and clinical safety assessor during the regular safety meetings. Any actions should be completed prior to the next scheduled safety review.

Appendix A: AE Flow Diagram



Appendix B: SAE Flow Diagram



Appendix C: Determination of hospitalization/death as primary outcome, or an SAE

4th May 2021 Version 2.0

Definition of COVID-19 related hospitalisation: As per the M-SAP:

- "Hospital admission within 28 days will be defined as an overnight stay in hospital and likely to be related to COVID-19. This can be recorded from the daily diaries, calls at days 7, 14 and 28, notes review CRF and death and hospitalisation CRF. If any of the sources indicate a hospital admission suspected to be related to COVID-19 within 28 days of randomisation then this variable will be coded as "Yes"."

Therefore, some cases initially described as SAEs will be updated once 28 day note review data is available.

Note: The Notes Review CRF comprises data from GP notes review, CTU nurse note review, RSC data and SUS/CHESS data. GP/RSC/CTU nurse review data takes priority over SUS/CHESS data in case of any conflicts.

Clarifications to above definition:

In addition:

- if a participant is hospitalized but there is no entry for whether the admission is suspected to be related to COVID-19 in *any* of the above sources, then it will be assumed that the admission is COVID-19 related and this variable will be coded as "Yes".
- If "Have you/participant been admitted to hospital since enrolling in this trial?" in the Daily Diary, Call CRF or Death Hospitalisation CRF is answered as "Yes", but there is no record of whether this was an overnight admission, then it will be assumed that this was an overnight admission.

Definition of COVID-19 related death:

Death in a person with a laboratory-confirmed positive COVID-19 test and died within (equal to or less than) 28 days of the first positive specimen date. Definition given by Public health England

Definition of SAEs: As per the M-SAP:

- "Any hospitalisation or death not thought to be related to suspected COVID-19 should be recorded as an SAE"

New process to check and confirm SAEs:

All participants who have been admitted but where the hospitalisation is not thought to be related to suspected COVID-19 will be reviewed by two independent clinicians, blinded to study arm, to ensure there are no overt omissions of clear COVID-19 related hospitalisations. As a guide:

- If the participant is admitted before first reporting recovery from COVID-19, and the reason for admission is a recognised complication of COVID-19, then this will be classified as likely to be related to COVID-19.
- If the hospital admission occurred after the participant first reports recovery, then in general the classification will not be changed.

For this blinded review, the study ID should be replaced by a separate identifier that is not identifiable to the clinical reviewer, but which the trial team is able to match back to the study ID. Study arm **must be** removed and any information that could give away the study arm or treatment allocation should be redacted. The following information should be provided, with all identifying details removed:

- baseline CRF
- time to first reported recovery
- hospitalization date
- any information on reason for hospitalization (including discharge summary if available through RSC/GP notes or SUS/CHESS data)
- source of information for Notes Review (ie GP, CTU nurse, RSC, SUS, CHESS?)

All confirmed SAEs will then be reviewed for relatedness to IMP by a research clinician.

Definition of COVID-19 recovery:

Clinical definition:

1. Asymptomatic patients: 14 days after initial positive test (N/A for PRINCIPLE trial)
2. 14 days after the onset of their symptoms for cases of mild disease (this is defined as SpO₂ ≥95% and respiratory rate <25 and heart rate <120 and temperature 36-39°C and mental status normal)
3. 14 days after achieving clinical stability (e.g. after supplemental oxygen was discontinued) for cases with moderate-severe disease
4. Patients who are still symptomatic at the end of their isolation period, when fever has resolved and their symptoms have shown improvement.

Appendix D: A Guide to Interpreting the causality question when making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an (S)AE may have been caused by the drug

- Time Course. Exposure to IMP. Has the participant actually received the IMP? Did the AE occur in a reasonable temporal relationship to the administration of the IMP?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the IMP (pharmacology and toxicology) or drugs of the same pharmacological class? Or, could the AE be anticipated from its pharmacological properties? See SmPC/IB for further information
- De-challenge experience. Did the AE resolve or improve on stopping the IMP?
- No alternative cause. The AE cannot be reasonably explained by another etiology, such as the underlying disease, other drugs, other host, or environmental factors
- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if, following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data, including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix E: Safety Review Form

PRINCIPLE Safety Review

Date: dd/mm/yyyy

Completed By: name and signature of reviewer

Update on action from previous report (if required):

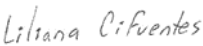
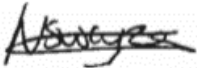
- 1) Review all new* SAE reports and check all reports logged on SAE log and vice versa
- 2) Review all new* AE reports and check all reports logged on AE log and vice versa
- 3) Review ongoing SAEs – check for follow up actions/closure
- 4) Check for any new notes review info for SAEs - which may indicate primary outcome and not an SAE
- 5) Review ongoing AEs – check for follow up actions/closure
- 6) Check at least 5 new* SAE/AE reports for accurate completion
- 7) Check 5 new* hospitalisation alerts for accurate logging and reporting (as required)
- 8) Check 5 new* AE alerts for accurate logging and reporting (as required)
- 9) Check correspondence related to above 5 hospitalisations and AE alerts have been filed

Outcome (circle):

Complete – no further action / Complete – action required / Incomplete - comment / Other - comment

Action (if required):

*new = since last completed safety review

	NAME	TITLE	SIGNATURE	DATE
Author:	Emily Bongard	Senior Trial Manager		21/06/2021
Reviewed By:	Liliana Cifuentes Gutierrez	Clinical Safety Officer		21/06/2021
Reviewed By:	Jared Robinson	Trial Manager		25/06/2021
Approved by:	Hannah Swayze	Senior Trial Manager		28/06/2021