Safety Reporting

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Summary

- Reportable events
- SAEs
- SUSARs
- Notable Events
- Reporting Procedures
- Non-serious Adverse Events
- Safety Reporting Requirements Form

Reportable Events in PediCAP

The following events are reportable to the MRC CTU:

- Serious Adverse Events (SAEs)
- Notable Events (NEs)
  - overdose of IMP
  - abuse or misuse of IMP
- Adverse Events (AEs)
  - all grade 3 or 4
  - any grade that leads to a modification of antibiotics
  - any grade that is considered related to antibiotics.

SAEs

Any adverse event, adverse reaction or unexpected adverse reaction that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is another important medical condition

Life threatening

- Refers to an event in which the patient is at risk of death at the time of the event.
- Does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

SAEs

Any adverse event, adverse reaction or unexpected adverse reaction that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is another important medical condition

Hospitalisation

- Defined as an inpatient admission, regardless of length of stay.
- In PediCAP, as patients are recruited whilst they are already in hospital, they would have to be discharged and then readmitted as an inpatient to meet the SAE reporting criteria.
- If the hospitalisation is a precautionary measure for continued observation, this **is** a SAE.
- Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure **do not** constitute a SAE.

SAEs

Any adverse event, adverse reaction or unexpected adverse reaction that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is another important medical condition

Another important medical condition

- Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations.
- Important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the child or may require intervention to prevent one of the other outcomes listed in the SAE reporting criteria.
- For example:
  - a secondary malignancy,
  - an allergic bronchospasm requiring intensive emergency treatment,
  - seizures or blood disorders that do not result in hospitalisation or development of drug dependency.

SUSARs

SUSAR = **S**uspected
Unexpected (per labeling of the suspect agent)
Serious (per ICH GCP Guidelines)
Adverse
Reaction

This means that the event:

- has a real, not hypothetical risk of being life-threatening, causing or prolonging hospitalisation, or causing permanent disability
- is either definitely, probably or possibly related to the trial drug
- is not expected as per the SmPCs for the trial drug

Notable Events

- In PediCAP, NEs are overdose, abuse or misuse of IMP
- Misuse of a medicinal product is defined as situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the marketing authorisation.
- Abuse of a medicinal product is defined as persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

Reporting SAEs and NEs

Reporting to MRC CTU

- SAEs and NEs must be reported to MRC CTU within 1 working day of site awareness.
- A copy of CRF08a should be emailed to mrcctu.pedicap@ucl.ac.uk
- Investigators should notify MRC CTU of all SAEs and NEs occurring from the time of signing consent until the child exits the trial.
- Form08a should be entered on to the database within 3 working days of sending the form to MRC CTU.

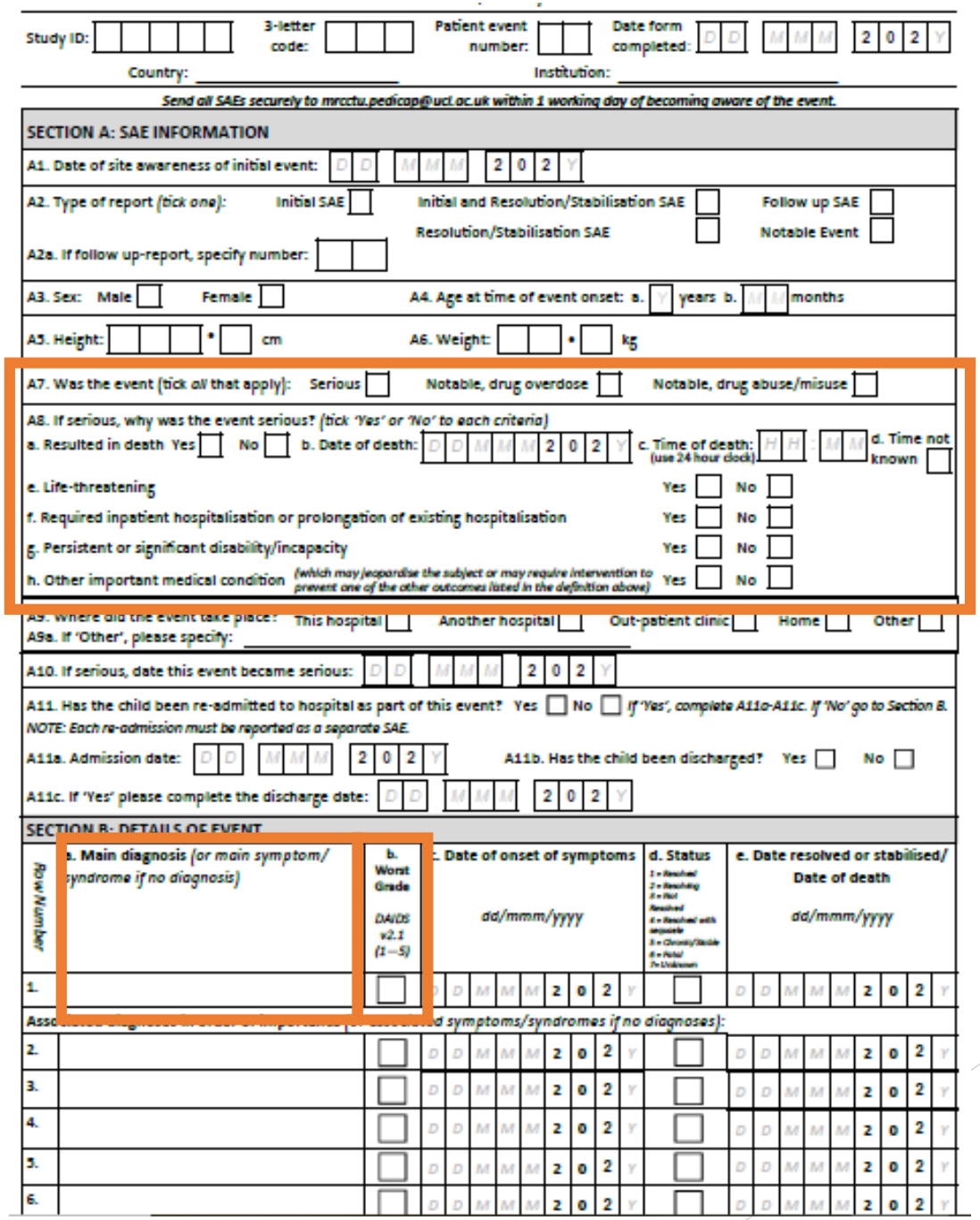
Onward reporting

- It is the responsibility of the lead site in each country to onward report to ethical and regulatory bodies.
- Each country involved in PediCAP has different timelines and requirements for reporting local and foreign SUSARs and SAEs – it is very important to adhere to these requirements.

CRF08a – Page 1

It is the responsibility of the investigator to assess whether an event meets the criteria of serious

The main diagnosis must be a single unifying diagnosis



Study ID: | 3-letter code: | Patient event number: | Date form completed: D D M M M 2 0 2 Y

Country: | Institution:

Send all SAEs securely to mrcctu.pedicap@ucl.ac.uk within 1 working day of becoming aware of the event.

SECTION A: SAE INFORMATION

A1. Date of site awareness of initial event: D D M M M 2 0 2 Y

A2. Type of report *(tick one)*: Initial SAE ☐ | Initial and Resolution/Stabilisation SAE ☐ | Follow up SAE ☐ | Resolution/Stabilisation SAE ☐ | Notable Event ☐

A2a. If follow up-report, specify number:

A3. Sex: Male ☐ Female ☐ | A4. Age at time of event onset: a. Y years b. M M months

A5. Height: . cm | A6. Weight: . kg

A7. Was the event (tick *all* that apply): Serious ☐ | Notable, drug overdose ☐ | Notable, drug abuse/misuse ☐

A8. If serious, why was the event serious? *(tick 'Yes' or 'No' to each criteria)*

a. Resulted in death Yes ☐ No ☐ | b. Date of death: D D M M M 2 0 2 Y | c. Time of death: H H : M M (use 24 hour clock) | d. Time not known ☐

e. Life-threatening — Yes ☐ No ☐

f. Required inpatient hospitalisation or prolongation of existing hospitalisation — Yes ☐ No ☐

g. Persistent or significant disability/incapacity — Yes ☐ No ☐

h. Other important medical condition *(which may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above)* — Yes ☐ No ☐

A9. Where did the event take place? This hospital ☐ | Another hospital ☐ | Out-patient clinic ☐ | Home ☐ | Other ☐

A9a. If 'Other', please specify:

A10. If serious, date this event became serious: D D M M M 2 0 2 Y

A11. Has the child been re-admitted to hospital as part of this event? Yes ☐ No ☐ *If 'Yes', complete A11a-A11c. If 'No' go to Section B.*

NOTE: Each re-admission must be reported as a separate SAE.

A11a. Admission date: D D M M M 2 0 2 Y | A11b. Has the child been discharged? Yes ☐ No ☐

A11c. If 'Yes' please complete the discharge date: D D M M M 2 0 2 Y

SECTION B: DETAILS OF EVENT

Row Number	a. Main diagnosis *(or main symptom/ syndrome if no diagnosis)*	b. Worst Grade *DAIDS v2.1 (1–5)*	c. Date of onset of symptoms *dd/mmm/yyyy*	d. Status *1 = Resolved 2 = Resolving 3 = Not Resolved 4 = Resolved with sequelae 5 = Chronic/Stable 6 = Fatal 7 = Unknown*	e. Date resolved or stabilised/ Date of death *dd/mmm/yyyy*
1.		☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y
Associated diagnoses in order of importance *(or associated symptoms/syndromes if no diagnoses):*					
2.		☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y
3.		☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y
4.		☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y
5.		☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y
6.		☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y

The investigator should grade the severity of the event using the 2017 Division of AIDS (DAIDS) toxicity grading scale v2.1, with a minor modification of the neutrophil count grading to reflect norms in the African population. This can be found in Appendix I of the PediCAP protocol.

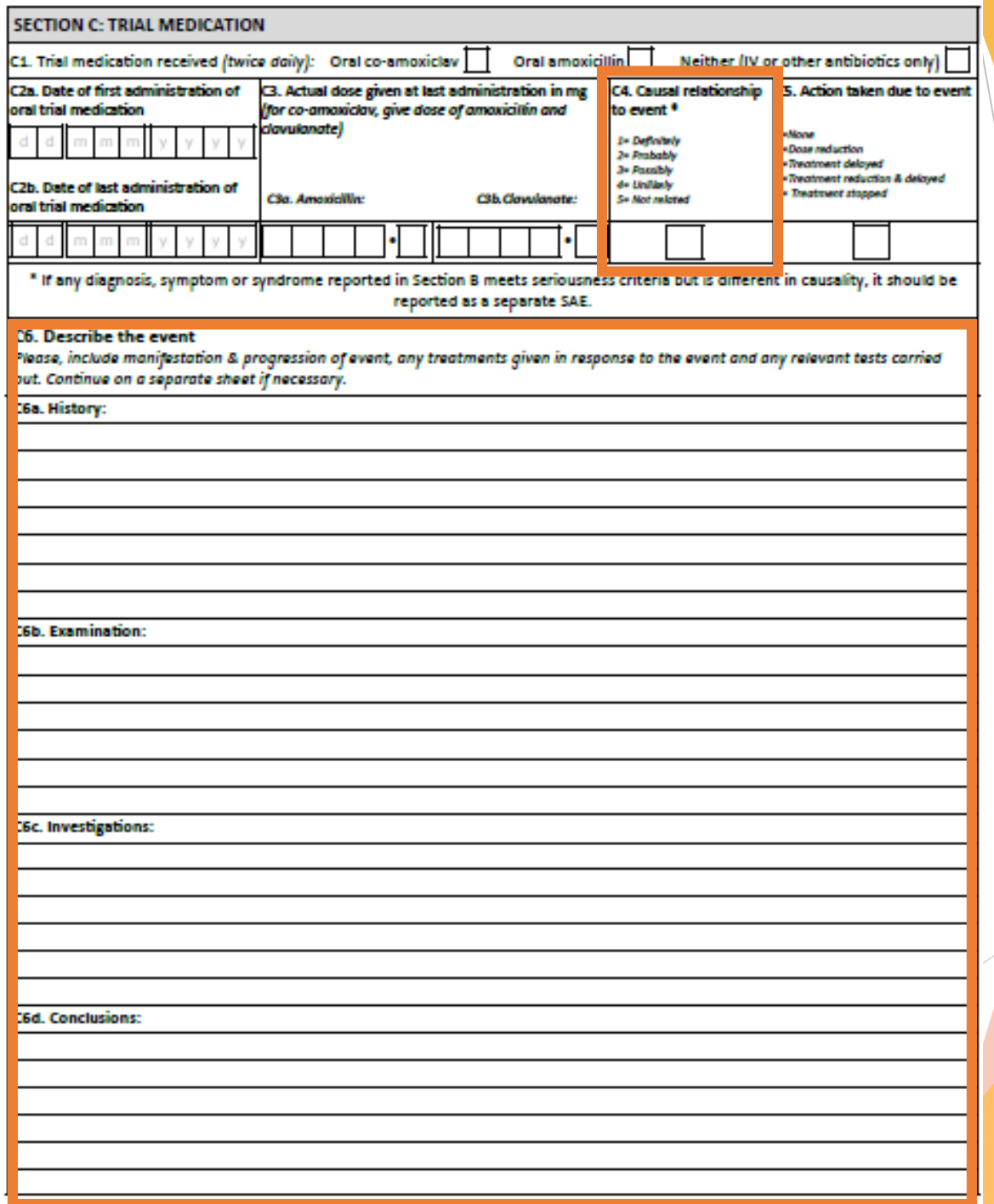
Main Diagnosis

- It is likely that in PediCAP, many children will present to hospital with multiple interrelated diagnoses.
- In these situations the investigator must ensure that one single unifying diagnosis is made and record this as the main event. All other diagnoses should be recorded as ‘associated diagnoses’.
- The main event should be the main reason why the event meets the criteria of ‘serious’. This may depend on whether the diagnoses are commonly presented together or whether one diagnosis is commonly caused by the other.
  - For example, malaria and anaemia are very commonly presented together with anaemia being caused by the malaria. Therefore, these diagnoses should be reported as one event, with malaria as the main event and anaemia as an associated diagnosis.
  - Another example is sepsis and kidney failure, which are commonly presented together. The main diagnosis here is sepsis and the associated diagnosis is kidney failure, as the sepsis leads to kidney failure.
- If the diagnoses are distinct in time or causality, and each diagnosis individually meets the reporting criteria, they should be reported as multiple events.
  - ie. if a new diagnosis meets the serious event reporting criteria, develops after initial presentation, or the relatedness to the study medication is different, then it should be reported as a separate SAE.

CRF08a – Page 2

Assess the causality of the event - events should be assessed as either ‘definitely’, ‘probably’, ‘possibly’, ‘unlikely’ or ‘unrelated’ to the study drugs.

The investigator should classify the event as ‘unlikely’ or ‘unrelated’ to the study drug if there is little or no evidence of a causal relationship between the event and the study drug



SECTION C: TRIAL MEDICATION

C1. Trial medication received *(twice daily)*: Oral co-amoxiclav ☐ Oral amoxicillin ☐ Neither (IV or other antibiotics only) ☐

C2a. Date of first administration of oral trial medication	C3. Actual dose given at last administration in mg *(for co-amoxiclav, give dose of amoxicillin and clavulanate)*	C4. Causal relationship to event *	C5. Action taken due to event
d d m m m y y y y	C3a. Amoxicillin: C3b.Clavulanate:	*1= Definitely 2= Probably 3= Possibly 4= Unlikely 5= Not related*	*•None •Dose reduction •Treatment delayed •Treatment reduction & delayed •Treatment stopped*
C2b. Date of last administration of oral trial medication			
d d m m m y y y y			

* If any diagnosis, symptom or syndrome reported in Section B meets seriousness criteria but is different in causality, it should be reported as a separate SAE.

C6. Describe the event

Please, include manifestation & progression of event, any treatments given in response to the event and any relevant tests carried out. Continue on a separate sheet if necessary.

C6a. History:

C6b. Examination:

C6c. Investigations:

C6d. Conclusions:

Provide details of the event, including manifestation, progression, any treatments given in response and any relevant tests.

CRF08a – Page 3

List any concomitant medication and their causal relationship to the event

C7. If a serious adverse event, is the child taking any other treatments? Yes ☐ No ☐

Please, exclude any therapy given for management of the event; include concomitant medication. Continue on a separate sheet if necessary. If 'Yes' please complete the following

Row Number	a. Treatment *Please give generic name*	b. Total daily dose and units	c. Route *1 = Oral 2 = IV 3 = Subcutaneous 4 = Other*	d. Start date	e. On-going 0=No 1=Yes	f. End date	g. Causal relationship to event*	h. Action taken due to event*
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐
			☐	D D M M M 2 0 2 Y	☐	D D M M M 2 0 2 Y	☐	☐

** Causal relationship to event codes: 1=Definitely 2=Probably 3=Possibly 4= Unlikely 5=Not related*

**Action codes: 0=None 1=Dose reduction 2=Treatment delayed 3=Treatment reduction & delayed 4= Treatment stopped*

C8. If a serious adverse event, do you consider this event likely to have been caused by anything other than the treatment listed previously on this form? Yes ☐ No ☐

C8a. If 'Yes', please specify (include medical history, family history, findings from special investigation)

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SECTION D: INVESTIGATOR DETAILS

Name of the investigator: ______________________ Telephone: ______________________

Form 08a must be completed and signed by the investigator who is responsible for the care of the participant and who is named on the Site Signature and Delegation of Responsibilities Log.

In the absence of the responsible investigator, the form should be completed and signed by a member of the site trial team and submitted to MRC CTU in the required timeframe. As soon as possible, the responsible investigator should subsequently check the form, make changes as appropriate, sign the form and re-send to MRC CTU.

- When an SAE is initially reported it may not have all of the information about the event. However as soon as the following minimum data set is completed the SAE should be submitted:
  - The patient study ID
  - Patient age
  - The SAE name
  - There must be an indication of why the event was serious
  - Causality should have been assessed (but if necessary the event can be sent for review before the Investigator has assessed this)
  - The report must come from an identifiable source i.e. must be signed by an appropriate person.

- If the investigator feels it is important for the Medical Reviewer to see extra, annotated information and/or copies of test results, these may be provided separate to the CRF.
- The child must be identified by study ID only. The child's name should not be used on any correspondence and should be deleted from any test results.
- All information recorded on CRF08a should also be recorded in the medical notes of the patient. Nothing should be recorded on the CRF that cannot be verified in the medical notes

MRC CTU procedures

- Upon receipt of the CRF, MRC CTU will do an initial check of the form and query any errors on the CRF that need immediate resolution or clarification.
- MRC CTU will send an email acknowledging receipt of the event within 1 working day of receiving the event form.
- MRC CTU will forward the event on to the medical reviewer.
- The medical reviewer will assess each event for seriousness and expectedness and document this review on Form08b.
- We aim to return reviewed events (with the Form08b) that have been assessed as definitely, probably or possibly related to the trial drug, and any fatal or life-threatening events to site within 4 working days of receipt of the event. This is to enable quick onward reporting of any events that may require this.

Classification of Events

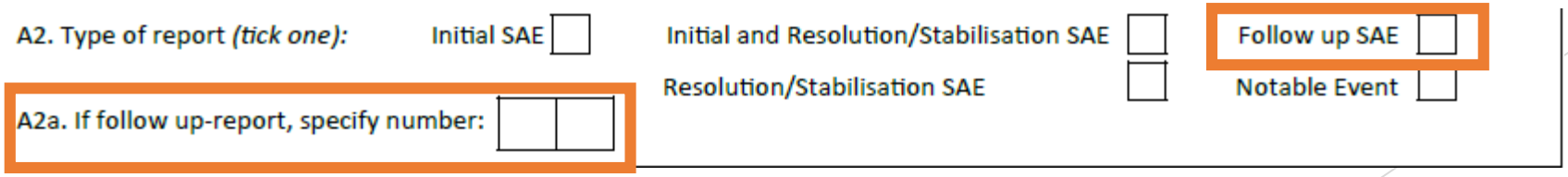
Causality	Expectedness	Classification
Definitely **Probably** **Possibly**	Unexpected	**SUSAR**
Definitely **Probably** **Possibly**	Expected	**SAR**
Unlikely **Not related**	**Expected** **or** **Unexpected**	**SAE**

Site responsibility

MRC CTU responsibility

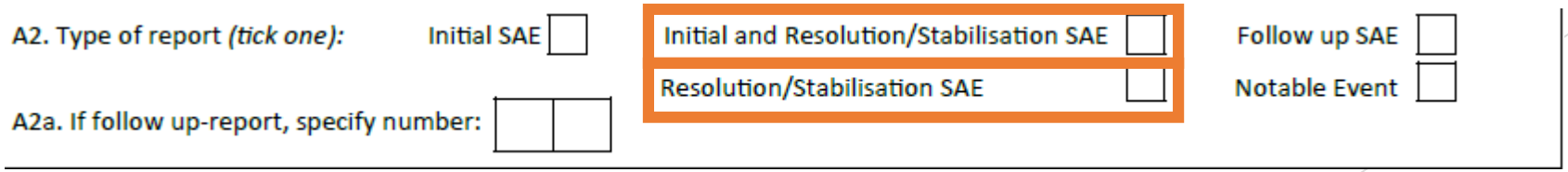
Follow-up

- Children must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised.
- A follow-up form should be submitted when any new information relating to a previously reported SAE becomes available.
- Follow-up forms should be completed on a new CRF08a and added as a new form on the database.
- You do not need to repeat information already submitted, however the header information and the Type of report and follow-up report number should always be completed.
- All follow-up reports and resolution reports should be submitted and entered on the database to the same timelines as initial reports.



Resolution

- Once an event is resolved, a final follow-up report should be submitted on a CRF08a.
- This final report should include all information from onset to resolution. This means that all information from the initial report and all follow-up reports should be included in the final report.
- The type of report should be marked as Resolution/Stabilisation SAE.
- Usually, an event is resolved at the point that it stopped meeting the serious event reporting criteria, for example, for an event that was reported due to a hospital admission, the event will be resolved upon discharge.
- Some events may have resolved at the point of submitting the initial report. In this instance, submit one report containing all the information and mark the type of report as Initial and Resolution/Stabilisation SAE.



Event Logs

- The Site Event Log and Patient Event Log should be completed for each reported SAE and NE.
- Each patient should have their own Patient Event Log.
- Assign a Patient Event Number, consecutively as reported.
- The Patient Event Number should also be recorded on the header of Form08a.

Patient Event Log

Site Name:	Patient Study ID:	Patient 3 letter code:

Record all Serious Adverse Events and Notable Events reported for this patient.

Please also complete the PediCAP Site Event Log.

Patient Event Number	Date of Onset (DD-MMM-YYYY)	Date Initial Event Form Completed (DD-MMM-YYYY)	Main Event Name	Date Resolved (DD-MMM-YYYY)	Date Resolution Event Form Completed (DD-MMM-YYYY)	Total Number of Event Forms for this Event (Including Initial, Follow-up and Resolution)
1						
2						
3						
4						

Event Logs

- Events for all patients should be added to the Site Event Log.
- Assign a Site Event Number, consecutively as reported.
- Record the Patient Event Number as assigned on the Patient Event Log
- Record the dates that any onward reporting was performed.
- Upon completion of a resolution report, ensure that both event logs are checked and updated.

Site Event Log

Site Name:	Principal Investigator:

Record all Serious Adverse Events and Notable Events occurring at your site.

Onward reporting to Ethics and Regulatory Authorities (and any other governing bodies) should be carried out as per local and national guidelines.

Site Event Number	Patient Event Number	Patient Study ID	Main Event Name	Date of Onset (DD-MMM-YYYY)	Date Site Aware (DD-MMM-YYYY)	Date Initial Event Form Reported (DD-MMM-YYYY or N/A)		Type of Event (Y/N)		Date Resolved (DD-MMM-YYYY)	Date Resolution Event Form Reported (DD-MMM-YYYY)	
1						CTU		SAE			CTU	
						Ethics		Notable			Ethics	
						RA		SAR			RA	
						Other		SUSAR			Other	
						If other, specify		Fatal/life-threatening			If other, specify	
2						CTU		SAE			CTU	
						Ethics		Notable			Ethics	
						RA		SAR			RA	
						Other		SUSAR			Other	
						If other, specify		Fatal/life-threatening			If other, specify	

Non-serious Adverse Events

- The following AEs are reportable in PediCAP:
  - all grade 3 or 4
  - any grade that leads to a modification of antibiotics
  - any grade that is considered related to antibiotics

- AEs should be reported on CRF11 – Adverse Event Log within 1 week of site awareness.

Safety Reporting Requirements Form

- Will need to be completed during site set-up phase, before site opening.
- Record all local and national requirements for reporting to ethics and regulatory bodies.
- A copy should be sent to MRC CTU to enable us to check our local procedures allow all reporting requirements to be met.
- The form can then be used as a reference document for all site team members to review onward reporting requirements.
- The document should be reviewed annually and updated if any requirements have changed.