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1. **Background**

After initiation of study treatment, the study drugs should be closely monitored for its clinical safety. Therefore, according to national and international agreements, rules, and regulations, all serious adverse events (including events related to the underlying disease or the suspected drugs) should be reported. The site investigator should promptly provide written/electronic reports to the Sponsor/ CRA, IEC, IRB for Cancer Trials, Data Monitoring Safety Committee.

2. **Scope**

The standard operation procedure of serious adverse reporting is to implement definition, reporting period, formats and standards as recommended by the ICH requirements for safety reporting. The purpose of this SOP is to provide the necessary definitions, policies, principles and guidance to personnel involved in SAE reporting. It is applicable to all CCTU investigators, study nurses, programmer, and data-entry clerks.

Study nurse to ensure that all relevant information relating to the SAE report is collected and send to the local authorities and Data Monitoring Safety Committee within the timeframe.

3. **Definition of serious adverse event**

The definitions below are in accordance with the principles of the ICH definitions (ICH E2A).

1. **Fatal**

Any death occurring within the trial period or within 28 days after the last dose of chemotherapy except for any death that is unequivocally due to progression of disease.

2. **Life threatening**

The patient was at substantial risk of dying at the time of the adverse event
Or
Use or continued of the device or other medical product might have resulted in the death of the patient

3. Disabling or incapacitating
If the AE resulted in significant or persistent change, impairment, damage, or disruption in the patient’s ability to conduct normal life functions.

4. Hospitalization
If the AE resulted in admission to a hospital overnight, or necessitated prolongation of a stay in hospital. This excludes hospital stays for elective surgery or planned procedures.

5. Congenital anomaly
If exposure by either parent to trial drug, before conception, or by the mother during pregnancy, is associated with the presence of developmental abnormalities at birth.

6. New cancer
Malignancy tumors (histologically different from primary tumor)

7. Overdose
Drug misuse, drug overdose

4. **Serious adverse event reporting system**
All SAEs should be reported immediately to the Sponsor/ CRA, CCTU, local authorities, except for those SAEs that the protocol or other documents identifies as not needing immediate reporting.

4.1. **In- house studies**

4.1.2. **To principle investigator**
Inform principle investigator within 1 working day of learning of SAE.
The investigator should sign and date the SAE report to certify that the information recorded in the form is accurate.

4.1.2. To CCTU
1. Study nurse to complete the initial report in the generic SAE form within 24 hours of receipt.
2. Principle investigator should sign the SAE form.
3. Study nurse to enter the initial report date on the SAE front sheet with the SAE report.
4. The filled SAE form will be placed in a “SAE IN” tray for data-entry.
5. After CCTU obtaining the SAE form, the detailed/partial adverse event information will be logged into the database with priority at daily data entry section. In no cases later than 2 working days of receipt of the SAE form.
6. The clerk to sign and date on the column of “date entry” of the SAE front sheet.
7. The printed out data will be laid in a “SAE OUT” tray for verification.
8. Study nurse to verify the printed out data within 2 days. The procedure of verification and correction is same as the CRF data entry.

4.1.3. CUHK Ethic Committee
1. All initial reports and follow up reports must be submitted to CUHK IEC within 15 working days.
2. The copy of SAE form will be send to IEC with a covering letter and signed by principle investigator.
3. Acknowledge receipt from IEC will be filed in the respective investigator’s file.

4.1.4. Data Monitoring Safety Committee
1. CCTU Data Monitoring Safety Committee will review the tracking log on monthly basis. The data manager will generate a SAE tracking log with the following information: study protocol no, patient no, onset date, reaction event and seriousness, and follow-up date if applicable.
4.2. Industry studies

4.2.1. To Sponsor
1. The study that is sponsored by industry will follow the industries’ policy of SAE reporting system as state in the respective protocol and complete within the agree-upon timeframe and to follow the CCTU policy as closely as possible.
2. The study nurse will report the details of the SAE to the Sponsor or CRA by fax within 24 hours of becoming aware of the event.
3. Sponsor or CRA may submit the overall SAE reports for the whole study to the Local IRB if necessary.

4.2.2. To Principle investigator
1. Inform principle investigator within 1 working day of learning of SAE.

4.2.3. To CCTU
1. Most SAE information captured in the Company’s SAE form will be transferred to CCTU central database to assess the number and the event of SAE as per industry study.
2. The minimal SAE reporting requirement for industry study is similar to as the requirement for in-house studies.
3. Study nurse will fill in both industry and in-house SAE form at the same time, the industry SAE form will fax to the sponsor within the timeframe, the in-house SAE form will be send to CCTU for data-entry within one working days of learning SAE.
4. The in-house SAE form will be placed in a “SAE IN” tray.
5. Data to be verified upon receiving the SAE copy within 2 working days.
   Please refer to verification procedure for in-house study.
4.2.4. To CUHK Ethic Committee
1. All initial reports and follow up reports must be submitted to CUHK IEC within 15 working days.
2. The copy of in-house SAE form for industry study will be send to IEC with a covering letter and signed by principle investigator.
3. Acknowledge receipt from IEC will be filed in the respective investigator’s file.

4.2.5. To CUHK IRB for Cancer Trials
1. The data manager will send an electronic copy within 15 working days. It is applied to all industry studies which were approved by IRB for Cancer Trials after March, 2001.

4.2.6. To Data Monitoring Safety Committee
1. The procedure is same as in-house studies.

5. SAE Reminder System
1. A reminder list for all SAEs which is classified by disease site, by patient, will be generated via computer and forward to all study nurses 10 days from the logging date of initial report, reminding them to monitor and follow up the SAE until it has receded.

6. Safety Follow-up information
1. Study nurses are required to obtain the missing information from the previous initial report and oversee the entry of the information in a timely fashion. (Please refer to no. 2 – 8 for data-entry procedure)
2. All SAE must be monitored and follow-up until resolution, unless condition is unlikely to resolve in investigator’s opinion. Additional sheets of paper may be used for to complete any narrative sections of the form.
7. Central SAE filing system

1. All completed and verified SAE follow up report and printout will be placed in SAE filing tray. The clerk will centralized the report in the SAE report file with indexes for individual study in CCTU.

8. Key elements for generic data collection form

General information for database

1. Protocol No.
   A. In-house study
   B. Industry study

2. Patient Details
   A. Initials
   B. Subject number
   C. Gender
   D. Age/ date of birth
   E. Weight
   F. Height

3. Details of SAE
   A. Date of initial/ follow up report with principle investigator’s signature
   B. Date of onset of event
   C. AEs should be documented in terms of a medical diagnosis and graded according the NCI-CTC attached to the protocol / CTC booklet
   D. When this is not possible, the AE should be documented in terms of signs and/ or symptoms in the column of “Others, specify” in the appropriate sections of the individual category
   E. Other unclassified adverse event, eg. decreased in general condition will be graded in the “Constitutional symptom, specify,” category
   F. Severity grade: NCI CTC toxicity grading
      Grade 1 – mild
      Grade 2 – Moderate
      Grade 3 – Severe
Grade 4 – Life-threatening / disabling

Grade 5 – Fatal

G. Narrative description of adverse event

H. Adverse event classification
   - Fatal
   - Life threatening
   - Disabling/ incapacitating
   - Hospitalization required or prolonged
   - Congenital anomaly
   - New cancer
   - Overdose
   - Other

I. Outcomes attributed to adverse event
   - Resolved
   - Ongoing
   - Died
   - Not available

J. Date of resolution or death

4. Suspected Study Drug
   - A. Brand name
   - B. Last date of administration

5. Action taken with trial medication as a result of the SAE
   - A. None
   - B. Dosage adjusted
   - C. Temporarily interrupted
   - D. Permanently discontinued

6. Relationship to trial medication
   - A. Unrelated (The AE is clearly not related to the study drug)
   - B. Unlikely (The AE is doubtfully related to the study drug)
   - C. Possible (The AE may be related to the study drug)
   - D. Probable (The AE is likely related to the study drug)
   - E. Definite (The AE is clearly related to the study drug)
7. Withdrawal of therapy statement
   A. Yes
   B. No

8. Additional comment on follow up

9. Minimum reporting criteria for initial report

Information and evaluation for the SAE report may not be available within the required timeframe. Nevertheless, for regulatory purpose, initial report should be submitted within the prescribed time as long as the minimum criteria are met.

Those data element is presented in **bold Italic type** on the SAE form.

1. Trial/Protocol number
2. Patient ID number
3. Initial report date
4. Patient information (patient initial, date of birth, sex, weight, height)
5. Description of adverse event
6. Date of onset
7. Severity grade
8. Adverse event classification
9. Information on study medication
10. Outcome at the time of initial report

10. Retrospective SAE reports

10.1 In-house study
1. The procedure of entering the SAE report is same as above. The date of initial report and the date of follow up report will be the same if the SAE has been resolved.

10.2 Industry study
1. The date should be same as the date of report which was sent to the Sponsor or CRA.