Manual of Procedures (MOP)
Section 14. Safety and Adverse Events Reporting

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14.1 DATA SAFETY MONITORING PLAN

The D2d Data Safety Monitoring Plan (DSMP) is included in the Appendix. It is expected that all investigators and research staff will strictly follow the DSMP.

14.2 ADVERSE EVENT DOCUMENTATION

- ✓ Details regarding adverse events, including all supporting information such as diagnostic reports etc., must be included in the source documents.
- ✓ All adverse events (non-serious and serious) and unanticipated problems will be entered into the electronic data capture (EDC) system on the Adverse Event eCRF, as soon *as possible after the site becomes aware of the event*, but no later than 2 business days for unanticipated problems (UAP), 5 business days for serious adverse events (SAE) and 15 business days for non-serious adverse events.
- ✓ In many instances, not all the relevant information will be available at the time of initial data entry; however, having incomplete information should not delay entering the event in EDC. Additional information should be entered as it becomes available.

  Instructions on the completion of eCRF are included in MOP section 15.

14.3 SAFETY AND OUTCOMES SUBCOMITTEE (SOS) REVIEW OF SAE / UAP

The D2d Safety and Outcomes Subcommittee (SOS) will review all SAE and UAP as they occur.

- Completion of the adverse event e-CRF in EDC and classification of the event as a SAE/UAP will trigger an e-mail notification to the CC (see Figure).
- If needed, the Project Manager (or designee) will contact the site for clarification and to request additional supporting information to be entered into the e-CRF, as the data entry fields permit. It is expected that in many instances, supporting documentation (e.g. medical records) will need to be submitted to the Coordinating Center (CC) by secure email, fax or mail, as described below.
- The CC will review the submitted supporting documentation for completeness, to ensure that identifying information is not showing.
- The CC will forward to the masked SOS chair (or designee) a packet containing the following documents:
    - SAE/UAP e-CRF with the event summary
    - Supporting documentation, including medical records
    - SAE/UAP SOS Individual Reviewer Form (see appendix)
  - If the SOS reviewer determines that additional supporting information is needed to evaluate the SAE/UAP, the request will be recorded on the SAE/UAP SOS Individual Reviewer Form and will be sent back to the CC.
  - Upon receipt of the request for additional information by the SOS reviewer, the CC will ask the site PI and/or research coordinator to provide the additional information and will forward it to the SOS reviewer.
- The SOS reviewer will assess each SAE/UAP to (1) confirm that that the event was an SAE or UAP and (2) determine whether immediate action is required. The reviewer will record his assessment in the form and return to the CC.

- If the SOS reviewer determines no additional action is needed, the event will be discussed at the next scheduled SOS meeting.
- If the SOS reviewer determines that action should be considered or the event needs to be further discussed with the SOS committee before a decision is made on action or not action, the CC will set up a conference call with other members of the subcommittee as soon as possible (typically within one week) to discuss the event.
- After review of the event by the SOS, the subcommittee will recommend a course of action by completing the SAE/UAP SOS Review Form
- Any recommendation for action by the SOS will be communicated to the Executive Committee and Steering Committee for further discussion and subsequently to the DSMB for approval and implementation.
- If immediate action is needed, it will be taken while at the same time notifying the Executive Committee, Steering Committee and DSMB.

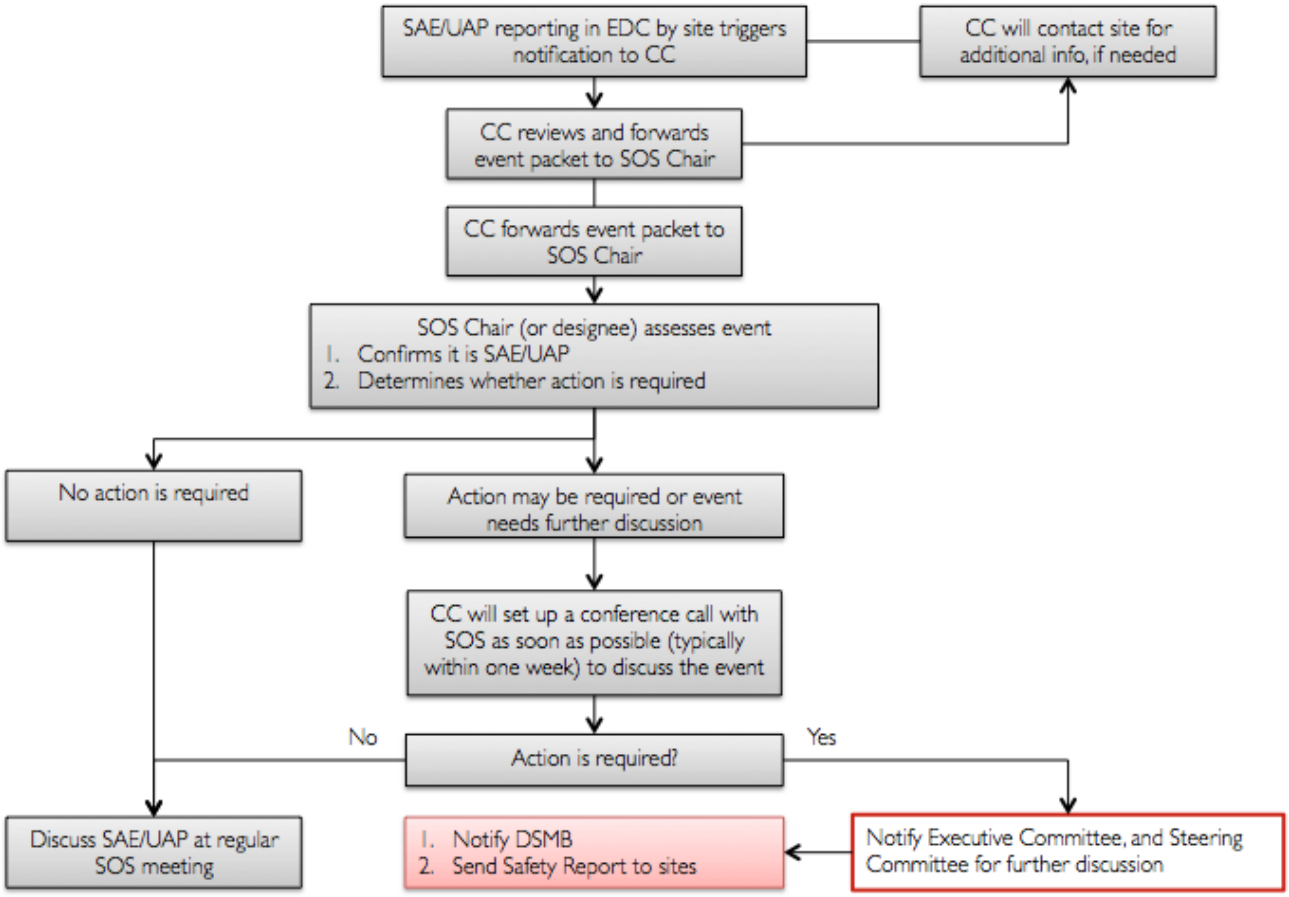
14.3.1 Safety reports to the sites

The CC will send a safety report to sites, if one of the following applies:

- Unanticipated Problem (UAP), whether action is required or not. A UAP is an event that is (1) unexpected and (2) possibly, probably or definitely related to the study intervention, and (3) places the participant or others at a greater risk of harm.
- Serious adverse event that requires action.

A safety report will be accompanied by a recommended action plan.

Figure. Assessment of SAE and UAP



14.4 SUBMITTING RECORDS TO THE COORDINATING CENTER

Sites will send records related to an adverse event to the CC using the D2d SAE-UAP Source Document Cover Sheet (see appendix) according to the following procedures:

1. Participant study ID must be recorded on all pages being sent.
2. All pages should be numbered in the following format: page # / # of pages, e.g., if 3 pages are sent, these should be numbered 1/3, 2/3, 3/3.
3. Any information that could identify the participant must be concealed. Submitting any participant documents to the CC that include identifying information is a serious violation.
    a. Identifying information includes:
        i. Name
        ii. Date of birth
        iii. Medical record or social security number
        iv. Address or place of residence
        v. Identifying information of family members
    b. To conceal identifiers:
        i. Make a copy of the source documents. Keep the original in your files.
        Note: The original source documents with the identifying information should not be altered. The identifiers must always be visible on the original source documents.
        ii. With a black Sharpie type marker and mark/cover over all identifying information on the copy. Care must be taken to not cover non-identifying information.
        iii. Make a photocopy of the marked up document and review it to ensure the identifiers are not visible prior to sending it to the CC.

14.5 APPENDICES

14.5.1 D2d Data & Safety Monitoring Plan

14.5.2 D2d Event Source Document Coversheet

14.5.3 D2d SAE/UAP SOS Individual Reviewer Form

14.5.4 D2d SAE/UAP SOS Review Form