

1.0 PURPOSE

The purpose of this Standard Operating Procedure is to ensure the accurate identification, delineation, and reporting of study related events requiring expedited reporting, occurring in interventional and non-interventional human subjects research studies at the National Institute of Neurological Disorders and Stroke (NINDS) and other institutes under the oversight of the NINDS Clinical Director (CD).

2.0 POLICIES AND REGULATIONS

Per OHSRP SOP 16, *Reporting Requirements for Unanticipated Problems, Adverse Events and Protocol Deviations*, the Principal Investigator (PI) is responsible for identifying, tracking and/or reporting Unanticipated Problems (UPs), Protocol Deviations (PDs), Adverse Events (AEs), and deaths. PIs report these events to their NIH IRB, NIH Institute CD, and/or, if applicable, to the Sponsors of FDA-regulated research or to the FDA. The type and severity of the event dictates the timing of the reporting and to whom the event must be reported.

3.0 DEFINITIONS

Adverse Event (AE): Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. In the context of FDA-required reporting, an AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Event* (SAE): is any Adverse Event that:

1. Results in death
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
3. Results in inpatient hospitalization or prolongation of existing hospitalization
4. Results in a persistent or significant disability/incapacity
5. Results in a congenital anomaly/birth defect; OR
6. Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*In IND-regulated research, additional terms including "serious suspected adverse reaction" (21 CFR 312.32(a)) and "Unanticipated adverse device effect" (21 CFR 812.3(s)) are used.

Version: 1.0
Initial Approval: 10/20/2017

Problem Report: A standardized mechanism to report a protocol related event (SAE, UP, or PD) that may require expedited reporting to the IRB and CD. The elements of a Problem Report are defined by the Office of Human Subjects Research Protections (OHSRP).

Protocol Deviation (PD): Any change, divergence, or departure from the IRB-approved research protocol. The impact of a PD is characterized by designation as serious or not serious.

Serious: A UP or PD is serious if it meets the definition of a Serious Adverse Event (see above) or if it compromises the safety, welfare or rights of subjects or others.

NINDS Clinical Practice Committee (CPC): A NINDS committee tasked to review current practices and identify areas of improvement in relation to patient safety and clinical practice. The committee meets monthly to review compliance with Clinical Center guidelines, develop plans for implementation for new policies, and review SAEs as well as other problems to determine if any further action is needed. The CPC may initiate root cause analyses as well as suggest M&M conferences.

Further definitions can be found at the NINDS Clinical Trials Unit (CTU) Intranet site and in OHSRP SOP16.

4.0 Procedures

The elements of ensuring timely reporting of events include 1) research staff training, 2) monitoring and oversight, and 3) remediation as needed. All interventional and non-interventional protocols under the oversight of the NINDS Clinical Director (i.e., NINDS and NCCIH protocols) are within the scope of the procedures outlined in this SOP.

4.1 Training and Education

All research staff are required to take in-person training in the identification and reporting of events conducted by the Office of Human Subjects Research Protection.

Required training for **on-boarding of new research staff** includes the following:

- a. OHSRP training in the identification and reporting of expedited events.
- b. Elements of a Successful Consent conducted by Human Subjects Protection Unit, for research staff obtaining informed consent
- c. Monitored first consent for all new clinical fellows

On-going education of research staff will be conducted via a) monthly Topics in Clinical Research meetings; b) monthly Research Coordinator Forum; c) NINDS CTU newsletters; d) posting of pertinent regulations and policies on the NINDS CTU KATie website.

4.2 NINDS Data Management (DM) and Quality Assurance (QA) Protocol Start-Up meetings

All new protocols may undergo a DM meeting and a QA protocol start-up meeting.

4.2.1 A *Data Management Meeting* is offered to all PIs following approval of the protocol by the Scientific Review Committee. During the Data Management meeting, the NINDS Data Manager, in cooperation with the PI and study team, develop a comprehensive Data Management Plan to determine the method of collecting all research data, including safety data and reportable events.

NINDS protocols are required to utilize an Adverse Events log for the collection and monitoring of all adverse events occurring while the protocol is open. Utilization of an adverse events log facilitates the tracking of adverse events, as well as the timely reporting of events to all required entities.

4.2.2 The NINDS Quality Assurance office offers *Protocol start-up meetings* for all newly IRB approved protocols. During the QA start-up meeting, the reporting requirements, as per the IRB approved protocol, is discussed in detail with the PI and study team.

4.3 Regular Research Team Clinical Care Meetings

NINDS developed a Standard Operating Procedure for weekly meetings of research teams, during which the PI will facilitate a discussion of all patient cases and study processes, as well as review patient care and protocol related events conducted during the prior week.

A review of activities involving research subjects, which may include clinical data, consent documents, and subject-specific protocol milestones, is meant to ensure that any previously undetected events such as adverse events or deviations from study protocols will be detected.

All protocols should include a statement regarding regular research team clinical care meetings, under the Data and Safety Monitoring section of the protocol. The following sample language may be included in the protocol: *The PI will conduct regular research team clinical care meetings to review recent study subjects and study processes, as well as to review patient care and protocol related events, including adverse events, unanticipated problems and protocol deviations.*

4.4 Periodic Review of Timeliness of Reporting

4.4.1 On-going monitoring of late reporting

The on-going monitoring of late reporting will be conducted by the NINDS Clinical Trials Unit as part of its monthly problem review procedure. The NINDS CTU Director reviews all submitted Problem Reports (including UPs, PDs, and SAEs) on a monthly basis. The NINDS CTU Director

designates a review team to advise in the review process, including the head of the NINDS Quality Assurance office.

The goal of the review is to determine:

- a) whether events were reported in the appropriate timeframe, based on the PIs determination of the event. Timeliness of reporting will be assessed by reviewing the notification and submission dates for each event contained in the Problem Report and comparing them to the reportable events timeframe in their respective protocol;
- b) whether the PI identified all appropriate entities requiring expedited event reporting, e.g., IRB, CD, Sponsor, FDA, on the Problem Report submission. If the response from the PI omits necessary reporting, the PI will be notified to ensure proper reporting;
- c) whether the event represents a clinical center deficiency and warrants reporting to the Clinical Center Occurrence Reporting System (ORS);
- d) whether the event should be reviewed by the Clinical Practice Committee for further analysis and possible root cause analysis (see attached algorithm).

The NINDS CTU Review will generate a monthly report on the Institute's status of late reporting to measure the impact of the training and education measures. Monthly reports are submitted to the NINDS Clinical Director (CD) and staff during monthly NINDS Clinical Care and Safety Meetings. If an increase in the rate of late reporting is noted, the NINDS CD in conjunction with the NINDS CTU will evaluate and implement measures to improve the timing of reports (see Section 4.4.5).

4.4.2 Clinical Practice Committee Review

The Clinical Practice Committee (CPC) meets monthly to review all events identified during the NINDS CTU Review for more detailed analysis. Members of the CPC investigate the events to determine if the event represents a) a systemic NINDS problem; b) a recurring branch/lab/section problem; c) a systemic Clinical Center problem, or d) an isolated event. Measures to correct the problem will follow, depending on the nature and magnitude of the problem.

The CPC makes a final determination if the event requires review during Morbidity and Mortality (M&M) rounds for in depth analysis. If so, the PI is invited to M&M rounds and the event is reviewed during the M&M conference held during Consult Rounds (see Appendix A). If additional actions are warranted, such as a review of practice and procedures, an individual or committee is tasked with determining "next steps". The M&M analysis and any follow-up are reported to staff during the Clinical Care and Safety Meeting.

4.4.3 Monitoring of FDA-regulated protocols and Auditing of non-FDA regulated protocols

As noted in Section 4.2, all investigators are offered a Start-Up meeting following IRB approval of the protocol and prior to subject enrollment. In lieu of a Start-Up meeting, FDA regulated protocols undergo a Site Initiation Visit, at which time a Monitoring Plan is developed. As part of the Start-Up meeting and Site Initiation Visit, the reporting requirements are reviewed with the study team.

Following start of subject enrollment, all FDA-regulated protocols are monitored at a pre-determined frequency either by a Contract Research Organization or by the NINDS Quality Assurance Office, at least once yearly. Non-FDA regulated protocols are audited by the NINDS Quality Assurance Office at a frequency determined by protocol risk (risk as determined by the procedures involved or the population studied), whereby protocols of increased risk are audited within the first year of subject enrollment, followed by additional audits within approximately every three years thereafter. Non-FDA regulated protocols which are minimal risk are randomly audited. The monitoring and auditing of research records determines whether all adverse events and UPs are appropriately reported within the time period required by GCP, the protocol, the CNS IRB, the sponsor, and the applicable regulatory requirements. In addition, the review of research records verifies that the investigator and the staff are performing the specified protocol functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator. 100% of AEs and Problem Reports are reviewed during monitoring and auditing visits. Evidence of protocol non-compliance are to be submitted by the PI to the CNS IRB as Protocol Deviations and reported within the 7 or 14 day time frame as determined by the seriousness of the event.

4.4.4 Providing Data to the Principal Investigator on the Timeliness of Reporting

Events are reported to the CNS IRB on a Problem Report Form submitted to the CNS IRB through the electronic protocol tracking and management system (at NINDS largely PTMS). Upon submission of the Problem Report to the CNS IRB, the NINDS Clinical Director simultaneously receives notification of the event. If an event is determined to be late in reporting, the CNS IRB will require the PI to submit a protocol deviation for late reporting.

Late reporting to entities other than CNS IRB will be identified by the monthly CTU Problem Review (4.4.1) and the NINDS study monitoring and auditing procedures (4.4.2.). The PI will be notified by the CTU Director (or his/her designee), if late reporting is detected during the CTU Problem Report Review or by the NINDS Quality Assurance Monitor if noted during the monitoring or auditing visit.

4.4.5 Remediation for Late Reporting

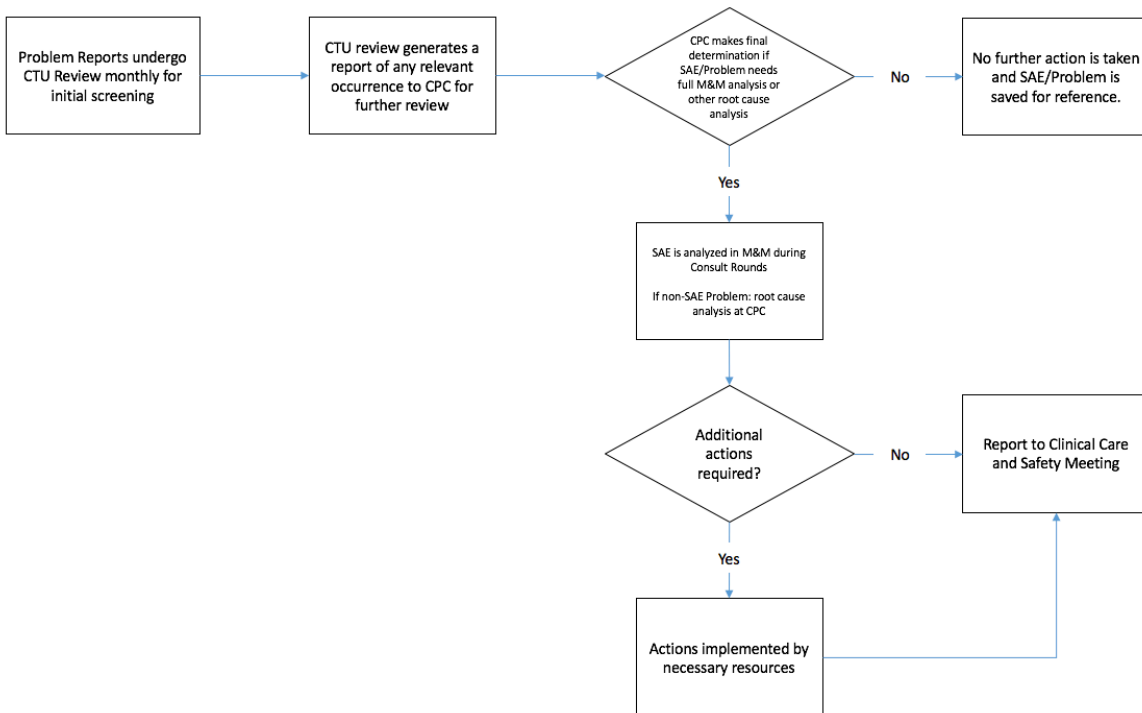
Specific responses to late reporting will be based upon the nature of the event(s) and whether the late reporting is on-going or an isolated event. Initial response(s) to late reporting may include a root cause analysis with the PI and study team, with intervention based on the cause.

In the event that late reporting is on-going, the CNS IRB and the NINDS CD may require the investigator develop a remediation or corrective action plan. The investigator, in conjunction with the NINDS Office of the Clinical Director (OCD) will develop a plan to reduce or eliminate the occurrence of late reporting events. The remediation plan may include additional or refresher training for the PI and/or some or all members of the study team, increased oversight conducted by the PI or NINDS OCD designee, real-time monitoring, or reduction of protocols in a PI's portfolio.

In addition, ratings on individual Performance Management Appraisal Program (PMAP) benchmarks for timely reporting will reflect late reporting.

5.0 Appendices

Appendix A



Version: 1.0
Initial Approval: 10/20/2017

Appendix B

SOP: Adverse Events Log (click on hyperlink or refer to Maintaining a Regulatory Binder on the NINDS CTU KATie site)