Responsibility for Monitoring of Study Progress and Evaluation and Reporting of Adverse Events

Each CTN Principal Investigator has ultimate responsibility for assuring the safety of research subjects participating in CTN sponsored studies at the CTPs affiliated with his/her node. This includes responsibility for assuring the proper monitoring of study progress and the evaluation and reporting on adverse events and serious adverse events at the Node. The Principal Investigator may delegate any of these tasks for any given protocol to other appropriately qualified persons affiliated with his/her node.

For those Nodes in which the Principal Investigator is not a physician, responsibility for monitoring study progress and evaluation and reporting on adverse events from trials involving pharmacotherapy will be delegated to an appropriately qualified physician.

Responsibility for Compliance with FDA Regulations Regarding the Responsibilities of IND Sponsors and Investigators (For Studies Conducted Under An IND)

The responsibility for ensuring compliance with FDA regulations regarding the responsibilities of sponsors and investigators will rest with the sponsor of the IND under which the study is conducted (e.g., the Lead Investigator or NIDA).

Definition of Appropriate Safety Monitoring

The nature and extent of the safety monitoring employed in each protocol is expected to vary based on the risk of the interventions being studied and the size and complexity of the trial. Specific ongoing monitoring for each trial will be determined by the Lead Investigator as part of the protocol development process. This will be documented in the data and safety monitoring plan for that protocol

Definition of Serious Adverse Events

A serious adverse event includes any event for which the outcome for the subject is any of the following:

Death

Life threatening

Hospitalization or prolongation of hospitalization

Persistent or significant disability or incapacity

Birth Defect or Congenital Anomaly

Definition of Expedited Reporting of Serious Adverse Events
For adverse events for which the outcome to the subject is considered to be Serious, a report of the event will be made within 1 working day of the event being reported to the investigator. A different timeframe for expedited reporting of serious adverse events may be specified in a protocol so long as the timeframe is sufficiently rapid to allow the Lead Investigator, other participating Investigators and NIDA adequate time to meet any additional reporting responsibilities they may have (e.g. to FDA, local IRBs or the CTN DSMB.)

Expedited reports of Serious Adverse Events should be made once the following criteria are met:

1. The report concerns an identifiable subject in a CTN clinical trial

2. The source of the report can be identified

3. The outcome or event reported meets the definition of Serious

It is understood that information available at the time of the initial report may not be sufficient to fully assess the event; however, the need for additional information should not delay the initial report once the above criteria are met.

Content of Serious Adverse Event Reports
All Serious Adverse Events occurring during the active treatment phase of CTN pharmacotherapy studies will be reported in enough detail to allow a full assessment of the event as described in ICH E2a.

All Serious Adverse Events occurring during the post treatment follow up phase of a CTN pharmacotherapy study or at any time during the study of a behavioral intervention may be reported in an abbreviated manner, in most cases based primarily on knowledge of the event gained from interviewing the reporter. The period when abbreviated reporting of serious adverse events will be used in pharmacotherapy trials should be specified in the protocol based on considerations such as the duration of active treatment and the half life of the experimental drug. Information requirements for abbreviated Serious Adverse Event Reports are summarized in the following table:

Information Requirements for Abbreviated Reports of Serious Adverse Events	
Serious Adverse Event	**What to report**
Death of Subject (any known cause)	Source of report (e.g., collateral contact). Any information available from the source of the report relating to the date and cause of death (e.g., AIDS pneumonia) and any available information from clinic records supporting the cause of death (e.g., Patient known to be HIV positive).
Death of Subject (cause not known to reporter or cause not substantiated from clinic records) and all overdose deaths	Any information regarding the date and cause of death. Sources might include Death Certificate, Autopsy Report or Medical Record. (This information is in addition to information reported for death from known cause above)
Hospitalization of Subject (any cause)	Source of report (e.g. reported by subject as reason for missed visit). Any information from the source of the report relating to the cause of the hospitalization (e.g. infection, injury, heart attack, asthma attack, detoxification). Reporter should be queried for information suggesting a possible relationship between the event and drug abuse/addiction (e.g., was the infection a skin infection, heart infection associated with drug abuse?, does the reporter state whether the subject was intoxicated at the time of the event?, does the reporter know if the subject was told that the hospitalization was related to drug addiction or abuse?). Any information from clinic records supporting the diagnosis (e.g. subject has history of asthma since childhood, subject known to have relapsed at time of the event)
Suicide	Report as for death from unknown cause above. In addition, provide information concerning the mechanism of death (e.g. hanging, drug overdose, self-inflicted gunshot wound, if known).

Information Requirements for Abbreviated Reports of Serious Adverse Events	
Serious Adverse Event	**What to report**
Suicide Attempt (requiring hospitalization for medical treatment of injuries or supportive treatment of poisoning or psychiatric hospitalization)	Report as for hospitalization above. Note the means of attempted suicide, if reported (e.g. intentional drug overdose, slashing of wrists)
Drug Overdose (requiring hospitalization or treatment in a hospital emergency department)	Report as for hospitalization above. Note drug and means used.

Reporting of Serious Adverse Events
All adverse events whose outcome meets the definition of Serious, will be reported to the following individuals:

Lead Investigator

NIDA Medical Safety Officer

CTP/Node IRB where SAE occurred

The Lead Investigator will assure that all reports of serious adverse events (regardless of causality or expectedness) are forwarded to the Principal Investigators of all Nodes participating in each protocol within 1 working day of receipt unless another timeframe for reporting is specified in the protocol.

The Principal Investigators will, in turn, inform co-investigators at their Nodes and CTPs and assure that the necessary information is available for submission to local IRBs, if required.

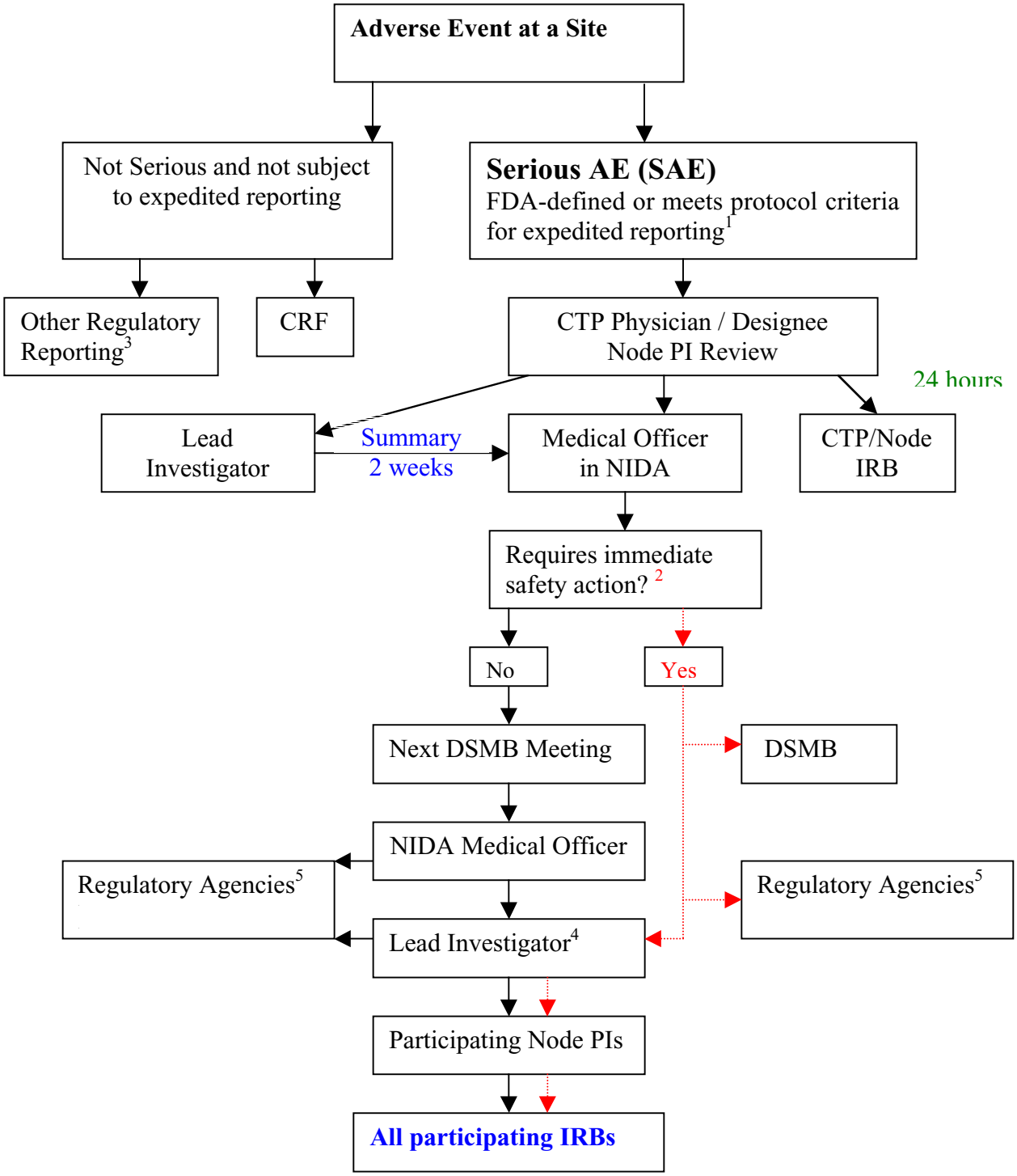
Follow Up Reports On a Serious Adverse Events
Subjects experiencing Serious Adverse Events will be followed periodically at a frequency appropriate to the nature of the SAE and the protocol requirements, until the outcome of the event is known. This information should be reported to the Lead Investigator and to NIDA for appropriate regulatory follow up.

Reports to an IND
For those studies that require an IND, Annual Reports and IND Safety Reports will be filed with FDA by the holder of the IND as required by 21 CFR 312.

Mechanism of Reporting of Non-serious Adverse Events
Non-Serious adverse events observed in the course of any trial will be reported on the CRF in the manner specified for that protocol.

Mechanism for Reporting of Serious Adverse Events
All adverse events meeting the definition of Serious will be reported within the timeframes listed above. Initial report should be by phone. This report should be followed up by a fax copy of supporting documentation, including but not limited to, the signed adverse event or serious adverse event portion of the CRF for that subject. Notification should be made to both the lead investigator, the principal investigator of the Node where the SAE occurred and the respective IRB, and NIDA Medical Safety Officer. Later, the Lead Investigator will submit a summary of the SAE to NIDA medical officer, including a statement that the SAE was reported to the respective IRB(s).

Adverse Events (AE) Reporting Flowchart



[1] **Initial SAE report** must be submitted within 24 hours.
[2] CTN Medical Officer will determine the need for immediate report based on specific guidelines for reporting SAE. SAEs subject to expedited reporting to the FDA are subject to expedited reporting to DSMB and all participating IRBs.
[3] Regulatory reporting of AEs not involving the DSMB (e.g., reports to FDA or local IRBs) may be initiated by the Lead Investigator or the NIDA CTN Office as described in the protocol.
[4] Lead Investigator will ensure dissemination of Non-confidential DSMB reports to Node Principal Investigators and from them to all IRBs from his/her node that are participating in the protocol.