SOP Number: ADM 12
SOP NAME: Central Institutional Review Board (CIRB) Reporting
Effective Date: 3-Jun-2014 (Last updated 30-Oct-2023)

## 1. POLICY

The purpose of this Standard Operating Procedure (SOP) is to define the process as required by the Central Institutional Review Board (CIRB) of record for reporting sites engaged in National Institutes of Health (NIH) StrokeNet affiliated research. Sponsors and sites engaged in StrokeNet research are required to report unanticipated problems which meet the CIRB reporting criteria. This SOP and associated attached guidance documents provide descriptions of these types of required reports and defines the standards, time frames, and procedures for these reports.

**Definitions:**

**Central Institutional Review Board (CIRB)**: A single Institutional Review Board (IRB) that performs the required human subjects review under the Federal Policy for the Protection of Human Subjects and other applicable regulations as deemed necessary for a multicenter trial.

**Data Coordinating Unit (DCU):** Data coordinating unit located at the National Data Management Center.

**Investigator**: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

**National Coordinating Center (NCC):** An institution designed and directly funded by NINDS/NIH to provide leadership for the NIH StrokeNet on a national level.

**National Data Management Center (NDMC):** An institution designed and directly funded by NINDS/NIH to oversee all aspects of data collection and management as well as full statistical support for StrokeNet research protocols.

**Prime Protocol Principal Investigator (PI):** The individual who is responsible for the development of the protocol and the coordination of the conduct of the clinical investigation at multiple sites, including required regulatory reporting to the CIRB. If this person is the IND or IDE holder, s/he is also responsible for all applicable FDA and NIH regulatory requirements, which includes all Sponsor-Investigator responsibilities.

**Regional Coordinating Center (RCC)**: An institution designed and directly funded by the NINDS/NIH to provide leadership for the NIH StrokeNet on a regional level.

**Relying Institution:** An entity engaged in StrokeNet research and that has contractually agreed to rely upon the review of the CIRB.

**Sponsor**: An individual, company, institution, or organization that assumes or delegates responsibility for the initiation, management, regulatory reporting and/or financing of a clinical trial. Within the NIH StrokeNet model NIH funded trials are considered Investigator Sponsored

Trials and certain agreed upon sponsor responsibilities can be delegated via the sub award process.

## 2. SCOPE

The policies and procedures in this SOP apply to parties involved with StrokeNet research, including the National Coordinating Center (NCC), the CIRB, the National Data Management Center (NDMC) and all StrokeNet Regional Coordinating Centers (RCC) and their Performance Sites (PS) engaged in StrokeNet research. For purposes of this SOP, a site is any institution that is engaged in StrokeNet research. The StrokeNet CIRB at the University of Cincinnati follows the University of Cincinnati Human Research Protection Program Policy HRP-092 for reporting unanticipated problems involving risks to participants and others, adverse events, and other problems to the IRB (see Attachment A). ADVARRA follows the IRB Handbook for Investigators, Institutions, Sponsors, and Sponsors' Representatives for reporting unanticipated problems involving risks to participants and others, adverse events, and other problems to the IRB (see Attachment C).

## 3. PROCEDURES

### A. CIRB Review Overview

Under Reliance Agreement terms, the CIRB is responsible for reviewing required reports that are received, which can include unanticipated problems involving risk to subject or others (UPIRTSO), protocol noncompliance issues, subject injuries, subject complaints, as well as protocol violations and deviations. When reviewing any of the required reports, the CIRB is responsible for making the determination as to whether the report 1) constitutes UPIRTSO or 2) rises to the level of serious or continuing noncompliance with applicable laws and regulations or the requirements and/or determinations of the CIRB.

Based on its review, the CIRB must take appropriate responsive action, which may include submitting a report to regulatory agencies and/or suspension or termination of CIRB approval of the research. Any required reporting to regulatory agencies or oversight authorities, including OHRP, will be coordinated based on a process of discussion and consensus with the reporting site and its institutional officials. These discussions will include working together to determine the responsible party for reporting, including reporting any UPIRTSO to OHRP. Per OHRP guidance, any required reporting to regulatory agencies or oversight authorities must take place within one (1) month from receipt of the UPIRTSO report. In the case of suspension or termination of CIRB approval, the CIRB will notify NCC leadership, NINDS staff and site officials, including the PI, and appropriate Institutional Officials, within one (1) business day.

After determining the course of action, the CIRB must then inform the appropriate site(s) of the findings, determinations, actions taken, and any modifications or remedial action required by the CIRB in response to such report(s). In certain cases, such as when an adverse event is determined to be a UPIRTSO, the CIRB may determine that information contained in a report could impact either subject safety or the conduct of the trial at all sites. In this instance, the CIRB will inform all site PIs engaged in the trial.

**B. Event Reporting in WebDCU™**

The following information is intended to provide event reporting guidance for investigators participating in StrokeNet trials inclusive of serious adverse events, unanticipated problems, protocol deviations, violations, and noncompliance. The guidelines outlined herein incorporate common data elements and are in compliance with both the FDA and Health and Human Services (HHS) defined Code of Federal Regulations (CFR) for the protection of human research participants, the procedures and requirements governing the use of Investigational New Drug (IND), and the monitoring of serious and unexpected adverse events codified under Title 21 CFR part 56 (Institutional Review Boards), part 312 (Investigational New Drug) and 45 CFR part 46 (Protection of Human Participants).

**Trials using the StrokeNet CIRB at the University of Cincinnati:**

Before reporting, refer to Appendix B of this SOP and the associated trial manual of procedures to determine whether an event is reportable. To report an event, the "Unanticipated Event-PD Report" (UAE-PD) must be completed. Contact the NCC Project Manager for assistance if uncertainly exists surrounding need for event reporting. Events requiring prompt reporting should be reported to the CIRB within 10 days of the research staff learning of the event. The UAE-PD from WebDCU will be submitted to the CIRB electronic protocol system by the NCC Project Manager on behalf of the site, and they will provide the site with the CIRB letter of acknowledgement following CIRB review. Other deviations/violations, unanticipated problems, and/or complaints not meeting the prompt reporting criteria will be reviewed by the Prime Protocol Principal Investigator (PI) or delegate and the study team regularly in aggregate as prepared by the NDMC team. Individual reports of minor protocol violations which are already documented in webDCU do not need to be re-entered in the UAE-PD, unless there is ongoing/egregious noncompliance in which case a single report will be entered.

**Trials using Advarra:**

Before reporting, refer to Appendix D of this SOP and the associated trial manual of procedures to determine whether an event is reportable. To report an event, the "Issues" Report must be completed in WebDCU. Contact the NCC Project Manager for assistance if uncertainly exists surrounding need for event reporting. Events requiring prompt reporting should be reported to the CIRB within 10 days of the research staff learning of the event. The Issues Report will be submitted to ADVARRA electronic protocol system by the NCC Project Manager on behalf of the site and they will provide the site with the CIRB letter of acknowledgement following review. Other deviations/violations, unanticipated problems, and/or complaints not meeting the prompt reporting criteria will be reviewed by the Prime Protocol Principal Investigator (PI) or delegate and the study team regularly in aggregate as prepared by the NDMC team. Individual reports of minor protocol violations which are already documented in webDCU do not need to be re-entered in as "Issues", unless there is ongoing/egregious noncompliance in which case a single report will be entered.

**C. Prime Protocol Principal Investigator (PI) Responsibilities for the Annual Continuing Review for Trials using the StrokeNet CIRB at the University of Cincinnati**

The Prime Protocol PI will provide information listed below to the CIRB and attest to the following applicable requirements:

1. The Prime Protocol PI must submit a data report provided by the NDMC to fulfill the requirement by the CIRB for the study team to evaluate the number of subjects enrolled in the research. This is to ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol.
2. The Prime Protocol PI must also submit a list of premature terminations (site withdrawals) provided by the NDMC to fulfill the requirement of the CIRB for the study team to evaluate participant withdrawals for early identification of problems related to the conduct of the research.
3. The Prime Protocol PI must provide a summary of new and relevant information, published or unpublished, since the last IRB review that includes a synopsis from the Prime Protocol PI of the relevance of this information to the study's risks, benefits, alternatives and applicable informed consent documents.
4. The Prime Protocol PI must attest that the approved safety monitoring plan is being followed and that the DSMB has determined the research is appropriate to continue. The following requirements must be verified:
    a. The enrollment rate is reasonable to meet the goals of the study.
    b. Selection of subjects is equitable and meets the goals of the study.
    c. No events (deviation/violation, unanticipated problems, complaints, noncompliance, etc.) have occurred that alter the risk/benefit analysis and qualify as an unanticipated problem.
    d. No changes to the study are required to decrease deviations/violations, unanticipated problems, and/or complaints in the future.

The Prime Protocol PI must attest that the NDMC consent monitoring process is being followed to ensure that each site is using the appropriate consent and HIPAA form versions.

D. **Prime Protocol Principal Investigator (PI) Responsibilities for the Annual Continuing Review for Trials using Advarra**

The Prime Protocol PI will provide information listed below to Advarra and attest to the following applicable requirements:

1. The Prime Protocol PI and approved sites must submit enrollment data fulfill the requirement by the CIRB for the study team to evaluate the number of subjects enrolled in the research. This is to ascertain whether enrollment is consistent with the planned number of subjects described in the IRB-approved protocol.

2. The Prime Protocol PI must also submit a list of premature terminations (site withdrawals) provided by approved sites to fulfill the requirement of the CIRB for the study team to evaluate participant withdrawals for early identification of problems related to the conduct of the research.
3. The Prime Protocol PI must provide a summary of new and relevant information, published or unpublished, since the last IRB review that includes a synopsis from the Prime Protocol PI of the relevance of this information to the study's risks, benefits, alternatives and applicable informed consent documents.
4. The Prime Protocol PI must attest that the approved safety monitoring plan is being followed and that the DSMB has determined the research is appropriate to continue. The following requirements must be verified:
    a. The enrollment rate is reasonable to meet the goals of the study.
    b. Selection of subjects is equitable and meets the goals of the study.
    c. No events (deviation/violation, unanticipated problems, complaints, noncompliance, etc.) have occurred that alter the risk/benefit analysis and qualify as an unanticipated problem.
    d. No changes to the study are required to decrease deviations/violations, unanticipated problems, and/or complaints in the future.

**4. REFERENCES TO OTHER APPLICABLE SOPs and Guidance Documents**

NINDS Guidelines for Data and Safety Monitoring in Clinical Trials, last updated August 8, 2013.

Advarra IRB Handbook for Investigators, Institutions, Sponsors, and Sponsors' Representatives v05, last updated September 2021.

**5. LINKS**:

http://researchhow2.uc.edu/home/browse-by-offices/hrpp

http://www.ninds.nih.gov/research/clinical_research/policies/data_safety_monitoring.htm

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

**6. DOCUMENT HISTORY**

| Version | Description of Modifications | Completion Date | Issue Date | Effective Date |
|---|---|---|---|---|
| 1.0 | Final | 03-Jun-2014 | 03-Jun-2014 | 03-Jun-2014 |
| 2.0 | September 2019 Revision | 05-Sep-2019 | 22-Nov-2019 | 22-Nov-2019 |
| 2.1 | Attached updated UC SOP | 06-Feb-2020 | 06-Feb-2020 | 06-Feb-2020 |

| | | | | |
|---|---|---|---|---|
| 3.0 | Added Prime Protocol PI responsibilities for Continuing Review and administrative changes | 29-Feb-21 | 29-Jun-21 | 29-Jun-21 |
| 4.0 | Adding Advarra reporting procedures | 01-Jun-23 | 10/30/2023 | 10/30/2023 |

University of CINCINNATI

| SOP: Reporting Unanticipated Problems Involving Risks to Participants and Others, Adverse Events and Other Problems to the IRB | | | |
|---|---|---|---|
| NUMBER | DATE | APPROVED BY | PAGE |
| HRP-092 | 9/23/2019 | J. Strasser | 1 of 5 |

## 1 PURPOSE

1.1 To ensure prompt reporting to the Institutional Review Board (IRB).

## 2 REVISIONS FROM PREVIOUS VERSION

2.1 Revised to add AAHRPP recommendations.

## 3 POLICY

3.1 The University of Cincinnati IRB complies with all applicable local, state, and federal regulations that pertain to reporting requirements. Federal regulations require institutions to have written policies and procedures in place that ensure prompt reporting of unanticipated problems involving risk to participants or others and certain adverse events to the IRB, regulatory agencies and institutional officials.

3.2 These problems can occur in any type of research (medical or non-medical) and may include occurrences such as adverse events, research participant complaints, protocol deviations, and other untoward events involving risk. Events requiring prompt reporting by Investigators and research staff may involve physical, psychological, social, legal, or economic harms.

3.3 When research is not covered by DHHS regulations, written materials specify that reports of unanticipated problems involving risks to participants or others are not to be reported to OHRP.

3.4 When research is not covered by FDA regulations, written materials specify that reports of unanticipated problems involving risks to participants or others are not to be reported to FDA.

3.5 When following VA regulations:

3.5.1 The unfounded classification of a serious adverse event as “anticipated” constitutes serious non-compliance.

3.5.2 The unfounded classification of a serious adverse event as “anticipated” constitutes serious non-compliance.

3.5.2.1

3.5.2.2 Within five business days after a report of a serious unanticipated problem involving risks to participants or others, or of a local unanticipated serious adverse event, the convened IRB or a qualified IRB member-reviewer must determine and document whether the reported incident was serious and unanticipated and related to the research.

3.5.2.3 If the convened IRB or the IRB reviewer determines that the problem or event was serious, unanticipated, and related to the research, the IRB chair or designee must report in writing the unanticipated problem or event within five business days after the determination to:

Facility director.

Associate chief of staff for research.

The Research and Development Committee.

3.5.2.4 If the convened IRB or the IRB reviewer determines that the problem or event was serious, unanticipated, and related to the research, a simultaneous determination is required regarding the need for any action (e.g., suspension of activities; notification of participants) necessary to prevent an immediate hazard to participants in accordance with VA regulations.

3.5.2.5

3.5.2.6 If it was determined that the problem or event is serious, unanticipated, and related to the research, the convened IRB must determine and document whether a protocol or consent document modification is warranted.

3.5.2.7 If the convened IRB determines that a protocol or consent document modification is warranted, the IRB must also determine and document:

Revised to add AAHRPP recommendations.

## 2 POLICY

2.1 The University of Cincinnati IRB complies with all applicable local, state, and federal regulations that pertain to reporting requirements. Federal regulations require institutions to have written policies and procedures in place that ensure prompt reporting of unanticipated problems involving risk to participants or others and certain adverse events to the IRB, regulatory agencies and institutional officials.

2.2 These problems can occur in any type of research (medical or non-medical) and may include occurrences such as adverse events, research participant complaints, protocol deviations, and other untoward events involving risk. Events requiring prompt reporting by Investigators and research staff may involve physical, psychological, social, legal, or economic harms.

2.3 When research is not covered by DHHS regulations, written materials specify that reports of unanticipated problems involving risks to participants or others are not to be reported to OHRP.

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2.5.2.3 If the convened IRB or the IRB reviewer determines that the problem or event was serious, unanticipated, and related to the research, the IRB chair or designee must report in writing the unanticipated problem or event within five business days after the determination to:

Facility director.

Associate chief of staff for research.

The Research and Development Committee.

2.5.2.4 If the convened IRB or the IRB reviewer determines that the problem or event was serious, unanticipated, and related to the research, a simultaneous determination is required regarding the need for any action (e.g., suspension of activities; notification of participants) necessary to prevent an immediate hazard to participants in accordance with VA regulations.

2.5.2.5

2.5.2.6 If it was determined that the problem or event is serious, unanticipated, and related to the research, the convened IRB must determine and document whether a protocol or consent document modification is warranted.

2.5.2.7 If the convened IRB determines that a protocol or consent document modification is warranted, the IRB must also determine and document:

Whether previously enrolled participants must be notified of the modification.

When such notification must take place and how such notification must be documented.

2.5.2.8 The report of unanticipated problems involving risks to participants or others be sent to:
The Office of Research and Development, if VA-funded.
The Regional Office of Research Oversight.

2.6 Potential risks and adverse events that may be reasonably anticipated (i.e., "expected") must be described in the informed consent process/form and do not require prompt reporting to the IRB. The following are examples of events that DO NOT require prompt reporting:

2.6.1 Adverse events or injuries that are BOTH not serious and unrelated;
2.6.2 Adverse device effects that are non-serious, anticipated, or unrelated;
2.6.3 Deaths not attributed to the research, e.g., from "natural causes," accidents, or underlying disease and the Investigator has ruled out any connection between the study procedures and the participant's death;
2.6.4 Protocol deviations or violations not involving risks to participants or unlikely to recur;
2.6.5 Data Safety Monitoring Board reports, interim analyses, or other reports, findings, or new information not altering the risk/benefit profile;
2.6.6 Investigator Brochure updates not involving safety information; and
2.6.7 Problems or findings not involving risk (unless the information could affect participants' willingness to continue in the research).

2.7 The following events may represent unanticipated problems involving risks to participants and others and shall be promptly reported:

2.7.1 Internal adverse events that are unexpected, related to the research, and involve new or increased risks to participants or others ;
2.7.2 Unanticipated adverse device effects
2.7.3 Significant protocol deviations (or other accidental or unintentional changes to the protocol or procedures) involving safety or integrity risks or with the potential to reoccur;
2.7.4 Events requiring prompt reporting according to the protocol Sponsor;
2.7.5 Complaints made by research participants indicating an unanticipated event, or complaints that cannot be resolved by the research staff.
2.7.6 Unapproved changes made to the research to eliminate an apparent immediate hazard to a research participant;
2.7.7 Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports/recommendations altering the risks/benefit profile;
2.7.8 New information indicating an unexpected change in risks or potential benefits (e.g., literature/scientific reports or other published findings);
2.7.9 Investigator's Brochure (IB or IDB) updates or revisions to safety information; and
2.7.10 Other problems or findings (e.g., breach of confidentiality, loss of study data or forms, etc.) that could influence the safe conduct of the research.

2.8 The UC IRB will accept non-site adverse event reports (safety reports submitted to FDA, etc.) submitted by Investigators and Sponsors on behalf of the Investigators, if in accord with federal regulations the event is:

2.8.1 Both serious and unexpected,
2.8.2 The report identifies all previous safety reports concerning similar adverse experiences
2.8.3 The report analyzes the significance of the current adverse experience in light of the previous reports, and
2.8.4 The report outlines a corrective action plan.

2.8.5 An Investigator participating in a multicenter study may rely on the Sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the Sponsor. In addition, if the Investigator knows that the Sponsor has reported the unanticipated problem directly to the IRB, because the Investigator, Sponsor and IRB made an explicit agreement for the Sponsor to report directly to the IRB, and because the Investigator was copied on the report from the Sponsor to the IRB, the FDA would not expect the Investigator to provide the IRB with a duplicate copy of the report received from the Sponsor.

2.8.6 If the Sponsor does not submit external adverse events that are determined to be unanticipated problems to the IRB on behalf of the investigative site, the Investigator is required to submit them, along with the required explanation, within 10 days of the date the Investigator receives them.

2.9 The IRB will accept reports when the Investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold requiring reporting.

2.10 All reports to the IRB of unanticipated problems will explain clearly why the event is "unanticipated" and clearly explain why the event represents a "problem involving risks to human subjects or others."

2.11 The UC IRB expects reports of unanticipated problems to include a corrective action plan to address the issue, or written justification for why none was provided.

2.12 Events identified as requiring prompt reporting will be reported to the IRB within 10 days of the research staff member's learning of the event.

2.13 Veterans Administration Medical Center (VAMC) researchers are required to report the event in writing to the IRB within 5 business days.

2.14 Events resulting in temporary or permanent interruption of the study activities by the PI or Sponsor to avoid potential harm to participants must be reported immediately (within 48 hours).

2.15 All internal and external events that may represent unanticipated problems involving risks to participants or others shall be promptly reported, regardless of whether they occur during or after the study, or to a participant who has withdrawn from or completed study participation. If changes to the research or consent process are proposed as a result of the event, or if additional information will be provided to current and/or past participants, a modification request must be submitted for IRB review.

2.16 For VAMC research, the terms "unanticipated" and "unexpected" refer to an event or problem that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population. The term "Unanticipated Problem Involving Risks to Subjects or Others" includes any event or problem that is serious, unexpected, and related to the research, where "related" means the event or problem might reasonably be regarded as caused by, or probably caused by, the research. Serious unanticipated problems involving risks to participants or others may include:

2.16.1 Interruptions of participant enrollments or other research activities due to concerns about the safety, rights, or welfare of human research participants, research staff, or others.

2.16.2 Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individuals, or leads to serious complications or death;

2.16.3 Any VAMC National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the VA facility's research projects;

2.16.4 Any Sponsor analysis describing a safety problem for which action at the VAMC facility might be warranted;

2.16.5 Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research participants, research staff, or others;

2.16.6 Any problem reflecting a deficiency that substantively compromises the effectiveness of the VAMC facility's HRPP.

## 3 RESPONSIBILITIES

3.1 The principal investigator is responsible for ensuring promptly reportable events are identified and submitted to the IRB in a timely manner.

## 4 PROCEDURE

4.1 Identify and assess the given incident, experience or outcome.

4.2 Document assessments and conclusions in the research record.

4.3 Report any incident, experience or outcome that meets the criteria for prompt reporting with any applicable documentation to the IRB using "FORM: Reportable New Information (HRP-214)".

4.4 Inform the appropriate research team members, support units, administrative officials, funding/sponsoring organizations, and regulatory agencies when needed and in accordance with applicable policies, procedures, agreements, and regulations.

## 5 MATERIALS

5.1 FORM: Reportable New Information (HRP-214)

5.2 HRP-024 – SOP – Review of Reportable New Information

## 6 REFERENCES

6.1 21 CFR §56.108(b)

6.2 45 CFR §46.103(b)(5), 45 CFR §46.108(a)

6.3 VHA Handbook 1058.01

# The NIH StrokeNet CIRB Unanticipated Event (UAE) and Protocol Deviation (PD) Report Guidelines for Site PIs (v06.01.2023)

## Events Requiring Prompt Reporting for trials using the StrokeNet CIRB at the University of Cincinnati

1. Certain events require prompt reporting by site principal investigators (PI). These are submitted via the WebDCU™ "StrokeNet Unanticipated Event-PD Report". Prompt reporting to the StrokeNet CIRB must occur no later than 10 days from the time the investigator learns of the event.

Examples:

A. Internal adverse events that are unexpected, related to the research, and involve new or increased risks to participants or others (*2.7.1);

B. Unanticipated adverse device effects (*2.7.2);

C. Significant protocol deviations (or other accidental or unintentional changes to the protocol or procedures) involving safety or integrity risks or with the potential to reoccur (*2.7.3);

D. Events requiring prompt reporting according to the protocol Sponsor (*2.7.4);

E. Complaints made by research participants indicating an unanticipated event, or complaints that cannot be resolved by the research staff (*2.7.5);

F. Unapproved changes made to the research to eliminate an apparent immediate hazard to a research participant (*2.7.6);

G. Problems or findings (e.g., breach of confidentiality, loss of study data or forms, etc.) that could influence the safe conduct of the research (*2.7.10).

H. Report any new information from written reports (i.e. study monitors, DSMB, etc.) (requirement from UAE-PD form)

** Based on Guidance for The NIH StrokeNet cIRB Event Reporting (HRP-092 SOP: Reporting Unanticipated Problems Involving Risks to Participants and Others, Adverse Events and Other Problems to the IRB)*

2. When an event occurs which requires prompt reporting, the Site PI will:

- Identify and assess the given incident, deviation, experience, or outcome.
- Document assessments and conclusions in the research record. Report any incident, deviation, experience, or outcome that meets the criteria **for prompt reporting** (see examples above) with appropriate documentation via the WebDCU™ "StrokeNet Unanticipated Event-PD Report" form. Contact NCC Project Manager for assistance if uncertainty exists surrounding need for event reporting.

- Inform the appropriate research team members, support units, administrative officials, funding/sponsoring organizations, and regulatory agencies about the event when needed and in accordance with applicable local policies, procedures, agreements, and regulations.


The NCC Project Manager will submit the event to the CIRB as Reportable New Information (RNI). The CIRB will provide a letter of acknowledgment that will be uploaded into WebDCU™ by the NCC Project Manager. If the CIRB requires further actions, the site will act on the letter requirements providing documentation of the completed requirements to the NCC Project Manager.

## Reporting Other Events

Site PIs do NOT need to report specific trial events that do not rise to the level of an Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO) in the WebDCU™ "StrokeNet Unanticipated Event-PD Report" form **unless requested by NCC Project Manager**.

Examples:

A. Adverse events or injuries that are both: not serious and unrelated (*2.6.1);

B. Adverse device effects that are non-serious, anticipated, or unrelated (*2.6.2);

C. Deaths not attributed to the research, e.g., from "natural causes," accidents, or underlying disease and the Investigator has ruled out any connection between the study procedures and the participant's death (*2.6.3);

D. Protocol deviations or violations not involving risks to participants or unlikely to recur (*2.6.4);

Notes:

1. The Awardee Prime Protocol PI or delegate is responsible for monitoring these in an ongoing manner for events that individually, or in aggregate, should be reported to the CIRB as UPIRTSOs. The Awardee Prime PI will verify at the time of continuing review that:
   A. The approved safety monitoring plan is being followed.

   B. The DSMB has determined the research is appropriate to continue.
   C. No events (deviation/violation, unanticipated problems, complaints, noncompliance, etc.) have occurred that alter the risk/benefit analysis.
   D. No changes are required to decrease deviations/violations, unanticipated problems, and/or complaints in the future.
2. The DSMB, Sponsor, and StrokeNet Awardee Prime PI team also review events regularly per the trial safety monitoring plan.

**References**

1. The NIH ADM SOP 12: Central Institutional Review Board (cIRB) Reporting
2. HRP-092 SOP: Reporting Unanticipated Problems Involving Risks to Participants and Others, Adverse Events and Other Problems to the IRB

If the dose level is included in the consent form, the IRB will generally not require that it be removed, but the information provided to participants must be accurate. Note that the IRB requires dose information to be included in the protocol.

### 17.3. Clinical Holds and Suspensions or Terminations

Any IRB notification of FDA Clinical Hold or other study hold/suspension or termination imposed by the sponsor/CRO, investigator, other reviewing IRB, other government agency, or other party, must include a summary of the reason(s) for the hold/suspension/termination and provide the IRB with adequate information to assess the impact to the study subjects.

The IRB must be notified when an FDA Clinical Hold, or any other study hold/suspension, is lifted. IRB notification should include a summary of how the issue(s) was resolved and any modifications made to study documents as a result of issue resolution, as applicable (e.g. protocol amendment).

### 17.4. Change of Investigator/Site Status

The IRB must be notified prior to replacing the current IRB-approved investigator at a site. The new investigator's CV and the reason for changing investigators must be included with the submission.

Submission to the IRB is also required when the IRB-approved investigator goes on a leave of absence, during which he or she will no longer retain responsibility as investigator and he or she is replaced by a new investigator.

The investigator must promptly report any pending or ongoing legal, regulatory, or professional actions or restrictions related to the practice of medicine or research at the site(s) (including sub-investigators, and site personnel). This information is required at the time of initial submission and post-approval as applicable.

The IRB should be promptly notified in the event the sponsor becomes aware (e.g., during a monitoring visit) of any unanticipated problems, evidence of serious or continuing noncompliance, scientific misconduct, undue influence on the conduct of the study, or any other event that may impact subject safety or alter the IRB's approval or sponsor's/sponsor's representative's status of the investigator/site.

## 18. Prompt Reporting Events (including Serious Adverse Events, Unanticipated Problems, Protocol Deviations, Violations, or Exceptions, and Noncompliance)

*Note: If blinded research staff listed as contacts in Advarra's CIRBI platform must remain blinded to safety-related submissions, the Advarra Safety Coordinator should be contacted BEFORE a report is submitted in CIRBI, to prevent unblinded information from being distributed.*

### 18.1. Serious Adverse Events (SAEs)

Investigators are required to submit any serious adverse events involving subjects enrolled at the site(s) that are determined to be **unexpected** and probably, possibly, or definitely **related** to the test article or research procedures. This notification to the IRB must occur promptly and no later than 2 weeks (10 business days) from the time the investigator learns of the event.

*Note: SAEs that have been determined to be unrelated to the test article should not be submitted to the IRB. In addition, for those SAEs where relatedness has not yet been determined (i.e., further analysis is required), submission to the IRB should only occur once it has been determined that the SAE was related to the test article.*

A serious adverse event that is expected, as identified in the study documentation (e.g., product information, protocol, and/or ICF), but is occurring at greater frequency or severity should be reported to the IRB as an unanticipated problem.

Investigators are expected to provide the IRB and sponsor with any additional requested information regarding SAEs, including follow-up reports, autopsy reports, and medical reports.

In addition, investigators are expected to report adverse events and other findings identified in the protocol as critical to safety evaluations, to the sponsor in accordance with the sponsor's reporting requirements and within the specified timeframe.

## 18.2. External Serious Adverse Events/Unexpected Adverse Device Events (Including IND Safety Reports)

External SAEs (e.g., IND safety reports, suspected unexpected serious adverse reactions or SUSARs), which are SAEs that occur at sites not under the purview of the IRB, should only be submitted if they meet the criteria of an unanticipated problem. Please refer to 18.4 Unanticipated Problems below to determine which external SAEs may qualify for an unanticipated problem involving risks to subjects or others that must be reported to the IRB.

Sponsors and investigators are encouraged to review FDA's Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs—Improving Human Subject Protection.

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3[s]). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150[a][1]).
- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46[b], 21 CFR 812.150[b][1]).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.

Prior to submitting copies of any safety report or UADE report to the IRB, investigators should confirm that the reports have not been submitted on their behalf by the sponsor.

When SAEs or safety reports that do not meet the unanticipated problem or UADE criteria are submitted to the IRB, the submitting party will receive acknowledgement of receipt only and the item will not be reviewed by the IRB. When these items are submitted by a sponsor or CRO, Advarra's default process is to generate an acknowledgement of receipt to all open sites and fees apply. If the sponsor/CRO does not wish to send a mass acknowledgement to all sites, they must opt out of this feature.

## 18.3. Protocol Deviations, Violations, or Exceptions

An investigator may not initiate a change in research activity without IRB approval unless the change is necessary to eliminate apparent immediate hazards to human subjects, in which case it should be reported to the IRB as an **unanticipated problem**.

Investigators and sites must notify the IRB in writing of any unapproved protocol deviations/violations (an accidental or unintentional change to the IRB-approved protocol) that, in the investigator's judgment, potentially caused harm to subjects or others, indicates that the subjects or others are at an increased risk of harm, or has adversely impacted data integrity. Unplanned or unintentional deviations are to be reported to the IRB as **unanticipated problem** or **noncompliance** as noted in 18.4 Unanticipated Problems and 18.5 Noncompliance.

This notification to the IRB must occur promptly and no later than 2 weeks (10 business days) from the time of identification of the unplanned or unintentional protocol deviation/violation. An automatic acknowledgement will be sent from CIRBI and no additional action is required, unless investigators are contacted by the IRB to provide further information.

There are many unplanned or unintentional violations/deviations or changes in study status that do not cause harm, place subjects at increased risk of harm, or adversely affect data integrity. The IRB does not require that these minor violations/deviations be reported. Examples of minor violations/deviations that do not need to be reported may include the following:

- Out of window visits
- Study procedures conducted out of timeframe
- Subject failure to initial each page of the ICF (as applicable)
- Subject failure to return subject materials (e.g., diaries, journals, etc.).
- Administrative hold on a study not related to safety issues

Examples of accidental or unintentional protocol violations/deviations that must be submitted to the IRB include:

- Changes necessary to eliminate apparent immediate hazards to the subject
- Failure to document informed consent
- Informed consent obtained after initiation of study procedures
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to report serious adverse event to the IRB and/or sponsor
- Failure to perform a required lab test that, in the opinion of the investigator, may affect subject safety or data integrity
- Drug/study medication dispensing or dosing error
- Study visit conducted outside of required timeframe that, in the opinion of the investigator, may affect subject safety
- Failure to follow safety monitoring plan
- Missing or unreturned investigational product

On occasion, an investigator may want to intentionally deviate from the IRB-approved protocol for an individual research subject (i.e., protocol exception). The investigator must get sponsor approval and obtain prospective IRB approval. The planned protocol exception cannot be initiated until the sponsor **and** the IRB have approved the deviation. Furthermore, to the extent investigators or sponsors request protocol exceptions for multiple research subjects, the IRB

may determine that a protocol amendment/modification to the IRB-approved protocol is the appropriate course of action.

### 18.4. Unanticipated Problems

The IRB requires that sponsors and/or investigators/sites (as appropriate) submit in writing any unanticipated problems (UAPs) involving risks to subjects or others, including adverse events that should be considered UAPs as described below. Notification to the IRB of a UAP must occur promptly but no later than 2 weeks (10 business days) from the time of identification.

UAPs are defined as any incidence, experience, or outcome that is:

- Unexpected (in terms of nature, severity, or frequency) given the information provided in research-related documents and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

The IRB uses the following criteria to determine whether an incidence, experience, or event is a UAP involving risk to subjects or others:

- Unanticipated or unexpected at the time of IRB approval;
- Involved new or increased risk to subjects or others; and
- Related to the research.

Examples of the types of adverse events (AEs) that must be promptly submitted to the IRB (regardless of whether they occur during the study, after study completion, or after subject withdrawal or completion) may include but are not limited to the following:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure, such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome.
- A single occurrence, or more often a small number of occurrences, of a serious unexpected event that is not commonly associated with drug exposure, but uncommon in the study population.
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be a UAP.
- A determination should be made as to whether the series of AEs represent a signal that the AEs were not just isolated occurrences and involve risk to human subjects.
- An AE that is described or addressed in the research-related documents (i.e., investigator's brochure, protocol, ICF) but occurs at a specificity or severity that is inconsistent with prior observations.
- A serious AE that is described or addressed in the research-related documents, but for which the rate of occurrence is a clinically significant increase in the expected rate of occurrence for the study.
- Any other AE that would cause the sponsor to modify study-related documentation or would prompt the IRB to take an action to ensure the protection of human subjects, such as:
- Any event that requires prompt reporting in accordance with the protocol or sponsor.
- Any accidental or unintentional change to the IRB-approved protocol that involved risks or has the potential to recur.

- Any change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research.
- Any complaint by a subject that indicates an unanticipated risk or which cannot be resolved by the research staff/sponsor.
- Any other event that may impact subject safety.

The IRB notifies the appropriate regulatory agency of any incidence, experience or outcome that the IRB has determined to be a UAP involving risks to subjects or others.

The investigator is responsible for the documentation, investigation, and follow-up of all unanticipated problems that occur at the site in which the investigator is responsible for the conduct of the research.

Sponsors must also report any unanticipated problems that occur at sites outside of the IRB's jurisdiction which are relevant to the sites that are under the IRB's jurisdiction.

If there are questions about unanticipated problems involving risk to subjects or others, please contact the IRB.

## 18.5. Noncompliance

Investigators/sites and sponsors are expected to comply with applicable regulations and IRB determinations/requirements when conducting research. Noncompliance with the regulations and/or IRB determinations and requirements can result in an action up to and including suspension or termination of IRB approval.

The IRB defines noncompliance as any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with applicable regulations, the IRB's *Handbook*, and/or the determinations and requirements of the IRB. Noncompliance may range from minor to serious; be unintentional or willful; and may occur once, sporadically, or continuously. The degree of noncompliance is evaluated on a case-by-case basis and takes into account whether subjects were harmed or placed at an increased risk of harm.

Serious noncompliance is defined as any action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of subjects, increases risk to subjects, or compromises the scientific integrity or validity of the research.

Continuing noncompliance is defined as a pattern of repeatedly failing to comply with applicable regulations, the IRB's Handbook, and/or the determinations and requirements of the IRB that may affect subjects' rights and welfare, increase risk to subjects, or may compromise the scientific integrity or validity of the research. Continuing noncompliance also includes frequent instances of minor noncompliance or failure to respond to a request to resolve an episode of noncompliance.

Sponsors, investigators and/or research staff must notify the IRB in writing of any instance of noncompliance with the regulations, this Handbook, and/or determinations and requirements of the IRB. This notification must be as soon as possible but no later than 2 weeks (10 business days) from the time of the event.

Any allegation of noncompliance should also be promptly reported via telephone or in writing to the IRB so that a thorough investigation can be conducted. Noncompliance reports or allegations should include the following information (as appropriate):

- Name of the submitting party

- CIRBI assigned protocol number
- Protocol title
- A description of the event
- The impact on subject safety (if any)
- The immediate action(s) taken to ensure subjects were not harmed
- A corrective action plan to prevent re-occurrence
- Non-compliance assertion
- Timetable of events
- Supporting information from other sources (e.g., sponsor) (if applicable)

Reports and allegations of noncompliance will be evaluated by the IRB and can result in an action up to and including suspension or termination of IRB approval. Any report of noncompliance determined by the IRB to be serious or continuing or determination to suspend or terminate IRB approval will be reported to the appropriate regulatory agency by Advarra.

### 18.6. Site Visits and Observing Informed Consent

The IRB has the authority to observe or have a third party observe the consent process and the research. If concerns about subject safety arise, or when other issues of noncompliance warrant such action, the IRB may conduct site visits or designate an authorized third party or third parties to observe the informed consent process and the research. The IRB may review study records and the site's written operating procedures to assure the integrity of the records and the protection of the rights and welfare of the study subjects.

The IRB may determine that submission of a copy of a subject's signed ICF is required in order to verify that the site is using the correct version of the document. If this determination is made, the IRB notifies the investigator, and the investigator is then responsible for submitting a complete copy of the subject's signed ICF to the IRB.

## 19. Continuing Review

The IRB determines the frequency of continuing review for the protocol and investigator's/site's conduct of the protocol at the time of initial approval.

Notification of an upcoming continuing review and the information required for submission to the IRB (i.e., report on the progress of the research) is communicated to the submitting party and/or the investigator well in advance of the submission deadline. Every effort is made to notify the sponsor and/or investigator that a continuing review report is due, however, it is the sponsor's and/or the investigator's responsibility to ensure that continuing review materials are submitted in a timely manner. Delays in providing the required documentation can jeopardize IRB approval. Without continuing review and approval, all study-related activities must stop unless continued participation is approved by the IRB to ensure subject safety.

- **Studies conducted under the Old Common Rule:** The frequency of continuing review may be changed at the discretion of the IRB; however, it shall be no greater than 12 months. Continuing review activities must continue as long as the research remains open to long-term follow-up of subjects, even when the research is permanently closed to new enrollment and all subjects have completed all research-related interventions, or when the remaining research activities are limited to the collection of private identifiable information.
- For studies conducted under an FWA, continuing review activities must continue in accordance with the criteria stated above and until all data analysis of identifiable private information is complete.

# The NIH StrokeNet Advarra IRB Event Reporting for Serious Adverse Events (SAEs), Unanticipated Problems (UAPs), Protocol Deviations (PDs), Violations, or Exceptions, and Noncompliance Guidelines for Site PIs (v6/1/2023)

## Events Requiring Prompt Reporting for the Advarra IRB

1. Certain events require prompt reporting by site principal investigators (PI). These are submitted in WebDCU™ via the "Issues" table under the Central IRB button. Prompt reporting to the Advarra IRB must occur no later than 10 business days from the time the investigator learns of the event.

A. Internal Serious Adverse Events involving subjects enrolled at the site(s) that are determined to be unexpected and probably, possibly, or related to the test article or research procedures (*18.1).

B. Unanticipated adverse device effects (*18.2)

C. Significant protocol deviations (or other accidental or unintentional changes to the protocol or procedures) involving safety or integrity risks or with the potential to reoccur (*18.3). Examples: failure to document informed consent, informed consent obtained after initiation of study procedures, enrollment of a subject who did not meet all inclusion/exclusion criteria, performing study procedure not approved by the IRB, failure to report serious adverse event to the IRB and/or sponsor, failure to perform a required lab test that, in the opinion of the investigator, may affect subject safety or data integrity, drug/study medication dispensing or dosing error, study visit conducted outside of required timeframe that, in the opinion of the investigator, may affect subject safety, failure to follow safety monitoring plan, missing or unreturned investigational product.

D. Unanticipated problems involving risk to subjects or others (UAPIRTSO) including AEs that are serious, unexpected, and related to research that increases risk (*18.4).

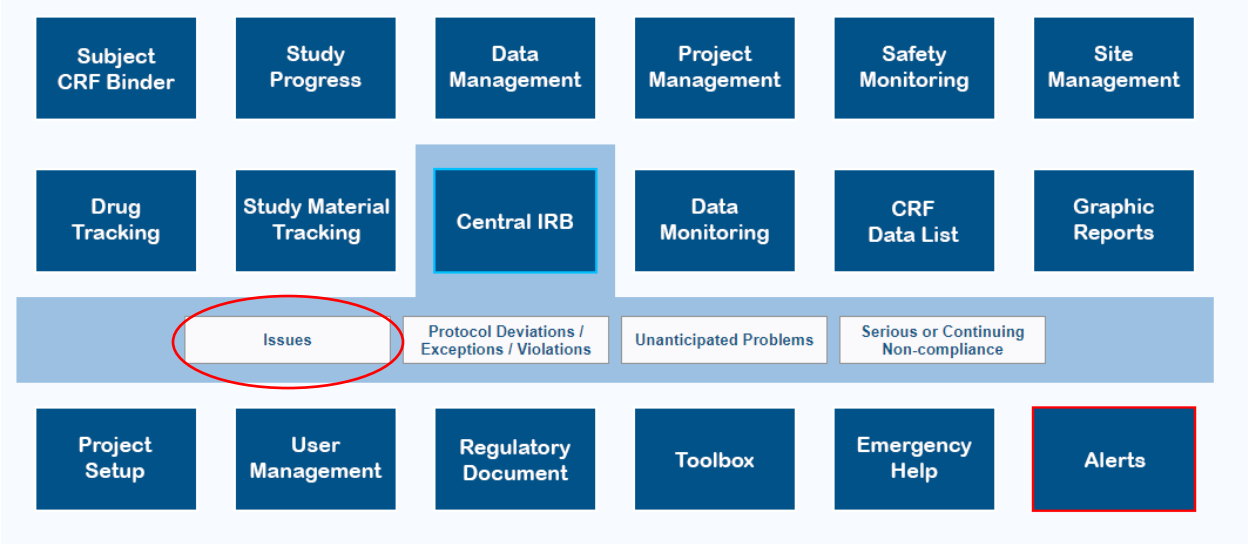
   Examples: Any event that requires prompt reporting in accordance with the protocol or sponsor, any accidental or unintentional change to the IRB-approved protocol that involved risks or has the potential to recur, any change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant, any publication in the literature, safety monitoring report, interim result, or other finding that indicates an unexpected change to the risks or potential benefits of the research, any complaint by a subject that indicates an unanticipated risk or which cannot be resolved by the research staff/sponsor.

E. Noncompliance either serious or continuing (*18.5)

** Based on Guidance from ADVARRA IRB Handbook for Investigators, Institutions, Sponsors, and Sponsors' Representatives v05 – Section 18 -Last updated September 2021.*

2. When an event occurs which requires prompt reporting, the Site PI will:

- Identify and assess the given incident, deviation, experience, or outcome.
- Document assessments and conclusions in the research record. Report any incident, deviation, experience, or outcome that meets the criteria **for prompt reporting** (see examples above) with appropriate documentation via the WebDCU™ "Issues" form. Contact NCC Project Manager for assistance if uncertainty exists surrounding need for event reporting.
- Inform the appropriate research team members, support units, administrative officials, funding/sponsoring organizations, and regulatory agencies about the event when needed and in accordance with applicable local policies, procedures, agreements, and regulations.




The NCC Project Manager will review all events entered in the Issues Table and determine/submit the event to CIRBI as either an unanticipated problem, protocol deviation, or serious or continuing noncompliance if prompt reporting is required. The Advarra IRB will provide a letter of acknowledgment that will be uploaded into WebDCU™ by the NCC Project Manager. If Advarra requires further actions, the site will act on the letter requirements providing documentation of the completed requirements to the NCC Project Manager.

## Reporting Other Events

1. Site PIs do NOT need to report specific trial events that do not rise to the level of an Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO) in the WebDCU™ Issues table unless requested by the NCC Project Manager. The Awardee Prime Protocol PI or delegate is responsible for monitoring these in an ongoing manner for events that individually, or in aggregate, will be reported to the Advarra IRB or result in a corrective action plan.

Examples:

A. Adverse events or injuries that are both: not serious and unrelated
B. Adverse device effects that are non-serious, anticipated, or unrelated
C. Deaths not attributed to the research, e.g., from “natural causes,” accidents, or underlying disease and the Investigator has ruled out any connection between the study procedures and the participant’s death
D. Protocol deviations or violations not involving risks to participants or unlikely to recur Examples: Out of window visits, study procedures conducted out of timeframe; subject failure to initial each page of the ICF, subject failure to return subject materials (e.g., diaries, journals, etc.), administrative hold on a study not related to safety issues.

**References**

1. The NIH ADM SOP 12: Central Institutional Review Board (cIRB) Reporting
2. ADVARRA IRB Handbook for Investigators, Institutions, Sponsors, and Sponsors’ Representatives v05, Section 18 -Last updated September 2021.

# NIH StrokeNet Network

Standard Operating Procedure (SOP)

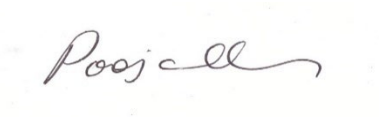
# Central Institutional Review Board (CIRB) Reporting

# Standard Operation Procedures

Version 4.0

ADM #12

Reviewed and Approved by:



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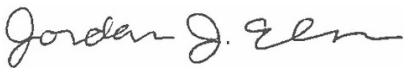

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