



NEALS

Northeast Amyotrophic
Lateral Sclerosis
Consortium

Standard Operating Procedure (SOP)
Central Institutional Review Board Reporting

Version 1.0

SOP NEALS CIRB 102

Originators: NEALS NCRI Coordinating Center Personnel

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STANDARD OPERATING PROCEDURE FOR CIRB REPORTING

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| SOP NEALS CIRB 101 Version No: 1.0 Effective Date: | CIRB REPORTING | Supercedes Document: N/A Effective Date: N/A |
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1. POLICY

Employees, professional staff or other agents of institutions participating as a Clinical Study Site (CSS) for a Northeast ALS (NEALS) Network human research study overseen by the NEALS Central IRB (CIRB) are required to report unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance and cessation of research activities that are determined, discovered, or learned by them in connection with the conduct of a NEALS human research study in accordance with the standards, time frames, and procedures specified in this CIRB Reporting SOP, which includes the attached CIRB Reporting Table (section 8: Procedures).

2. SCOPE

The policies and procedures described in this SOP apply to the Neurological Clinical Research Institute (NCRI) Coordinating Center (CC) within the context of their oversight and advisory roles for the NEALS CIRB Pilot Project, and to all CIRB Clinical Study Sites (CSS), CIRB Pilot investigators, staff, subcontractors, or other entities associated with the NEALS CIRB Pilot Project who manage, oversee, conduct, or are otherwise engaged in research in the CIRB Pilot Project.

3. ROLES AND RESPONSIBILITIES

A. NEALS Clinical Study Site Principal Investigator

The NEALS Clinical Study Site Principal Investigator (CSS PI) or designee is responsible for reporting to the CIRB any unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance, and cessation of research activities that are determined, discovered, or learned by them in connection with the conduct of a NEALS human research study, in accordance with the standards defined in the CIRB Reporting Table (section 8: Procedures).

Reports are made through the NCRI Coordinating Center as follows:

1. The CSS PI or designee completes the appropriate Report Form identified on the attached CIRB Reporting Table, and submits the completed form to the NCRI Coordinating Center CIRB Liaison (CC-CIRB Liaison) or designee via the online data entry system.
2. The CC-CIRB Liaison is then responsible for completing the CIRB Report Form and for submitting the completed form to the CIRB.
3. CSS and CC reports are to be made in accordance with the time frames specified in the CIRB Reporting Table.

B. NCRI Coordinating Center

The CC-CIRB Liaison or designee is responsible for submitting reports to the CIRB of unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance and cessation of research activities that they receive from CSSs in connection with the conduct of a NEALS human research study.

The CC-CIRB Liaison is responsible for completing the CIRB Report Form and for submitting the completed form to the CIRB in accordance with the time frames specified in the CIRB Reporting Table.

C. NCRI Data Coordinating Center

The NCRI Data Coordinating Center (DCC) is responsible for developing the data entry system for reporting by the CSS PI/designee of unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance and cessation of research activities that are determined, discovered, or learned by them in connection with the conduct of a NEALS human research study for review by the CC-CIRB Liaison to determine required reporting to the CIRB and in accordance with the standards defined in the CIRB Reporting Table.

DCC reports are to be made in accordance with the time frames specified in the CIRB Reporting Table.

D. NEALS Central Institutional Review Board

The CIRB is responsible for reviewing reports of the unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subject/s, complaints, non-compliance and cessation of research activities that they receive from the NCRI CC in connection with the conduct of a NEALS human research study.

When reviewing any of the aforementioned reports, the NEALS CIRB is responsible for making the determination as to whether the report constitutes an unanticipated problem involving risks to subjects or others or serious or continuing noncompliance with applicable laws and regulations or the requirements or determinations of the CIRB and for taking appropriate responsive action, which may include suspension or termination of CIRB approval of the research.

The NEALS CIRB is responsible for informing the reporting CSS PI/designee through the NCRI CC of the findings, determinations, actions taken, and any modifications or remedial action required by the CIRB in response to such reports and, when applicable, informing all NEALS CSS PIs participating in the Pilot CIRB Project of any discovery or determination that affects subject safety or the conduct of the trial at all CSSs.

E. External Reporting

Responsibilities regarding any required reporting to sponsors/funding agencies, OHRP, FDA and/or other oversight authorities of any serious or continuing non-compliance, unanticipated problems involving risks to subjects or others, and suspension or termination of CIRB approval in connection with a NEALS human research study will be coordinated as described in the NEALS CIRB Reliance Agreement executed by the CSS.

4. APPLICABLE REGULATIONS AND GUIDELINES

Ethical Principles

All parties shall be guided by the *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, generally known as the "Belmont Report."

45 CFR 46
21 CFR 56
21 CFR 50

5. REFERENCES TO OTHER APPLICABLE SOPs

NEALS Network CIRB Reliance Process SOP

6. ATTACHMENTS AND REFERENCES

Document History

7. TERMS AND ABBREVIATIONS

The following terms and abbreviations are used in this document:

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| ADE | Adverse Device Effect |
| AE | Adverse Event |
| CC | NCRI Coordinating Center at Massachusetts General Hospital |
| CC-CIRB Liaison | NEALS Clinical Coordinating Center Central Institutional Review Board Liaison |
| CFR | Code of Federal Regulations |
| CIRB | Central Institutional Review Board |
| CSS | Clinical Study Site that conducts research for a particular NEALS protocol |
| CSS PI | Principal Investigator who is responsible for implementing and conducting a specific NEALS protocol at a Clinical Study Site |
| DCC | NCRI Data Coordinating Center at Massachusetts General Hospital |
| DMC | Data Monitoring Committee |
| DSMB | Data and Safety Monitoring Board |
| DSMC | Data and Safety Monitoring Committee |
| eIRB | Electronic Institutional Review Board (Form) |
| FDA | US Food and Drug Administration |
| HIPAA | Health Information Portability and Accountability Act |
| NEALS | Northeast ALS Network |
| NCRI | Neurological Clinical Research Institute |
| OHRP | Office for Human Research Protections |
| PPI | Protocol Principal Investigator of a NEALS protocol |
| SAE | Serious Adverse Event |
| UADE | Unanticipated Adverse Device Effect |

8. SPECIFIC PROCEDURES

The specific requirements, timeframes, and procedures for making reports to the NEALS CIRB of unanticipated problems (including adverse events), injuries to subjects, protocol deviations/violations, changes initiated without CIRB approval to eliminate apparent immediate hazards to subjects, complaints, non-compliance and cessation of research activities as required by this SOP are outlined in the attached CIRB Reporting Table. Note that certain types of events need only be reported at Continuing Review.

NEALS CIRB REPORTING REQUIREMENTS

| Type of Report | Description | Reporting Procedures | Form | Time Frame |
|-------------------------------|---|---|----------------------------|--|
| Local CSS Adverse Events (AE) | Adverse event means any untoward or unfavorable 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 the research. | CSS PI/designee reports all Adverse Events to CC-CIRB Liaison via the online data entry system. | Adverse Event Form | Report all Adverse Events within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the Adverse Event except Serious Adverse Events as noted below |
| Serious Adverse Events (SAE) | Serious adverse event means any untoward or unfavorable medical occurrence in a human subject which results in death, life-threatening, hospitalization, disability or permanent damage, congenital anomaly/birth defect, or required an intervention to prevent permanent impairment and temporally associated with the subject's participation in the research. | CSS PI/designee reports all Serious Adverse Events to CC-CIRB Liaison via the online data entry system. | Serious Adverse Event Form | Report Serious Adverse Events (SAEs) within 24 hours of when CSS PI first becomes aware of the Adverse Event |

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| <p>Unexpected and Possibly Related Adverse Events Involving Increased Risks to Subjects</p> | <p>Any unanticipated untoward or unfavorable medical occurrence that indicates that the research places subjects at increased risk of physical or psychological harm than previously known or recognized.</p> <p>Unexpected means that the incident, experience, or outcome in terms of nature, severity or frequency is not described in the protocol-related documents, such as the CIRB-approved research protocol and informed consent document or the characteristics of the study population being studied.</p> <p>Possibly related means there is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research. Reasonable possibility means that the event is more likely than not related to participation in the research or, in other words, there is a >50% likelihood that the event is related to the research procedures.</p> | <p>CC-CIRB Liaison reports all Unexpected Adverse Events that are Possibly Related and to the Research to the CIRB via the online data entry system</p> | <p>Report Unexpected, Possibly Related Adverse Events within 5 working days/7 calendar days) of the date the CSS PI first becomes aware of the Adverse Event.</p> |
| <p>Continuing Review Progress Report - Adverse Events</p> | <p>At continuing review, the CIRB reviews all available information in a summary fashion to prevent unblinding regarding adverse events that have occurred in the trial.</p> | <p>CC-CIRB Liaison provides updated summary information on Adverse Events</p> | <p>Continuing Review</p> |
| <p>Local Adverse Device Effects (ADE)</p> | <p>Adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device.</p> | <p>CSS reports all Adverse Device Effects to CC-CIRB Liaison via the online data entry system</p> | <p>Report all Adverse Events within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the Adverse Device Effect, except Serious Adverse Device Effects as noted below</p> |

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| <p>Serious Adverse Device Effects (SAE)</p> | <p>Serious adverse device effect means any untoward or unfavorable medical occurrence in a human subject which results in death, life-threatening, hospitalization, disability or permanent damage, congenital anomaly/birth defect, or required an intervention to prevent permanent impairment and temporally associated with the subject's participation in the research.</p> | <p>CSS PI/designee reports all Serious Adverse Device Effects to CC-CIRB Liaison via the online data entry system</p> | <p>Adverse Device Effect Form</p> | <p>Report Serious Adverse Device Events (SAEs) within 24 hours of when CSS PI first becomes aware of the Adverse Device Effect</p> |
| <p>Unanticipated Adverse Device Effects (UADE)</p> | <p>Unanticipated adverse device effect means 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.</p> | <p>CC-CIRB Liaison reports all Unanticipated Adverse Device Effects to CIRB</p> | <p>eIRB Adverse Event Form</p> | <p>Report any Unanticipated Adverse Device Effect within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the Adverse Event</p> |
| <p>Continuing Review Progress Report - Adverse Device Effects</p> | <p>At continuing review, the CIRB reviews all available information in a summary fashion to prevent unblinding regarding adverse device effects that have occurred in the trial.</p> | <p>CC-CIRB Liaison provides updated summary information on Adverse Device Effects to CIRB</p> | <p>eIRB Continuing Review Form</p> | <p>Continuing Review</p> |

Local CSS

Unanticipated Problems Involving Risks to Subjects or Others

Unanticipated problem involving risks to subjects or others means any incident, experience, information, outcome, or other problem that is *unexpected* given the research procedures and that indicates that the research places subjects at a greater risk of physical, psychological, economic, legal, or social harm than was previously known or recognized.

Unanticipated problems include, but are not limited to:

- Medication, procedural or laboratory errors
- Breach of confidentiality or HIPAA violation
- Complaints that indicate subjects' rights, safety or welfare were adversely affected
- Change initiated without CIRB approval to eliminate apparent immediate hazards to subjects

1. CSS PI/designee reports to CC-CIRB Liaison via the online data entry system
2. CC-CIRB Liaison reports to CIRB

Reportable Event Form
eIRB/Other Event Form

Report within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the problem

Safety Monitoring Reports

Safety monitoring report means any DMC, DSMB, DSMC or sponsor analysis that describes a safety problem

1. CSS PI/designee reports to CC-CIRB Liaison via the online data entry system
2. CC-CIRB Liaison reports to CIRB

Apparent Serious or Continuing Noncompliance

Noncompliance means any failure to comply with any applicable federal, state, or local laws and regulations or the requirements or determinations of the PHRC, including institutional policies related to human subject protection.

Serious noncompliance means any noncompliance that negatively impacts the rights and welfare of subjects or compromises the integrity of the study data. For example, serious noncompliance might include, but is not limited to, the following violations: (1) failure to obtain prospective PHRC approval; (2) failure to obtain informed consent of subject(s); (3) enrollment of subject(s) who do not meet all eligibility criteria; (4) obtaining informed consent using an invalid/outdated research consent form that is missing information that might affect the individual's willingness to participate or continue to participate in the research; (4) failure to perform follow-up as outlined in the protocol where the lack of follow-up places the subject at increased risk of harm; and (5) failure to report a serious unanticipated problem involving risks to subjects or others, including adverse events.

Continuing noncompliance means any noncompliance that occurs

1. CSS PI/designee reports to CC-CIRB Liaison via the online data entry system
2. CC-CIRB Liaison reports to CIRB

Reportable Event Form
eIRB/Other Event Form

Report within 5 working days/7 calendar days of the date the CC receives the report

repeatedly after appropriate remedial education or corrective action has been instituted taking into consideration all relevant factors, including, for example: (1) whether the continuing noncompliance was intentional, or (2) whether the continuing collaborated in remedial activity and the continuing noncompliance was not intentional.

Major Unapproved Protocol Deviations

Major Unapproved Protocol Deviation means any alteration/modification to the PHRC-approved research that has the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data), or affect the subject's willingness to participate in the study.

1. CSS PI/designee reports to CC-CIRB Liaison via the online data entry system
 Deviation Form
 Report within 24 hours of the date the CSS PI first becomes aware of the deviation
2. CC-CIRB Liaison reports to CIRB
 eIRB Other Event Form
 Report within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the problem

Changes Initiated Without CIRB Approval To Eliminate Apparent Immediate Hazards To Subject/S.

See *Unanticipated Problems*

1. CSS PI/designee reports to CC-CIRB Liaison via the online data entry system

Deviation Form

Report within 24 hours of the date the CSS PI first becomes aware of the change initiated without CIRB approval.

2. CC-CIRB Liaison reports to CIRB

eIRB Other Event Form

Report within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the problem

Complaints that indicate subjects' rights, safety or welfare were adversely affected - See *Unanticipated Problems*

1. CSS PI/designee reports to CC-CIRB Liaison via the online data entry system

Reportable Event Form

Report within 5 working days/7 calendar days of the date the CSS PI first becomes aware of the problem

2. CC-CIRB Liaison reports to CIRB

eIRB Other Event Form

Cessation of research activities
See also *Unanticipated Problems* when cessation of research is for safety problems

1. CSS PI/designee reports to CC-CIRB Liaison

Site Close Out Form

Report within 30 calendar days of the date the CSS ceases research activities

2. CC-CIRB Liaison reports to CIRB

eIRB Amendment Form