Manual of Procedures

NEOLEV3: A Phase IIb Dose Escalation Study of Levetiracetam in the Treatment of Neonatal Seizures of Mild to Moderate Severity

National Clinical Trial (NCT) Identified Number: NCT05610085

Principal Investigators: Sonya Wang, MD, Cynthia Sharpe MBChB, Jeffrey Gold, MD, PhD, and Richard Haas MBBChir

IND Sponsor: Richard Haas, #109622

Sponsor-Investigator: Dr. Sonya Wang

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Table of Contents

Acronym Glossary: Definitions (alphabetical)

AE	Adverse Event
CIRBI	Center for IRB Intelligence
DOA	Delegation of Authority
EHR	Electronic Health Record
FDA	U.S. Food and Drug Administration
IP	Investigational Product
LEV	Levetiracetam
MOP	Manual of Procedures
NICU	Neonatal Intensive Care Unit
PHB	Phenobarbital
SAE	Serious Adverse Event

Manual of Procedures (MOP) History of Changes

Version	Version Date	Summary of Changes	Corresponds to Protocol Version
v1.0	**03/02/2023**	**N/A**	**v9.0**

Study Overview

This study is an open label, dose-escalation, preliminary safety and efficacy study with a randomized control treatment component. The main purpose of this study is to determine the maximum tolerated dose of LEV in the treatment of neonatal seizures. Our hypothesis is that optimal dosing of Levetiracetam (LEV) to treat neonatal seizures is significantly greater than 60 mg/kg.

Study Organization and Responsibilities

Site UMN: University of Minnesota
Role: Coordinating Center, Main Site, Data Coordinating Center, Site

Role	Name	Email	Phone
Principal Investigator	Sonya Wang, MD	sgwang@umn.edu	857-222-4599
Co-Investigator	Katie Pfister, MD	pfis0018@umn.edu	--
Project Manager	Brittany Faanes, MPH, CCRP	grego318@umn.edu	612-626-5929
Regulatory Manager	Elizabeth 'Liz' Ramey, MS, CCRP	eramey@umn.edu	--
Data Manager	Melina Cahnbley	cahnb001@umn.edu	--

Site UCSD: University of California - San Diego
Role: Site

Role	Name	Email	Phone
Principal Investigator	Jeffrey Gold, MD	jjgold@health.ucsd.edu	858-966-5819
Principal Investigator	Richard Haas, MD	rhaas@health.ucsd.edu	858-245-6667
Co-Investigator	Sarah Wiegand, MD	Swiegand@health.ucsd.edu	-

Site RCH: Rady's Children's Hospital - San Diego
Role: Site

Role	Name	Email	Phone
Principal Investigator	Jeffrey Gold, MD	jjgold@health.ucsd.edu	858-966-5819
Principal Investigator	Richard Haas, MD	Rhaas@health.ucsd.edu	858-245-6667
Co-Investigator	Brian Lane, MD	blane@rchsd.org	-
Co-Investigator	Jose Honold, MD	jhonold@rchsd.org	-
Co-Investigator	Sarah Wiegand, MD	Swiegand@health.ucsd.edu	-

Site SMB: Sharp Mary Birch Hospital for Women & Newborn
Role: Site

Role	Name	Email	Phone
Principal Investigator	Maynard Rasmussen, MD	maynard.rasmussen@ssharp.com	-
Co-Investigator	Shandee Hutson	shandee.hutson@sharp.com	-
Principal Investigator	Jeffrey Gold, MD	jjgold@health.ucsd.edu	858-966-5819
Co-Investigator	Sarah Wiegand, MD	Swiegand@health.ucsd.edu	-

Site NZS: Starship Children's Hospital - Auckland
Role: Site

Role	Name	Email	Phone
Principal Investigator	Cia Sharpe, MBChB	cynthias@adhb.govt.nz	+64-21924015
Co-Investigator	Suzanne Davis, MBChB	suzanneda@adhb.govt.nz	+64-21346402
Co-Investigator	Hannah Jones, MBChB	hannahJ1@adhb.govt.nz	+64-21953571
Co-Investigator	Malcolm Battin, MBChB	malcolmb@adhb.govt.nz	+64-212459076

Site NZM: Middlemore Hospital - Auckland
Role: Site

Role	Name	Email	Phone
Principal Investigator	Chris McKinlay, MB ChB, PhD	c.mckinlay@auckland.ac.nz	+64-274725099
Co-Investigator	Louisa Gooneratne	louisa.gooneratne@middlemore.co.nz	+64-21379000
Co-Investigator	Lindsay Mildenhall	lindsay.mildenhall@middlemore.co.nz	+64-21784022

Coordinating Center/Main Site Roles and Responsibilities

The responsibilities of the Coordinating Center include:

- Communications with study sites, scheduling of meetings and training sessions, and responding to and documenting ad hoc communications
- Development and maintenance of the MOP
- Manage Advarra IRB submissions
- Collect and maintain all study regulatory documents to ensure compliance
- Collate and track all FDA and IND submissions in conjunction with Dr. Richard Haas
- Communicate with the FDA
- Monitor and track submissions to ClinicalTrials.gov (Dr. Richard Haas to submit)
- Development of the REDCap database, data flow and data management procedures, including data entry, error identification, and correction
- Create reports and disseminate with appropriate (e.g., enrollment, AEs, participant status, site performance, quality control, and DSMB)
- Distribution of all changes, updates and policies of reports and documents to all participating study sites and the DSMB, as necessary
- Creation of study source documents
- Facilitate the contract and sub-award between the Coordinating Center and Sites
- Schedule and lead site-wide and individual site calls

Study Sites Roles and Responsibilities

The roles and responsibilities of the investigators and study sites include:

- Maintenance of site regulatory documents
- Compliance with protocol, MOP, IRB, federal and state regulations
- Recruitment, screening, and enrollment of participants
- Protection of participants' rights
- Data collection and participant follow-up through study completion
- Enter data in the REDCap database and resolution of all queries
- Compliance with and accountability of administration of study intervention
- Retention of specific records (e.g., laboratory or drug distribution records)
- Communication with the Coordinating Center
- Communication of questions, concerns, and/or observations to the Coordinating Center

Training Plan

Site Initiation Virtual Meeting

When a site is near activation, the Coordinating Center will schedule a virtual Site Initiation Meeting to discuss detailed implementation of the protocol procedures. The study coordinator and PI are required to be in attendance. Other study staff are encouraged to attend as well.

Training agenda would typically include:

- Study staff contact information
- Communication plan–contact info for study staff
- Recruitment plan
- Screening and enrollment process and expectations
- Study procedures overview
- Study drug preparation, administration and accountability
- Safety monitoring and reporting
- Standard of care vs. Research lab specimen collection
- EEG collection and storage
- Monitoring procedures and expectations
- Protocol deviations
- Data collection and entry
- Regulatory requirements
- Guidelines to optimize bedside nursing engagement

Following the virtual Site Initiation Meeting, the study team will document protocol training in the appropriate training log.

Site Activation

Prior to site activation, the site must send all required regulatory documents to Liz Ramey, eramey@umn.edu. Site staff must also satisfy and document all training requirements/certifications as required per their study role. The delegation of authority (DOA) must be completed.

Once all contractual, regulatory and training requirements are fulfilled, a site activation memo from the Coordinating Center will be distributed via email to the local site PI and study coordinator. This memo should be retained in the regulatory files as documentation of the date in which the site was activated.

Ongoing Training Requirements

The Coordinating Center will conduct ongoing training for each site as needed. In the event there is a protocol amendment, the tracked changes, amended protocol and a clean version of the amended protocol will be

provided to the Sites. A Virtual Training Meeting will occur depending on the complexity of the protocol amendment. That will be at the discretion of the Coordinating Center.

Any study-specific training should be documented in the appropriate study training log.

Neurologist-specific training

The study involves withholding the most effective treatment for neonatal seizures. As such there is a heavy responsibility on study neurologists to monitor patient cEEG frequently and ensure the patient exits the study and receives phenobarbital if seizures increase in severity. All treatment decisions are directed by the study neurologist and they will need to have an in-depth understanding of all aspects of the study. Therefore, prior to study initiation the neurologists who will be involved in the EEG monitoring and treatment recommendations will have a virtual in-service to review the protocol in detail.

In addition, all errors or disagreements between EEG readers (which did occur in NEOLEV2) will be formally reviewed by the group in the hope of reducing such errors and disagreements.

NICU Staff who are not Co-Investigators

In order to raise awareness of the study, increase recruitment, and ensure study success the site PI's and Co-I's will meet with NICU nursing staff, nurse practitioners and other appropriate neonatal staff in a small group training to provide information about the study. Such in-services should happen as the study begins at each site and again throughout the course of the study. Logs of attendees should be kept. Note: this is not required, but only a suggestion.

Communications Plan

All protocol and regulatory communications will come from the Coordinating Center/Main Site.

Any questions and/or concerns regarding:

- Protocol - main site project manager (PM) and main site principal investigator (PI)
    - Main Site will include appropriate study PIs in the email
- Contract/sub-awards - main site PM and main site PI
- Regulatory - main site regulatory manager and PM
- Data-related questions - main site PI, PM, and data manager
- REDCap - main site data manager and PM

Data Safety and Monitoring Board

All communications with the DSMB will occur between the Coordinating Site's Principal Investigator, Study PIs, Data Manager, Regulatory Manager, and Project Manager. These communications will typically occur in preparation for or during DSMB meetings. Site Co-Investigators will be included in communications when applicable.

U.S. Food and Drug Administration

All communications with the FDA regarding the grant will occur between the Coordinating Site's Principal Investigator, Regulatory Manager, and Project Manager.

All communications between the FDA regarding the IND and ClinicalTrial.gov will occur between the Coordinating Site's Principal Investigator, Regulatory Manager, Project Manager, Dr. Richard Haas, and University of California - San Diego's Regulatory Compliance Department.

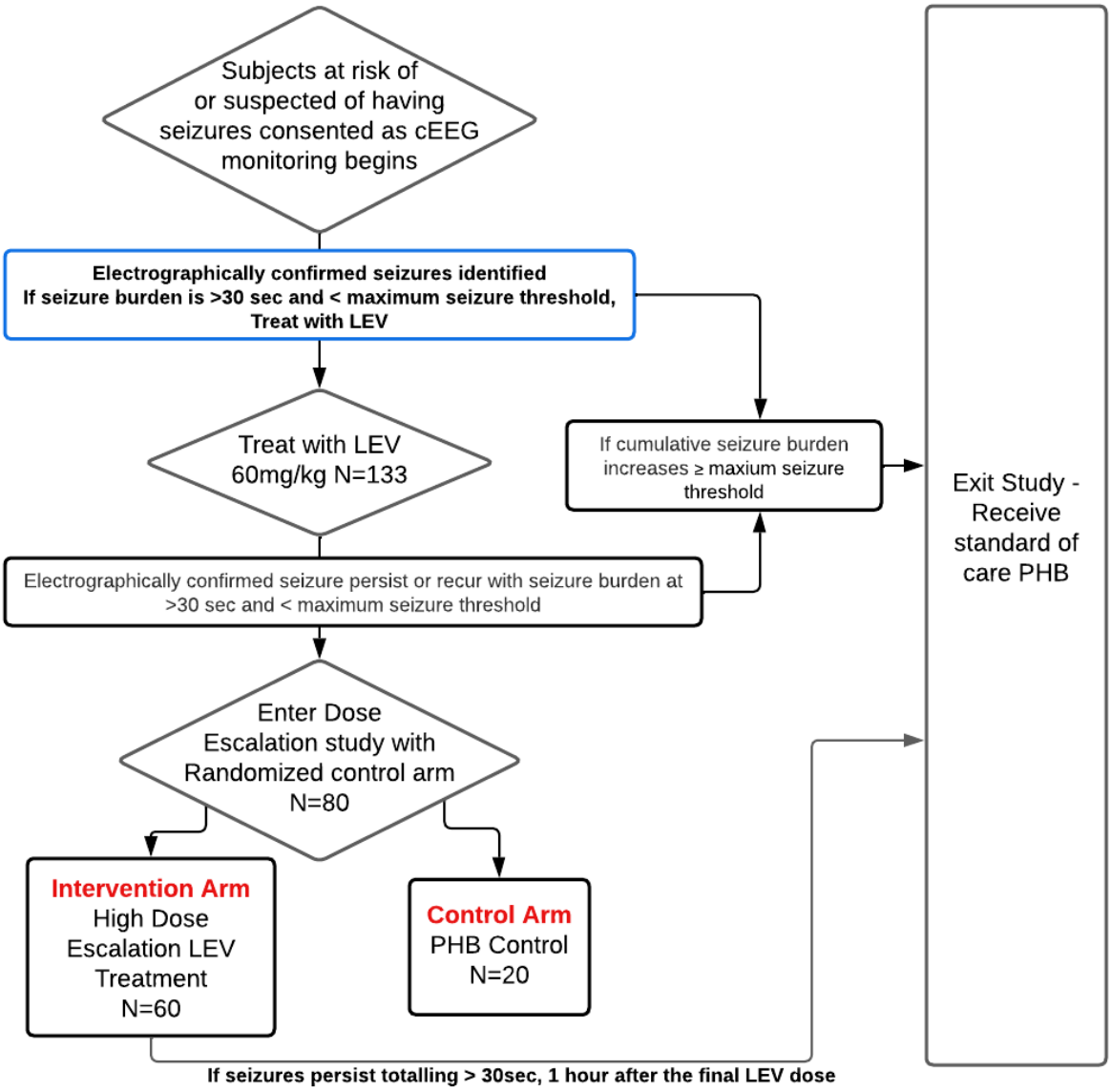
Recruitment

All sites should strive to screen and approach all potential patients. Each site is allowed to implement their own identification and screening processes. Potential ways to identify patients:

- Study staff screens the NICU census daily
- Set up Epic alerts that notify study staff of NICU admission
- Set up Epic alerts that notify study staff of neurology consult
- Create study information sheets and display it in the Neonatologist Attending Room to encourage attending physicians to notify the study team if a baby is admitted and at risk of seizures or suspected to be having seizures

Pre-screening can occur by reviewing the patient's medical record and in communication with the attending pediatric neurologist or neonatologist.

Schema A: Study Recruitment Flow Chart



Screening and Eligibility Criteria

All potential participants should be screened using the following criteria:

Inclusion:

1. At risk of have seizures or suspected to be having seizures
2. All seizure etiologies expect correctable metabolic abnormalities such has hypoglycemia and hypocalcemia
3. Term neonates (corrected gestational age between 35 and 44 weeks, postnatal age less than 28 days)
4. >2200 grams in weight
5. Parent is able to understand the consent process and provides informed consent and HIPAA authorization

Exclusion Criteria:

1. Cumulative seizure burden of 8 minutes/hour or more in Phases 1 and 2; Cumulative seizure burden of 30 minutes/hour or more in Phase 3
2. Renal failure
    a. Defined as anuria in the first 24 hours of life
3. Patients in whom death seems imminent
4. Seizures caused by correctable metabolic abnormalities such has hypoglycemia and hypocalcemia

Any patient who is at risk of having seizures or suspected to be having seizures should be added to the Excel Screening Log Spreadsheet (provided by the Coordinating Site or sites can create their own). Add all applicable patients to the spreadsheet. Include those who decline or don't meet inclusion/exclusion (but are having seizures or suspected of having seizures) so the study can keep track of why a patient may not be eligible for the study.

If a potential participant is eligible and consents:

1. Study staff completes the Inclusion/Exclusion Source Document to verify eligibility
2. The PI or Co-I signs the Inclusion/Exclusion Source Document
3. Obtain informed consent
4. Store the Inclusion/Exclusion Source Document and consent form in the participants binder

Only participants who agree to participate and sign the Informed Consent will be added to the REDCap database.

The Main Site will request screening log numbers at least quarterly.

Informed Consent

The following consent form can be found in the Advarra CIRBI system:

- Parental Permission
    - This form is designed for parents/guardians to provide permission for their minor child to participate in the research study. By signing and dating this form, the parent/guardian authorizes their child to participate in this study.

Sites should follow their respective institutions' informed consent standard operating procedure/process. Parental/guardian permission must be obtained in accordance with the requirement for informed consent (21 CRF 50.55(e)) and be documented in accordance with 21 CFR 50.27.

The PI at each site will delegate on the DOA who is able to obtain informed consent. If they are not delegated on the DOA they can't obtain consent. However, the PI is responsible for complete study oversight.

It should be explained to parents/guardians upfront that this study needs to obtain informed consent within a certain time frame.

Parents/guardians and eligible baby <u>are at the same hospital</u>:

1. PI and/or Co-I discuss the study with the family
2. The parental permission form (including the HIPAA authorization, US specific) will be signed by at least one parent/guardian prior to any procedures being done specifically for the study
    a. Date and time of consent must be documented on the Informed Consent Process Checklist
3. The PI or Co-I who discussed the study with the family should sign the parental permission form
4. A copy of the signed document should be given to the parent/guardian for their records
5. The informed consent process will be documented on the Informed Consent Process Checklist
6. The original, signed consent form and the Informed Consent Process Checklist will be stored in the participants binder

Parents/guardians and eligible baby <u>are NOT at the same hospital</u>:

This pathway is for babies who are transferred in from outside hospitals and the parent(s) are still at the outside hospital.

1. Study staff email or fax parental permission form to the family
    a. If emailed, family must request that consent form is printed
2. The PI and/or Co-I discuss the study with the family via telephone and an impartial witness
3. If parent/guardian consents, the parental permission form must be signed and dated by the family and emailed or faxed back to the PI/Co-I/study team
    a. Signed informed consent must be obtained prior to the first dose of LEV given. There are no exceptions. This is a FDA requirement.
    b. PI/Co-I should request that the family brings the paper consent form with them to hospital where the baby is located
    c. Date and time of consent must be documented on the Informed Consent Process Checklist
4. The PI or Co-I who discussed the study with the family should sign the parental permission form
5. A copy of the signed document should be given to the parent/guardian for their records
6. The informed consent process will be documented on the Informed Consent Process Checklist
7. The original, signed consent form and the Informed Consent Process Checklist will be stored in the participants binder

Remote consent utilizing a Part 11 compliant software/system is allowed. Sites must follow their local sites SOPs and guidance.

Parents will be notified via secure email or a letter of any unanticipated problems that change the risks of the study. Please collect an email for all study participants.

Non-English Fluent Participants

The only non-English language participants that can be enrolled are those who are Spanish speaking. The study will provide a Spanish translated long consent form (pending). Sites should follow their institutions standard operating procedures for consenting Spanish speaking participants. A Spanish speaking translator must be used for the consent conversation.

HIPAA (U.S. sites only)

The HIPAA form is embedded in the consent form for United States sites.

Enrollment

A participant is considered enrolled once they sign the informed consent/parent permission document.

Following the signing of the informed consent:

1) Go into the NEOLEV3 REDCap
2) Click “Record Status Dashboard”
3) Click “Add new record”
4) Click on the “Enrollment” instrument
    a) Add the requested information
5) If the patient is not eligible, click “Not Eligible”

If a participant is consented, but it is determined that they are not having seizures, they are considered Not Eligible. The site will still be responsible for entering the data in the “Enrollment”, “Demographics” and “AE/SAE” REDCap instrument.

Randomization

Following the first initial dose of LEV (60 mg/kg) and the patient continues to have seizures of mild to moderate severity (>30 sec but < 8 minutes/ hour) OR if the patient is temporarily seizure free but has seizure recurrence of mild to moderate severity within 24 hours the patient will be randomized. Patients in the dose escalation study will be randomly assigned to receive either higher dose LEV or treatment with the control drug PHB in a 3:1 allocation ratio, stratified by site.

1) Click “Randomize” in the Enrollment REDCap Tool
2) Participants will be assigned to either receive LEV or PHB.
3) Proceed with study procedures

Notes: if seizures of mild to moderate severity are persistent when the first infusion finishes, the randomization process should be done then, do not wait for a further 15 minutes. This will ensure there is no delay in preparing and giving the next medication.

In the event that REDCap is down and you need to randomize a patient, follow the below steps:

1) Call study PI, Dr. Sonya Wang at 857-222-4599
2) If she does not answer, call Brittany Faanes at 715-829-0123

Either person will be able to tell you the randomization assignment. Once REDCap is available again, you will need to “randomize” in REDCap again but you will receive the same assignment.

If either will be out of the office and unavailable, we will try and provide that information ahead of time.

Study ID Assignment

Participants will be assigned a Study ID once they are added to the REDCap Demographics Form. The patient's study ID will be the SITE INITIALS-NUMBER ENROLLED (3 LETTERS - 2 DIGITS). In the case where more than 99 patients are enrolled in one single site, the patient's study ID will be the SITE INITIALS-NUMBER ENROLLED (3 LETTERS - 3 DIGITS).

Example:

University of Minnesota: UMN-01, UMN-02, UMN-03, etc.

Auckland Hospital: NZS-01, NZS-02, -NZS-03, etc.

Middlemore Hospital: NZM-01, NZM-02, NZM-03, etc.

University of California - San Diego: USD-01, USD-02, USD-03, etc.

Rady's Children's Hospital: RCH-01, RCH-02, RCH-03, etc.

Sharp Mary Birch: SMB-01, SMB-02, SMB-03, etc.

Participant Exits Protocol

A participant who signs the consent form, but has seizures >= 8 minutes/hour before or after the first dose of levetiracetam will exit the protocol and be treated with standard of care phenobarbital. This participant is still considered enrolled, but will not be randomized. Site study staff should continue to collect applicable data ("Enrollment", "Demographics" and "AE/SAE" in the REDCap instrument) on this participant. This is not considered a screen fail.

A participant who signs the consent form, but then does not have any seizures will still be considered enrolled. They will not be given the initial dose of LEV, but study staff should continue to collect applicable data ("Enrollment", "Demographics" and "AE/SAE" in the REDCap instrument) on this participant. This is not considered a screen fail.

Study Intervention Overview and Study Design Diagrams

The study is a randomized, dose escalation study of levetiracetam in the treatment of neonatal seizures of mild to moderate severity. The control medication is phenobarbital. The study is unblinded. The participants will be randomized to either:

1. Levetiracetam: Patients will receive off-label IV Levetiracetam for the treatment of neonatal seizures. IV Levetiracetam is not licensed for use below 1 month of age. Furthermore, this dose escalation study will involve much higher doses than the doses for which Levetiracetam is currently licensed.

2. Phenobarbital: Patients in the control arm of the study will receive IV phenobarbital. Phenobarbital has recently received FDA indication as a treatment for neonatal seizures.

All participants who meet inclusion and exclusion criteria and consent will be monitored for seizures. Once electrographically confirmed seizures are identified and if seizure burden is > 30 seconds and <= 8 minutes cumulatively in one hour, all participants will be treated with an **initial standard LEV dose of 60mg/kg.** All

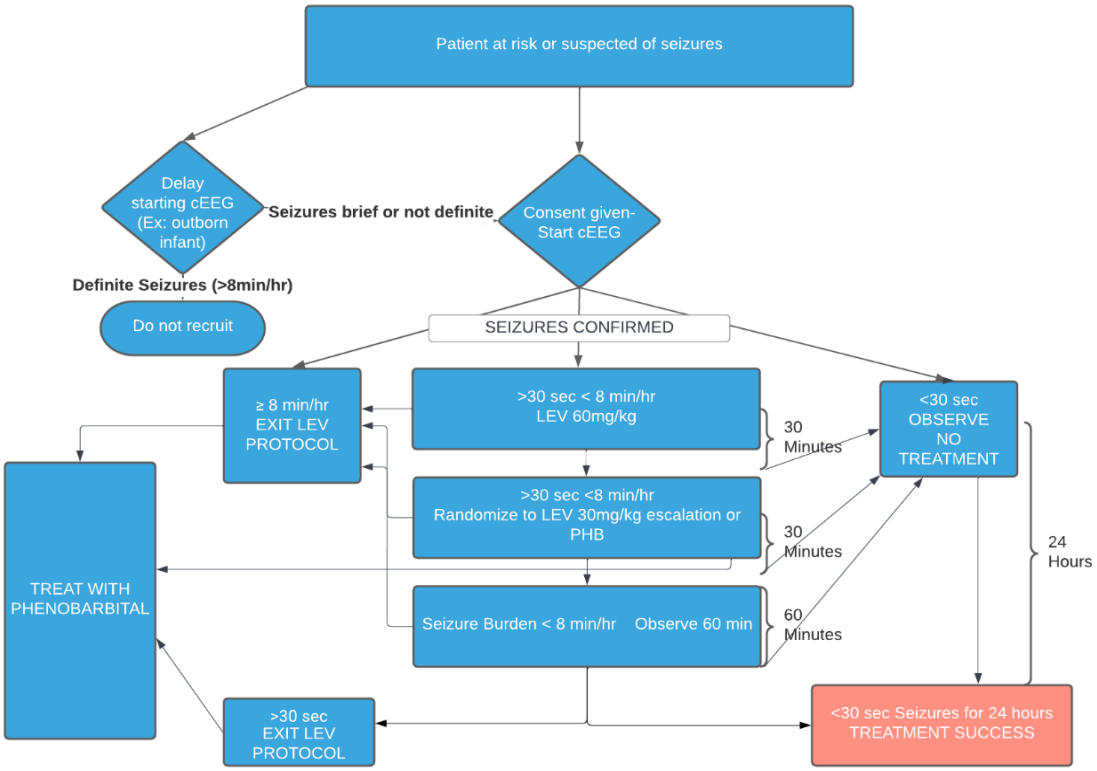
infusions of study drug are given over 15 minutes, with a further 15 minutes monitoring to allow for effect to take place.

If seizures persist at > 30 seconds and <= 8 minutes/hour, participants will be randomized to either receive LEV or PHB. Randomization will take place in REDCap.

The rolling cumulative seizure burden will be continuously monitored and if seizure burden escalates at any stage above the 8 minute/hour threshold, the patient will exit the study and receive PHB. If the seizure burden remains below the 8 minute/hour threshold, the patient will remain in the LEV dose escalation arm.

In phase 1 there is only one dose escalation step of 30mg/kg. After this escalation 30mg/kg dose the patient will be observed for 60 minutes. After that observation hour, if seizures persist > 30 seconds the patient will receive PHB

Schema B: Study Intervention Arm Timeline Flow Diagram Phase 1



Deta

1. Electrographically confirmed seizures identified.
    a. Seizure burden must be between > 30 seconds and <= 8 minutes cumulatively in one hour

2. Prior to the initial LEV dose:
    a. A blood sample for hematology and serum chemistry should be collected prior to the first dose (sent to your hospital lab)
    b. Obtain EKG (3- or 12-lead)
        i. Continuous telemetry monitoring through the first dose of LEV

3. All participants will be treated with an **initial LEV dose (60mg/kg over 15 min).**

4. Monitor during 15 min drug infusion + 15 min to reach peak effect = 30 min.

a. If seizures are frequent and not decreasing, you can randomize during this 30 min window and prepare the next anti-seizure medication to be ready to administer ASAP if seizures persist after 30 min.
b. Monitoring of vitals sign should continue and be documented at 30 min after LEV intial dose and per standard of care subsequently.

5. After the initial 30 minutes AND over the course of the next 24 hours:
    a. If seizure burden is > 30 seconds but < 8 minutes/ hour, randomize the participant in REDCap
    b. If seizure burden < 30 seconds, observe and administer maintenance dosing 8 hours after last loading dose (initial LEV dose) (see below)
    c. If seizure burden is >= 8 minutes in 1 hour, exit LEV protocol and administer PHB per dosing instructions below

<u>If Randomized to LEV</u>

1. Ask nurse/lab staff/appropriate staff to draw PK sample within 30 minutes prior to 2nd LEV dose
2. Administer **2nd dose of LEV**: LEV 30 mg/kg over 15 minutes urgently
3. Allow for drug to infuse and take effect (15 minutes drug infusion + 15 minutes to reach peak effect = 30 minutes)
4. Collect PK sample 60 - 90 minutes after the completion of the 2nd dose of LEV infusion
5. Observe the patient for 1 hour as long as the seizure burden remains < 8 minutes/ hour
6. Calculate post treatment seizure burden during this observation hour. If this is reduced from pre-LEV treatment seizure burden by at least 50% order ongoing maintenance LEV dosing.

If at any stage seizure burden escalates to >= 8 minutes in 1 hour, exit LEV protocol and administer PHB per dosing instructions below

1. Continuous video EEG monitoring will continue within the study for 24 hours
2. After the 1 hour observation period, if seizure burden is > 30 seconds the patient will receive PHB per standard of care protocol

A serum chemistry and hematology should be collected 24 hours post the first dose of LEV.

<u>If Randomized to PHB</u>

PHB should be ordered and administered as follows:

1. 20 mg/kg
2. 10 mg/kg as needed for persistent seizures
3. 10 mg/kg as needed for persistent seizures

PHB maintenance dosing is 2.25mg/kg/dose twice daily IV or PO starting 12 hours after the last loading dose. Maintenance dosing will be 5 days.

<u>LEV Maintenance Dosing</u>

The first dose of maintenance will be administered 8 hours after the last loading dose.

- If the patient is seizure free after the initial 60mg/kg load of LEV you will administer 10mg/kg/dose every 8 hours (q8) for 5 days.
- If the patient has received dose escalation LEV (60 + 30 total 90mg/kg load), you will administer: 15 mg/kg/dose every 8 hours (q8) for 5 days.

You should collect a PK sample only if the patient has received dose escalation LEV (60 +30 total 90mg/kg), do not collect PK samples for patients who are seizure free after the initial 60 mg/kg:

1. Prior to the 4th, 5th, or 6th maintenance dose
2. Prior to the 12th, 13th, or 14th maintenance dose

A serum chemistry and hematology should be collected during the LEV maintenance phase.

For Phase 1, you will only collect 4 PK samples.

Randomized to LEV but exits to PHB

PHB should be ordered and administered as follows:

1. 20mg/kg
2. Subsequent dosing (loading and maintenance) is per standard of care.

Every possible situation that could arise is not documented in the MOP. There will be a FAQ available with additional scenarios.

Detailed information regarding Phase 2 and 3 will be released prior to each phase opening to recruitment.

Drug Information

Information about the preparation, dispensing and administration of the Levetiracetam and Phenobarbital can be found in the Pharmacy Manual of Procedures.

Drug Dosing

Levetiracetam Dosing

All patients will receive the initial LEV dose will be 60 mg/kg.

A patient will be randomized to LEV to receive the following:

In Phase 1 the first escalation LEV dose will be 30 mg/kg.

In Phase 2 the first escalation LEV dose will be 30 mg/kg and if necessary a further dose will be given. The second escalation LEV dose will also be 30 mg/kg.

In Phase 3 the first escalation LEV dose will be 60 mg/kg and if necessary a further dose will be given. The second escalation LEV dose will be 30mg/kg.

Phenobarbital Dosing

A patient may receive phenobarbital:

1) If randomized following initial LEV 60 mg/kg, or
2) If at any stage the seizure burden escalates above the set threshold for remaining in the LEV arm and thereby exiting the study, or
3) If after the 1-hour efficacy assessment period seizures totaling more than 30 seconds persist or recur.

If a patient is randomized, the first phenobarbital dose will be 20 mg/kg given as an infusion over 15 minutes. If seizures persist, PHB will be given in 10 mg/kg increments (maximum total dose 20mg/kg +10mg/kg + 10mg/kg)

If patient exits the protocol or if after the 1-hour efficacy assessment period seizures totalling more than 30 seconds persist or recur, PHB will be given per standard of care has the research participant has exited the protocol

Maintenance LEV Dosing

Patients in whom LEV controls seizures or reduces seizures by at least 50% will receive maintenance LEV for 5 days, IV or oral depending on whether the patient can be fed orally. All IV infusions will be given over 15 minutes.

- Patients who have received a total load of 60 mg/kg will receive maintenance dosing of 10 mg/kg every 8 hours.
- Patients who have received a total load of 90 mg/kg will receive maintenance dosing of 15 mg/kg every 8 hours
- Patients who have received a total load of 120 mg/kg will receive maintenance dosing of 20 mg/kg every 8 hours
- Patients who have received a total load of 150 mg/kg will receive maintenance dosing of 25 mg/kg every 8 hours.

After the 5-day active study period, LEV will be reduced to standard dosing and continued treatment decisions will be at the discretion of the treating neurologist.

Maintenance PHB Dosing

Patients who receive phenobarbital will receive maintenance doses of 2.25 mg/kg twice a day either IV or orally.

Patients may receive maintenance treatment with both LEV and PHB.

Pharmacokinetic Samples

See the PK Sample MOP for detailed information on collecting and processing specimens.

You will collect up to 5 PK samples for those that are randomized to LEV. You will not collect any PK samples for those who are randomized to PHB.

It is imperative that you document that exact time that the PK sample was collected. Please note, at some sites the collection time in the HER is not actually when the sample was collected. Please discuss with your lab or whoever is collecting the sample on how to document the exact time the PK sample was collected. Time of collection is very important here.

Sample 1: collected within 30 minutes prior to LEV2 dose

Sample 2: Within 60-90 minutes following the administration (after the start of infusion) of escalation dose LEV2.

Sample 3: Within 60-90 minutes following the administration (after the start of infusion) of escalation dose LEV3 (Phase 2 and 3).

Sample 4 (Maintenance Dosing of LEV): Obtained prior to the 4^{th}, 5^{th} , or 6^{th} maintenance dose.

Sample 5 (Maintenance Dosing of LEV): Obtained prior to the 12^{th}, 13^{th}, or 14^{th} maintenance dose.

Study staff should complete the PK Sample Source Document to document any time a PK sample is collected. The following information is needed:

1) Time of PK sample collection
2) Time processed
3) Time frozen

In most EHRs the time processed and frozen are not documented. It is important that this is documented.

If you aren't able to collect a PK sample within the designated window, do continue to collect the sample as soon as possible. Make sure to document the exact time it was collected. We will still analyze this sample. If you collect a PK sample outside of window, please enter this as a protocol deviation.

Samples should be stored in an -20 or -80 degree C freezer. Samples will be shipped to the Main Site every 6 months or upon request.

EEG Storage and Management

EEGs will be archived and reported at each site according to local hospital protocol.

For study purposes, EEGs for patients treated with any medication (LEV or PHB) must be sent for independent neurophysiology review.

Appointed staff at each site will de-identify the EEG and save it with the patient study ID as the file name. The de-identified EEG will be sent via the internet using the secure, HIPAA-compliant file storage system "Box". The EEGs will be reviewed by Dr Suzanne Davis, study neurophysiologist. Dr. Davis will archive study EEGs on a secure, encrypted and password protected external hard drive.

The EEG will be reviewed by the independent neurophysiologist within 1 week of the patient's study completion.

Dr. Suzanne Davis will perform this independent neurophysiology review for all of the EEG studies that she has not been involved with as the on-site neurologist. Dr. Davis will mark the beginning and end of each seizure with Persyst seizure marking tool. She will independently determine pre-treatment seizure burden, post treatment seizure burden, and make an assessment of whether the patient remains seizure free for 24 hours after the final LEV dose. The EEG's that Dr. Davis was involved with as on-site neurologist will be independently reviewed by Dr. Hannah Jones, Neurophysiologist.

Safety Reporting

Adverse Event Reporting

An **adverse event (AE)** is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The

degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

In NEOLEV3 we will use the International Neonatal Consortium (INC) Neonatal Adverse Event Severity Scale (Appendix D). This resource provides a descriptive severity scale for the most common neonatal AE's. For grading of adverse laboratory results we refer to the DIADS scale and that scale is included in a table below, since the INC scale does not provide an adverse event scale for laboratory results. See appendix D for INC Neonatal Adverse Event Scale.

Site AE Reporting and Management

AEs will start being recorded once the consent is signed. Study staff will continue to report AEs until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information or until resolution or stabilization.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Upon notification of an AE, the SC will notify all appropriate parties as described below:

1) Site study staff will complete the AE Source Document.
2) The PI will determine severity and expectedness. See below for guidelines.
    a) If the PI determines that the adverse event is severe in nature, the SC and PI should complete the the Serious Adverse Event Source Document and report the SAE to the main site within 24 hours of knowledge of the event
3) Enter the adverse event information into the REDCap Adverse Event page
4) Store the Adverse Event Source Document in the participant's binder

The study is being conducted in a sick neonatal population, with a high rate of morbidity, clinical adverse events, abnormal laboratory values and mortality are expected due to the underlying causes of neonatal seizures.

Severity Grades

Severity scales are defined in the International Neonatal Consortium (INC) Neonatal Adverse Event Severity Scale in Appendix D. If there are no severity scales specified for an AE, this generic scale should be used.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild	Moderate	Severe	Life threatening	Death
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age- appropriate behavior; no change in baseline care or monitoring indicated	Moderate; resulting in minor changes of baseline age-appropriate behavior; requiring minor changes in baseline care or monitoring	Severe; resulting in major changes of baseline age-appropriate behavior* or non- life threatening changes in basal physiological processes; requiring major change in baseline care or monitoring	Life-threatening; Resulting in life-threatening changes in basal physiological processes; requiring urgent major change in baseline care	Death related to AE

Expectedness

The study PI is responsible for determining whether an AE is expected or unexpected, based on the patient's underlying clinical condition. The PI may need to consult with the attending neonatologist to make this determination.

Unexpected: an adverse event is unexpected if it is not listed in the package insert for the medication or based on the patient's underlying clinical condition.

Expected: an adverse event is considered expected if it is listed in package insert for the medication or based on the patient's underlying clinical condition.

Serious Adverse Events (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an 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 (21 CFR 312.32 (a)).

Site SAE Reporting and Management

1) The local PI/SC must notify the Main Site of all SAE within 24 hours of becoming aware of the event via the REDCap Serious Adverse Event Source Document
2) PI/SC reports SAE to the Advarra IRB and local IRB, per local regulations
3) The study PIs will review any **unexpected SAEs with a grade 3, 4, or 5 and possibly related to the study intervention** within 72 hours.

Unanticipated Problem Reporting

In addition to unanticipated AE reporting, any other unanticipated problems, such as a breach of confidentiality, should be reported to the main site as soon as possible. Report the problem to the main site PI and PM via email (sgwang@umn.edu, grego318@umn.edu). Unanticipated AEs will be reported in REDCap.

Study staff should report problems to their local IRB, per local site regulations.

Study Compliance

Protocol Deviations

A protocol deviation (PD) is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents.

In the event of a protocol deviation:

1) Study staff will record the PD in the Protocol Deviation Log Source Document with in 5 business days of identification or within 5 business days of the protocol-require activity
2) The PI will sign the log line acknowledging the protocol deviation
3) The SC should report the PD per Advarra Reporting Policies and local IRB regulations

If a specific protocol deviation is a reoccuring event at a site, additional training will be provided to the site by the Main Site.

Data Management

Electronic Data Capture (REDCap)

The Electronic Data Capture (EDC) will be REDCap created and maintained by the Data Coordinating Center/Main Site. REDCap is where the patient will be randomized and all study data is recorded electronically.

Source Documents

Source documents are the first place that data is recorded (e.g. hospital medical records, pharmacy dispensing records, copies or transcriptions certified after verification as being accurate copies, participant files, and records kept at the pharmacy or lab). Data from source documents will be directly entered into the EDC.

Data Collection and Entry

Data should be entered into the REDCap database within 5 business days of occurrence. Anyone of the DOA delegated to 'data entry' or 'data review' will have access to REDCap.

The University of Minnesota's REDCap is **not** 21 Part 11 compliant. Therefore, the following instructions must be strictly followed when collecting data and entering it into the REDCap database. **This is per FDA guidelines.**

For data that is entered into the Electronic Health Record (e.g. medications, lab values, etc):

1. Site study staff prints the EHR page that contains the required information
    a. ****THIS STEP ONLY HAPPENS IF YOU WILL NOT GIVE THE MONITOR OR FDA EHR ACCESS****
2. Site study staff signs and dates the page(s) printed (or copied if not in an electronic version)
    a. ****THIS STEP ONLY HAPPENS IF YOU WILL NOT GIVE THE MONITOR OR FDA EHR ACCESS****
3. Required data is entered into the REDCap database
4. Once data is completely entered, study staff prints off the completed REDCap pages and the PI signs and dates all pages
    a. This shouldn't be done after the intervention has been completed AND again after all data queries have been answered.

5. Store signed REDCap pages in the patient's binder or other appropriate place.

For data that is NOT entered into the Electronic Health Record (e.g. lab collection times) or for those who choose to complete source documents:

1. Site study staff enters data onto appropriate source document
2. Site study staff enter data into EDC/REDCap
3. Site study staff signs and documents on the source document the date of which the data was manually entered into REDCap
4. Once data is completely entered, study staff prints off the completed REDCap pages and the PI signs and dates all pages
    a. This shouldn't be done after the intervention has been completed AND again after all data queries have been answered.

5. Store signed REDCap pages and source documents in the patient's binder or other appropriate place.

AE and SAE Logs

1. Complete the paper AE and SAE logs completely
    a. PI must assess for expectedness, severity and relatedness
2. PI initials and dates each line
3. Enter the log information into the appropriate AE or SAE REDCap page

See the annotations document for more information about data entry.

Any questions regarding REDCap access should be directed to Melina Cahnbley (cahnb001@umn.edu) and Brittany Faanes (grego318@umn.edu)

Data and Safety Monitoring Activities

To assure that procedures are in place to protect the safety of participants while assuring validity and integrity of the study, study monitoring will be completed. Two formats will be used:

1) Site Monitoring
2) Data Safety and Monitoring Board

Site Monitoring

Plan

Sites will be monitored by a monitor appointed by the Main Site. Sites will be in direct communication with the monitor to schedule each visit. Once scheduled, the site will receive a confirmation letter.

All monitor visits will be done remotely (with the exception of the University of Minnesota). All requested documents must be scanned in and uploaded to Box to monitor review.

Following the visit, study staff, the PI, and the monitor can meet virtually to discuss any findings. The monitor will then send a final letter following the visit with any findings. This letter will be shared with the main site.

Frequency

The initial monitoring visit will occur within 1 month of the first enrolled participant, or within 6 months of IRB approval, whichever occurs first.

Visits will generally occur every six months, but can occur more frequently if agreed upon by the PI, study and monitor.

Monitoring may be reduced to annual visits if the site is closed to enrollment, all subjects are off study at the site, all subject-related findings and action items are resolved, and the investigator and monitor agree that reduced monitoring is appropriate.

Data Safety and Monitoring Board

Plan

The DSMB is responsible for safeguarding the interests of trial participants by assessing the safety of the interventions during the trial.

The DSMB will consist of at least 4 members. The members will include an experienced neonatologist, a pediatric neurologist, a research pharmacologist, and an independent biostatistician. Members of the DSMB shall have no financial, scientific, or other conflict of interest with the study.

A DSMB charter is available upon request.

Frequency

The DSMB will meet at least semiannually, after 10 patients have been randomized to Levetiracetam (LEV) in Phase 1 and 10 patients have been randomized to receive LEV in Phase 2. They will also meet if any SAEs or unanticipated problems occur.

Regulatory Guidance and Procedures

Your main contact for anything regulatory related is Liz Ramey (eramey@umn.edu) and cc Brittany Faanes (grego318@umn.edu).

Definitions

- Site PI = site Principal Investigator
- cIRB = central Institutional Review Board
- pSites = participating site
- Coordinating Center….
- TMF = trial master file

Human Subject Protections

- All sites will be conducted in accordance with 45 CFR 46 entitled "Protection of Human Subjects" under the 2018 Common Rule which includes
    - Reviewing of research by an Institutional Review Board/Ethics Committee
    - Requirements for obtaining and documenting informed consent
    - Addition protections for Neonates under 45 CFR 46 Subpart B (section 46.205)
- As this study is under an IND application, all sites will conduct the trial in accordance with additional regulations by the US FDA which includes:
    - 21 CF 11: Electronic Records and Signatures
    - 21 CFR 50: Protection of Human Subjects
    - 21 CFR 54: Financial Disclosure by Clinical Investigators
    - 21 CFR 312 Investigational New Drug Application
- All sites will conduct the trial in accordance with regards to IRB/EC oversight and policies; along with any local (institutional) polices/SOPs

IRB/EC Review and Approval

US Sites:

Sites in the US will conduct the trial under the central IRB Advarra.

- Access to the Advarra IRB site can be found on: www.cirbi.net
- Responsibilities of the sites:
    - Initial Submission for an "Investigator Application" in order to have your site join the approved study protocol (ID # Pro00065324)
        - This requires that your site follows your institutional IRB processes for obtaining approval to cede (or rely) between your institution's IRB and the Advarra IRB.
        - Local (institutional) IRB communication, such as submission and approval to cede/rely letters must be provided to UMN for the trial master file
    - Prompt Reporting:
        - Sites are required to report the following through the Advarra IRB website
            - SAEs, Unanticipated Problems, Protocol Deviations, Violations or Noncompliance
            - Protocol exceptions will be submitted to UMN prior to Advarra submission

        - Reporting Requirements are outlined in the Advarra *IRB Handbook for Investigators, Institutions, Sponsors and Sponsors' Representatives* which can be located in the Advarra website under Reference Materials Advarra IRB Reference Materials
            - Refer to this as IRB requirements may change during the conduct of this trial
    - Local reporting:
        - Sites are required to follow any local (institutional) reporting requirements that are in addition to reporting to the central IRB
        - These must be done promptly, within your institutional policy, and all communication (submissions and approvals) must be provided to UMN and filed

- Responsibilities of UMN:
    - UMN will manage oversight of the full study protocol, consent and other study material submissions with Advarra on behalf of all sites
        - Requests for site-specific amendments will go through UMN review and approval before a site submission can be made
    - Approvals of IRB submissions will be automatically notified to the sites, through an direct email from cirbi@advarra.com but in addition the UMN study team will communicate this approval to all sites
        - Note: Approved protocols are not retained in the Advarra system, therefore communication from UMN of the approved protocol will occur

NZ Sites:

- Sites in New Zealand will conduct the trial under their local ethics committee, Health and Disability Ethics Committees (HDECs) in addition to their locality approvals.
- Responsible for submission of amendments - changes in protocol, consents or other specific study materials requested by UMN
    - Will follow submission timelines as per US sites even if considered to be minor changes
- Responsible for submission for annual reporting
- Filing of approved documents and letters/memos and to notify UMN promptly of all approvals

To All Sites:

- Ensure that changes are not implemented until confirmed approval from the IRB/EC are received
    - IF an immediate change is made for the safety or welfare of the participant this must be reported to UMN within ____ hours of occurrence
- Ensure that training is conducted by study site PI or staff prior to implementation (see Training section of this MOP)

Confidentiality

- Responsible for appropriate record storage and limited access as per institutional requirements, protocol and IRB requirements
- US Sites will conduct this study in compliance with
    - Health Insurance Portability and Accountability Act (HIPAA): CFR Title 45, Parts 160 and 164, which cover "Standards for Privacy of Individually Identifiable Health Information" (also known as the "Privacy Rule"), which include subparts related to:
        - Standards for use and disclosure of protected health information (PHI)
        - Authorizations to use and disclose PHI or waivers of authorization
        - Tracking of PHI uses and disclosures
    - NOTE: HIPAA Authorization must be obtained as part of the consent process. This documentation is found in the IRB approved consent form
- NZ Sites will conduct this study in compliance with Health Information Privacy Code 2020

Essential Documents

- Will follow collection and maintenance of essential documents as outlined in ICH GCP
    - E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) section 8

- Electronic signatures- see Florence below
- Signature sheets – provide Florence's example
- Responsibility of sites to maintain their Participant Site Binder
- Responsibility of sites to maintain oversight of drug receipt, dispensing and use
    - If an investigational pharmacy is not required then this must be documented in a memo (note) to file and signed by the investigator
- Essential Regulatory Documents to be completed (or provided) and maintained on file are as listed below
    - **Form FDA 1572**
        - A formal, documented agreement to conduct the study in accordance with the study protocol and applicable US regulations
        - Signed by the Principal Investigator of the site only
        - Maintained when changes in sub-investigators, PI or study sites occur
    - **Financial Disclosure Form**
        - In compliance with 21 CFR 54 this document to document and review any potential financial disclosures by the site PI and sub-investigators (or other staff listed on the 1572)
        - Maintained in study files with recommended review yearly to ensure no changes occur and would require an updated disclosure
    - **Curriculum Vitae:**
        - Updated every 2 years; with signature to attest authorship/review of the document
    - **Training Certificate of Good Clinical Practice**
    - **Medical Licensures (as applicable to staff member)**
    - **Delegation of Authority (or Responsibility) Log**
    - **Study Specific and Study Conduct Training Log(s) (see below)**
    - **Laboratory Documents (see below)**
    - **IRB approval(s) and submissions**
    - **Any site specific Notes to File or applicable site SOPs**
- Retain all versions or expired documents through the trial. Documents should not be removed or discarded due to expiration.

Training

- The site Investigator of Record (IoR) is responsible for ensuring that study site staff are appropriately qualified and trained to carry out their delegated duties, and that all training is adequately documented.
- Study-specific site training prior to study initiation and prior to new staff conducting study activities (after IRB approval)
- Sites are required to maintain up-to-date and accurate training records for updates in protocols
- Maintain GCP training through trial conduct (renewal every 3 years)
- IATA, Biohazardous handling
- Other trainings as applicable to institution requirements

Laboratory Practices

- Study will require local laboratory processing, along with shipment to UMN
- Each site's laboratory must have documentation of the following maintained with essential documents:
    - Certifications (i.e. CAP/CLIA in United States)
    - Lab Director CV and Medical Licensure
    - Local reference ranges

Florence

The study will utilize the University of Minnesota electronic regulatory binder, Florence for:

• Trial Master File (managed & accessed by UMN only)
• Participant Site Binders (managed by each site; access given to site only)
• General Study Document location (i.e. protocol, MOP, etc. location)

This is a 21 CFR Part 11 compliant regulatory binder to utilize in an FDA regulated clinical trial. It will replace and/or supplement a paper binder for regulatory materials. This will be used for capturing signatures on 1572s, delegation, training and safety reports, along with maintenance of Essential Documents.

To gain access, please complete the following steps according to your role:

1. Register for your UMN guest account through directions: https://it.umn.edu/services-technologies/how-tos/training-hub-create-guest-account.
2. Proceed to Training Hub https://training.umn.edu/.
3. Complete

MOP Maintenance

The MOP will be maintained by the Main Site. Any changes to the MOP will be sent with the sites via e-mail and will be stored in Florence.

Appendix A: Schedule of Activities

Procedures	Enrollment Day -4 to 1	Electrographic Sz Visit 1, Day 1	15 min post LEV1	Seizures persist or recur 15 min- 24 hours post LEV1	15 min post LEV2 - 1 hour post LEV2	1 hour post LEV2	Seizures persist or recur 15 min- 24 hours post LEV2	15 min post LEV3 - 1 hour post LEV3	1 hour post LEV3	Seizures persist or recur 15 min- 24 hours post LEV3	24 hours post LEV	5 days maintenance LEV high dose	If PHB given at any stage	7 days after study drug complete	Before discharge	Neurodevelopmental testing at 24 months +/- 1 month	Neurodevelopmental testing at 48 – 60 months*
Informed consent	X																
Demographics	X																
Medical history	X																
cEEG	x·										x						
Administer LEV 60 mg/kg IV (LEV1) over 15 minutes		X															
Randomization to higher LEV intervention or PHB control if seizures persist		X										X					
Administer escalation dose LEV2 over 15 minutes				x													
Administer escalation dose LEV3 over 15 minutes **Only in Phase 2 and 3							x										
PHB 20mg/kg IV over 15 minutes- PHB load timing dependant on randomization arm and response to LEV		x		x			x			x							
Physical exam (including weight, head circumference, length)		x													x	x	x
Hammersmith exam															x		
Vital signs		X	x	x	x		x	x				X	x				
Hematology		X									X	X					
serum chemistry [a]		X									X	X					
EKG (as indicated)		x	x				x										
LEV PK specimen **trough**				X							X	X			X		
LEV PK specimen **peak**						x			x								
Daily adverse event review and evaluation, CRF if AE			x·										x	X	X		
Neurodevelopmental testing																x	x
Stakeholder interview															x	x	

Appendix B: Neonatal Adverse Event Grading

Adapted from the International Neonatal Consortium (INC) Neonatal Adverse Event Scale. Relevant AE's have been included in this table

The grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING	GRADE 5 DEATH
Bronchopulmonary Dysplasia	Supplemental oxygen at 28 days AND breathing room air at 36 weeks PMA in infants born <32 weeks' gestation; breathing room air by 56 days postnatal age in infants born >32 weeks' gestation; breathing room air at discharge.	Supplemental oxygen at 28 days AND need for 22-30% oxygen at 36 weeks PMA in infants born <32 weeks' gestation; need for 22-30% oxygen by 56 days postnatal age in infants born >32 weeks' gestation; need for 22-30% oxygen at discharge.	Supplemental oxygen at 28 days AND need for >30% oxygen or positive pressure at 36 weeks PMA in infants born <32 weeks' gestation; need for >30% oxygen or positive pressure by 56 days postnatal age in infants born >32 weeks' gestation; need for >30% oxygen and/or positive pressure at discharge.	Supplemental oxygen at 28 days AND need for >30% oxygen AND positive pressure at 36 weeks PMA in infants born <32 weeks' gestation; need for >30% oxygen AND positive pressure by 56 days postnatal age in infants born >32 weeks' gestation; need for >30% oxygen AND positive pressure at discharge.	Death.
Feeding Intolerance	Mild feeding intolerance (e.g. increased gastric residual volume or abdominal distension); without discomfort; no change in care indicated.	Moderate feeding intolerance; resulting in minor discomfort or alteration of drinking behavior; minor care changes indicated (e.g. feeds withheld).	Severe feeding intolerance; requiring major changes in feeding support indicated (e.g. change to TPN or gavage).	Life-threatening consequences.	Death.
Hypoxic Ischemic Encephalopathy	An event clinically classified as perinatal asphyxia, but not resulting in encephalopathy.	Mild transient clinical signs* of encephalopathy resulting from a perinatal asphyxia event; necessitating observation and additional care. Note: *see Sarnat stages for further guidance	Moderate clinical signs* of encephalopathy resulting from a perinatal asphyxia event; meeting criteria for therapeutic hypothermia. Note: *see Sarnat stages for further guidance on mild,	Severe clinical signs* of encephalopathy resulting from a perinatal asphyxia event with life-threatening consequences (e.g. respiratory depression, refractory seizures). Note: *see Sarnat stages for further guidance on mild, moderate and severe clinical signs of encephalopathy.	Death.

		on mild, moderate and severe clinical signs of encephalopathy.	moderate and severe clinical signs of encephalopathy.		
Infant Irritability	Mild, self-limiting, irritability, not affecting feeding and sleeping.	Moderate irritability, minor changes in feeding and sleeping behavior, requiring minor additional care (e.g. occasional analgesics).	Severe irritability, major changes in feeding behavior, requiring support other than oral feeding; requiring long term medical treatment (e.g. sedatives).	Life threatening irritability, with loss of autonomic control of temperature or heart rate; requiring urgent care change.	
Infant Sedation	Mild, self-limiting or transient sedation or sleepiness; transient loss of interactions; not requiring care change.	Moderate sedation; limiting interactions and minor changes in feeding behavior; requiring increased monitoring.	Severe sedation, major changes in feeding behavior; requiring support other than oral feeding (e.g. tube feeding).	Life-threatening sedation with cardiorespiratory instability; requiring urgent care change.	
Infantile Apnea	Self-limiting apnea.	Apnea responsive to stimulation or intermittent FiO2-increase.	Apnea requiring stimulation and sustained FiO2 increase; requiring non-invasive ventilation; reoccurrences requiring start of or relevant increase in dose of respiratory stimulants or other major care changes.	Life-threatening respiratory and/or hemodynamic compromise; (semi-)urgent intubation required.	Death.
Infantile Vomiting	Increase in vomiting over baseline, self limiting.	Persistent increase in vomiting over baseline; no dehydration; minor changes in feeding support indicated.	Persistent increase in vomiting over baseline; signs of dehydration; major changes in feeding support indicated (e.g. change to TPN or gavage).	Life-threatening consequences (e. g. severe dehydration).	Death.
Necrotizing Enterocolitis			NEC confirmed; major care change indicated (e.g. NPO, antibiotics, non-urgent surgery). Note: If NEC is not confirmed (Bell stages I): please record severity of individual symptoms (e.g. feeding intolerance).	Bowel perforation (pneumoperitoneum)(Bell IIIB); shock, DIC, combined respiratory and metabolic acidosis (Bell IIIA); urgent major care change indicated. Note: If NEC is not confirmed (Bell stages I): please record severity of individual symptoms (e.g. feeding intolerance).	Death. Note: If NEC is not confirmed (Bell stages I): please record severity of individual symptoms (e.g. feeding intolerance).
Administration Site	Painless edema.	Erythema with associated symptoms (e.g.,	Ulceration or necrosis; severe tissue damage;	Life-threatening consequences; urgent intervention indicated.	Death.

Complication Neonatal		edema, pain, induration, phlebitis).	operative intervention indicated.		
Neonatal Bradyarrhythmia	Brief, self-limiting, episodes of asymptomatic bradyarrhythmia; no care changes.	No change in age-appropriate behavior; requiring minor care changes (e.g. increased monitoring).	Resulting in non-life threatening hemodynamic compromise; requiring major care changes (e.g. new medication or intervention).	Life-threatening consequences (e.g. shock); requiring urgent major care changes.	Death.
Coagulation Disorder Neonatal	Minor biochemical coagulation abnormalities without clinical signs; no care changes indicated.	Biochemical coagulation abnormalities with clinical signs; requiring increased monitoring.	Biochemical or clinical coagulation abnormalities; requiring intervention.	Life threatening consequences (e.g. severe pulmonary embolism, limb ischemia, hemorrhagic shock, DIC); requiring urgent major care changes.	Death.
Constipation Neonatal	Reduced number of stools or hard stools; no apparent discomfort.	Reduced number of stools or hard stools; apparent discomfort; minor care changes indicated.	Reduced number of stools or hard stools; signs of obstruction; apparent discomfort or affecting feeding; major care changes indicated (e.g. long term medical treatment, enema).	Life-threatening consequences.	Death.
Neonatal Convulsion	Single, self-limited suspected seizure, no treatment.	Suspected seizures controlled with 1 anti-seizure drug (no recurrence within 3 days after treatment).	Suspected seizures uncontrolled with 1 anti-seizure drug (recurrence within 3 days after treatment or requiring 2 or more anti-seizure drugs).	Suspected seizures with life-threatening consequences (e.g. need for ventilation); suspected status epilepticus* despite multiple anti-seizure drugs. Note: *>30min of convulsions within any 60-minute period.	Death related to suspected seizures.
Culture Positive Neonatal Sepsis	Blood culture positive; no care change indicated (e.g. contamination suspected).	Blood culture positive with mild or ambiguous signs; anti-infectives initiated.	Blood culture positive with severe signs; support treatment escalated or initiated.	Life-threatening consequences (e. g. state of shock, DIC); urgent major care change required.	Death.
Culture Negative Neonatal Sepsis		Suspected sepsis with mild or ambiguous signs; anti-infectives initiated.	Suspected sepsis with severe signs (e.g. fever, grunting); support treatment escalated or initiated.	Life-threatening consequences (e.g. state of shock, DIC); urgent major care change required.	Death.
Diarrhea Neonatal	Increase of 2-4 stools per day over baseline; mild increase in ostomy output compared to baseline.	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline.	Increase of >=7 stools per day over baseline; severe increase in ostomy output compared to baseline; signs of dehydration.	Life-threatening consequences (e.g. severe dehydration).	Death.
Edema Neonatal	Mild edema; no change in age	Moderate edema; no change in age	Severe edema; limiting age	Life threatening consequences (e.g. respiratory failure, shock);	Death.

	appropriate behavior; no care changes indicated.	appropriate behavior; requiring minor care changes (e.g. alteration in fluid management).	appropriate behavior; requiring major care changes (e.g. diuretics).	requiring urgent major care changes (e.g. intubation, dialysis).	
Neonatal Epileptic Seizure	Single, self-limited EEG-proven seizure*, no treatment. Note: *Electrographic confirmation required: can be electro-clinical or electrographic only.	EEG-proven seizures* controlled with 1 anti-seizure drug (no recurrence within 3 days after treatment). Note: *Electrographic confirmation required: can be electro-clinical or electrographic only.	EEG-proven seizures* uncontrolled with 1 anti-seizure drug (recurrence within 3 days after treatment or requiring 2 or more anti-seizure drugs). Note: *Electrographic confirmation required: can be electro-clinical or electrographic only.	EEG- proven seizures* with life-threatening consequences (e.g. need for ventilation); status epilepticus**despite multiple anti-seizure drugs. Note: *Electrographic confirmation required: can be electro-clinical or electrographic only.**>30min of seizure activity within any 60-minute period.	Death related to seizures*. Note: *Electrographic confirmation required: can be electro-clinical or electrographic only.
Fever Neonatal	Isolated, not sustained fever, no change in baseline age-appropriate behavior.	Fever, minor change in baseline age-appropriate behavior; minor changes in care (e.g. environmental settings, symptomatic treatment).	Fever, major change in baseline age-appropriate behavior and without resolution to symptomatic treatment.	Life-threatening consequences.	Death.
Gastro-intestinal Bleeding Neonatal	Mild, self-limiting, bleeding; no change in care required.	Moderate bleeding; minor change in care or monitoring required.	Severe bleeding; non-life threatening hemodynamic consequences; major care change required (e.g. invasive intervention, transfusion, long term medical treatment).	Life-threatening consequences (e.g. hemorrhagic shock); urgent major care change required.	Death.
Neonatal Hypertension	Systolic or diastolic BP >90th percentile but<95th percentile; self-limiting. Note: For percentile values: e.g. Dionne et al. Ped Nephrol 2012.	Persistent or recurrent hypertension, with systolic or diastolic BP between the 95th percentile and the 99th percentile. Note: For percentile values: e.g. Dionne et al. Ped Nephrol 2012.	Persistent or recurrent hypertension, with systolic or diastolic above the 99th percentile; need for antihypertensive medication. Note: For percentile values: e.g. Dionne et al. Ped Nephrol 2012.	Life-threatening consequences (e.g. malignant hypertension: shock, cardiac failure or neonatal encephalopathy). Note: For percentile values: e.g. Dionne et al. Ped Nephrol 2012.	Death.
Neonatal Hypotension	Transient (<60 min), asymptomatic hypotension; not affecting perfusion; not requiring intervention.	Persistent (>60 min) hypotension; not affecting perfusion; requiring minor	Persistent hypotension affecting perfusion; requiring major care change (e.g.	Life-threatening consequences (e.g. shock, organ failure).	Death.

		care changes (e.g. additional fluids).	vaso-active drugs or hydrocortisone).		
Intraventricular Hemorrhage Neonatal	Asymptomatic hemorrhage confined to the germinal matrix; minimal hemorrhage within the ventricle (<10% on parasagittal view).	Moderate hemorrhage occupying <50% of ventricular volume without ventricular dilatation > 4mm above the 97th percentile.	Hemorrhage occupying >50% of the ventricle volume; ventricular dilatation > 4mm above the 97th percentile; parenchymal venous infarction; requiring temporizing neurosurgical procedure (drain, shunt or reservoir).	Hemorrhage with parenchymal venous infarction; resulting in life threatening consequences (e.g. refractory seizures, hypotension, respiratory depression); requiring urgent stabilization or surgical decompression.	Death.
Neonatal Pneumothorax	Radiological evidence of pneumothorax; no clinical signs; no care change required.	Radiological evidence of pneumothorax; minor clinical signs; minor care change required (e.g. oxygen, increased monitoring).	Radiological evidence of pneumothorax; with clinical signs; major care change required (e.g. chest drainage).	Life-threatening respiratory and/or hemodynamic compromise (e.g. tension pneumothorax); urgent major care change required.	Death.
Neonatal Pulmonary Hemorrhage	Limited hemorrhagic secretion in ET tube.	Hemorrhagic secretion in ET tube; without relevant increase in PCO2 or decrease in oxygenation; requiring minor changes in care (e.g. increase PEEP).	Hemorrhagic secretion in ET tube; with relevant increase in PCO2 or decrease in oxygenation; requiring major change in ventilatory support or transfusion.	Life-threatening respiratory and/or hemodynamic compromise.	Death.
Rash Neonatal	Localized rash.	Diffuse rash or target lesions.	Diffuse rash and vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site.	Extensive or generalized bullous lesions or ulceration of mucous membrane involving 2 or more distinct mucosal sites or Stevens-Johnson syndrome or toxic epidermal necrosis.	Death.
Neonatal Respiratory Distress Syndrome	Radiological evidence without clinical signs; clinical evidence of mildly increased respiratory distress (e.g. increased work of breathing) without significant deterioration in gas exchange (increase in pCO2 or decrease in oxygenation); no supportive care required.	Clinical evidence of increased respiratory distress without significant deterioration in gas exchange (increase in pCO2 or decrease in oxygenation); corrected by minor adjustments in current ventilatory support, supplemental	Clinical evidence of increased respiratory distress with relevant deterioration in gas exchange (increase in pCO2 or decrease in oxygenation); requiring major care change (e.g. start invasive support).	Life-threatening respiratory and/or hemodynamic compromise; requiring urgent care change (e.g. urgent intubation).	Death.

		oxygen or non-invasive support.			
Neonatal Respiratory Insufficiency	Clinical evidence of mildly increased respiratory distress (e.g. increased work of breathing) without significant deterioration in gas exchange (increase in pCO2 or decrease in oxygenation); no change in baseline functioning; no care changes required.	Clinical evidence of increased respiratory distress without significant deterioration in gas exchange (increase in pCO2 or decrease in oxygenation); corrected by minor adjustments in current ventilatory support, supplemental oxygen or non-invasive support.	Clinical evidence of increased respiratory distress with relevant deterioration in gas exchange (increase in pCO2 or decrease in oxygenation); requiring major care change (e.g. start invasive support).	Life-threatening respiratory and/or hemodynamic compromise; requiring urgent care change (e.g. urgent intubation).	Death.
Neonatal Sinus Bradycardia	Brief, self-limiting, episodes of bradycardia; no care changes.	Persistent bradycardia; no change in age-appropriate behavior; requiring minor care changes (e.g. concomitant medication adapted, intermittent increase FiO2).	Persistent bradycardia; resulting in non-life threatening hemodynamic compromise; requiring major care changes (e.g. new medication or intervention).	Life-threatening consequences (e.g. shock); requiring urgent major care changes.	Death.
Neonatal Sinus Tachycardia	Brief, self-limiting, episodes of tachycardia; no care changes.	Persistent tachycardia; no change in age appropriate behavior; requiring minor care changes (e.g. concomitant medication changed).	Persistent tachycardia; resulting in non-life threatening hemodynamic compromise; requiring major care changes (e.g. new medication or intervention).	Life-threatening consequences; requiring urgent major care changes.	Death.
Neonatal Spontaneous Intestinal Perforation			Presence of SIP, non-urgent medical stabilization and surgical intervention indicated.	Life-threatening consequences (e.g. shock, organ failure); urgent intervention indicated.	Death.
Neonatal Tachyarrhythmia	Brief, self-limiting, episodes of asymptomatic tachyarrhythmia (e.g. extra systolic beats); no care changes.	No change in age-appropriate behavior; requiring minor care changes (e.g. increased monitoring).	Resulting in non-life threatening hemodynamic compromise or changes in age-appropriate behavior; requiring major care changes (e.g. new medication or intervention).	Life-threatening consequences (e.g. shock); requiring urgent major care changes.	Death.
Periventricular Leukomalacia	Transient periventricular echo	Transient periventricular	Periventricular echo densities,		

	densities persisting > 7 days and resolving completely.	echo densities evolving in to small localized fronto-parietal cysts or persistent diffuse echo densities.	evolving in to extensive cystic periventricular lesions; or densities extending in to the deep white matter.		
Persistent Pulmonary Hypertension of the Newborn	Technical evidence of increased RV-pressures; no clinical symptoms.	Increased estimated RV-pressures; with moderate clinical symptoms; oxygenation index <25; minor care changes required.	Increased estimated RV-pressures; with severe clinical symptoms; oxygenation index >25; major care changes required (e.g. iNO).	Life-threatening respiratory and/or hemodynamic compromise; ECMO required; oxygenation index >40.	Death.
Retinopathy of Prematurity	Zone 2 ICROP stage 1 with or without plus disease; zone 2 ICROP stage 2 without plus disease; zone 3 any ICROP stage; no care changes indicated.	Type 2 prethreshold ROP (zone 1 ICROP stage 1 or 2 without plus disease; zone 2 ICROP stage 3 without plus disease); requiring more frequent ophthalmic monitoring.	Type 1 prethreshold ROP (zone 1 any stage with plus disease; zone 1 ICROP stage 3 without plus disease; zone 2 ICROP stage 2 or 3 with plus disease); threshold ROP; requiring major care changes (e.g. laser intervention, intravitreal anti-VEGF or operative management).	Unilateral retinal detachment.	Blindness (bilateral retinal detachment) .
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**	**GRADE 5 DEATH**