PROTOCOL APPROVAL WITH MODIFICATIONS

DATE: 25 Jul 2025

TO: Vincent Cervantes

PROTOCOL: NINDS - KESETT, Ketamine add-on therapy for Established Status Epilepticus Treatment Trial (KESETT)
A multicenter, randomized, blinded study of treatment of patients with benzodiazepine-refractory status epilepticus in the emergency department, with either levetiracetam or levetiracetam combined with 1 mg/kg or 3 mg/kg dose ketamine to determine which treatment leads to more effective control of status epilepticus (Pro00086552)

APPROVAL DATE: 23 Jun 2025

EXPIRATION DATE: 23 Jun 2026

IRB APPROVED DOCUMENTATION:

Protocol Version(s):

- Protocol (Version 1.0, Dated 28 May 2025)
- Exception from Informed Consent (EFIC) Investigators' Implementation Plan (Dated May 14, 2025)

Consent Template(s):

- Prospective Informed Consent Form (Advarra IRB Approved Version 23 Jul 2025)
- Continued Participation of Participants Enrolled Under EFIC Informed Consent Form (Advarra IRB Approved Version 23 Jul 2025)

Product Information:

- Product Information for Ketamine Hydrochloride Injection (Dated 11/2024)
- Product Information for KETALAR (Ketamine Hydrochloride) Injection (Dated 04/17)
- Product Information for KEPPRA® (levetiracetam) Injection (Dated 05/2008)

Other Material:

- Mass distributed print publication (ex: newspaper, magazine, newsletter), Website Content (Not Dated)
- Mass distributed print publication (ex: newspaper, magazine, newsletter), Trifold Content (Not Dated)
- Mass distributed print publication (ex: newspaper, magazine, newsletter), Survey Content (Not Dated)

The IRB approved the above referenced protocol with the modifications listed below on 23 Jun 2025:

- **Modification(s) to the EFIC Plan**
- **Modification(s) to the Conduct of the Study to require submission of Next of Kin letter before enrollment can be initiated at any site**
- **Modification(s) to the Informed Consent Form Templates**
- **Modification(s) to the Mass distributed print publication (ex: newspaper, magazine, newsletter), Website Content**
- **Modification(s) to the Mass distributed print publication (ex: newspaper, magazine, newsletter), Trifold Content**
- **Modification(s) to the Mass distributed print publication (ex: newspaper, magazine, newsletter), Survey Content**

On 23 Jul 2025, the IRB reviewed and approved additional revisions to the Prospective Informed Consent Form and the Continued Participation of Participants Enrolled Under EFIC Informed Consent Form template(s).

Please note that all community/subject-facing materials should be submitted to the IRB for review prior to being used in Community Consultation or Public Disclosure. These include the survey, Facebook ads, webpage, PowerPoint slide deck or other presentation materials used for the online forums as well as any other materials used for Public Disclosure (such as press releases or flyers).

A post-trial public disclosure plan must be submitted to and approved by the Board before the protocol can be closed with the IRB.

Please Note: This approval notice is for the IRB approval of the protocol only. The Principal Investigator for each site must complete a separate site submission to receive an IRB Approval notice allowing them to conduct the study.

The above referenced recruitment/subject material is available on your Advarra CIRBI Platform workspace under the "IRB Issued Documents" tab.

Documentation of Full HIPAA Waiver Approval

The IRB has approved the Full Waiver of HIPAA Authorization after determining that the waiver of authorization satisfies the criteria set forth in the HIPAA Privacy Rule at (45 CFR 164.512(i)(2)).

The waiver of authorization was reviewed and approved under full board review procedures. The IRB has determined that the protected health information necessary to be used/accessed is as outlined in the protocol and/or IRB application.

The IRB reviewed the project in accordance with the 21 CFR Part 50, Subpart D Federal Regulations / 45 CFR Part 46, Subpart D Federal Regulations which provide for additional protections for children as research subjects.

The IRB determined that the research study meets the criteria found in the risk category described as follows:

- 21 CFR 50.52 / 45 CFR 46.405: "*Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects*." *Permission of one parent is required.*

Documented Assent from minor participants is not required.

The IRB determined that the use of a Legally Authorized Representative (LAR) is approved for this study. During the course of the study, if the subject regains the capacity to consent, informed consent must be obtained from the subject and the subject must be offered the ability to leave the study if desired.

If the study is expected to last beyond the approval period, you must request and receive re-approval prior to the expiration date noted above. A report to the Board on the status of this study is due prior to the expiration date or at the time the study closes, whichever is earlier. It is recommended that you submit status reports at least 4 weeks prior to your expiration date to avoid any additional fees or lapses in approval.

If the study is in an FDA 30-day wait period, subjects **may not** be consented or screened, as consent would be required before study-specific screening activities may begin. However, some initial activities related to determining a potential subject's interest in the upcoming study may occur. Such activities should be limited to recruitment efforts to inform potential subjects, or a community that a study may soon begin on a given condition. However, screening subjects to determine eligibility would not be acceptable until the IND is in effect.

It is the IRB's expectation that any placeholders in approved subject-facing material(s) will be accurately populated with the IRB approved content in all applicable instances.

Audio/visual recruitment or subject material approved in script format only must be submitted in final format for the IRB to review what potential subjects will see or hear. The IRB does not review the content found in embedded links or QR codes, therefore this content must be submitted for review and approval separately, prior to use.

If you wish to appeal the IRB's determinations and/or imposed modifications, please submit supporting documentation to address the IRB's concerns by creating an Appeal Modification in CIRBI.

Approved investigators and sites are required to submit to Advarra for review, and await a response, prior to implementing any amendments or changes in the protocol; informed consents; advertisements or recruitment materials ("study-related materials"); investigators; or sites (primary and additional).

Approved investigators and sites are required to notify Advarra of the following reportable events, including, but not limited to unanticipated problems involving risks to subjects or others; unanticipated adverse device effects; protocol violations that may affect the subjects' rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data; subject death; suspension of enrollment; or termination of the study.

Compliance Statement/REB Attestation (Applicable for research conducted in Canada):

The IRB attests that this submission has been approved by an IRB whose membership complies with the requirements defined in Health Canada regulations, ICH GCP guidelines, FDA regulations at 21 CFR part 56, and HHS regulations at 45 CFR part 46. The IRB carries out its functions in accordance with FDA regulations at 21 CFR parts 50, 56, 312, and 812; HHS regulations at 45 CFR part 46, subparts A-E; good clinical practices; Health Canada regulations; and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, as appropriate to the research.

Advarra IRB is registered with OHRP and FDA under IRB#00000971.

Please review the IRB Handbook located in the “Reference Materials” section of the Advarra CIRBI™ Platform (www.cirbi.net). A copy of the most recent IRB roster is also available.

Thank you for selecting Advarra IRB to provide oversight for your research project.

Sincerely,

Luke Gelinas, PhD
Executive Board Chair