ESETT ANCILLARY PHARMACOKINETIC-PHARMACODYNAMIC (PK-PD) STUDY

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Established Status Epilepticus Treatment Trial

Rationale

- Substantial variability in drug concentrations following administration of AED loading doses
- ESETT protocol uses a mg/kg basis for dosing capped at 75 kg
- Variability in early drug concentrations can be high
- Unknown if drug concentrations correlate with efficacy in acute management of SE

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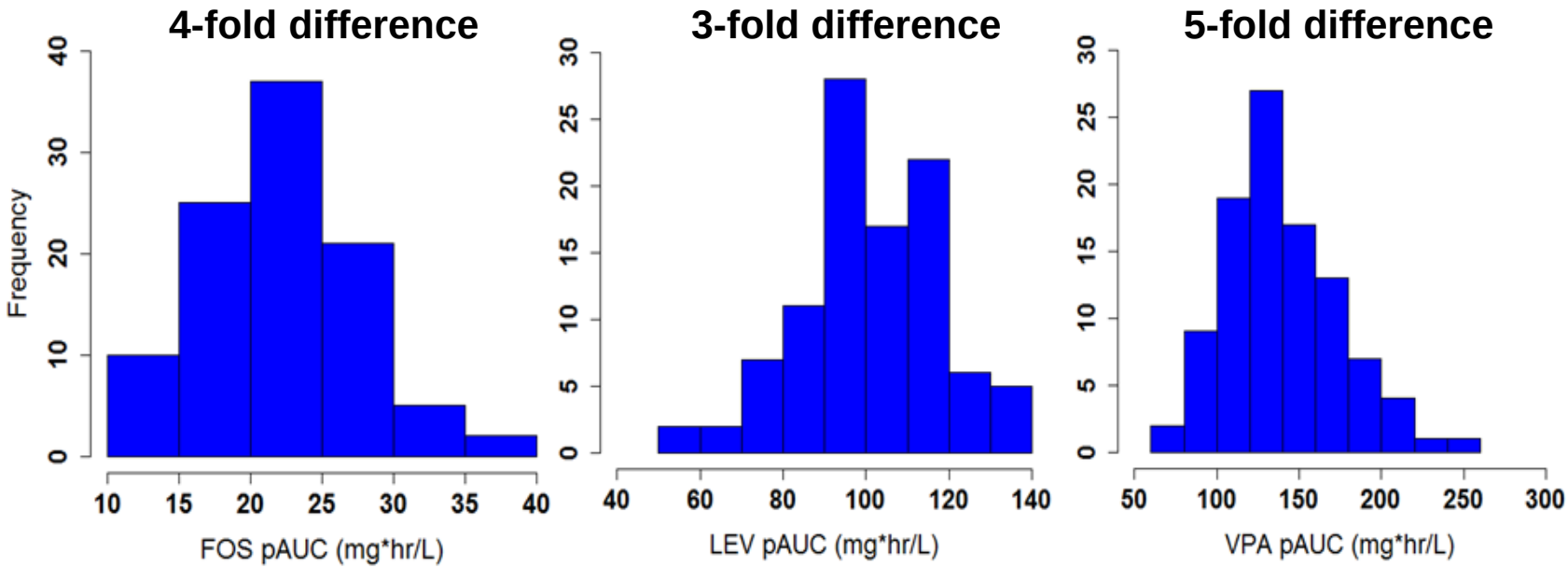
Simulations Show Wide Variability in Drug Exposure Following IV Dosing



Distributions of PHT, LEV, and VPA concentrations over 60 min (pAUC) simulated for 100 patients

Does variability predict response?

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Specific Aim

Relate drug exposure [concentration or partial area under the concentration-time curve (pAUC)] from time 0-60 min) with seizure cessation and the key secondary outcomes.

- ***Hypothesis 1: Patients with higher drug exposures (pAUC based on unbound or total plasma concentrations of FOS, LEV, and VPA) will more likely respond.***
- ***Hypothesis 2: Patients with higher drug exposures will have a higher incidence of serious adverse effects commonly associated with the study drugs.***
- ***Hypothesis 3:*** **The relationship between drug exposure and response will differ by gender, age, and weight or BMI.**

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Study Overview

Population - Same as ESETT

Inclusion Criteria

- **All subjects randomized under the ESETT protocol.**
- **Able to provide blood sample(s)**

Procedures

- **Two blood sample collected within specified time ranges**
- **VPA (total and unbound), PHT (total and unbound) and LEV (total) concentrations measured**
- **Statistical and pharmacometric analysis**

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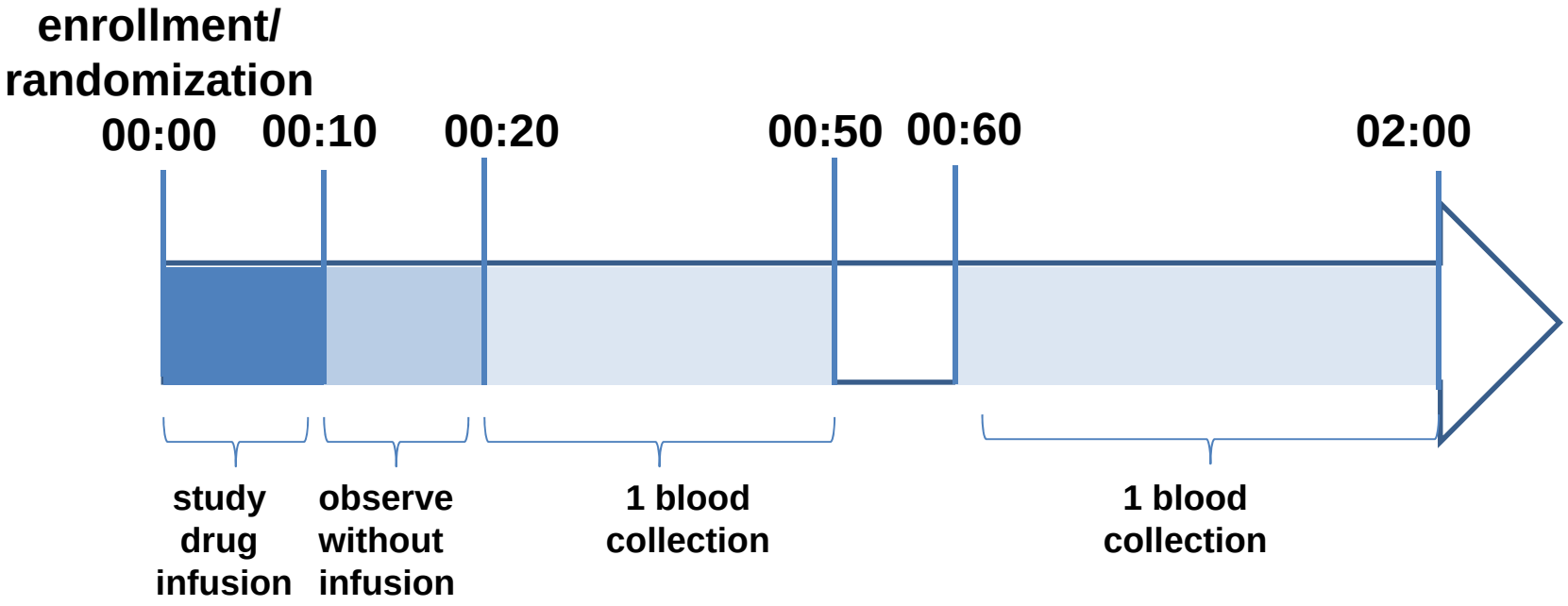
PK/PD Sample Collection Timetable

- **Two blood samples (minimum 2-3 mL/sample)**
  - **20-50 min and 60-120 min**



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Study Procedures

- **Record time of blood collection on CRF**
- **Sample centrifuged to separate plasma within 2 hr of the blood collection**
  - **Plasma aliquoted into labeled cryovial**

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Study Procedures

- Blood samples stored at ≤ -20° C until shipment
  - Samples may be stored and batched
- Plasma shipped to the Center for Orphan Drug Research (CODR)
- Shipping kits will be provided
  - labeled cryovials, extra labels, cold packs, and shipping material including pre-paid labels

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Plasma Sample Analysis

- **Samples will be analyzed for drug concentration at CODR using a validated, highly sensitive, specific assay (chormatographic mass spectrometry assay).**
  - **Unbound and total phenytoin (PHT)**
  - **Unbound and total valproic acid (VPA)**
  - **Total levetiracetam (LEV)**

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Data Analysis at ESETT Completion

- Use pharmacokinetic models to estimate drug concentration-time profiles and partial area under the curve (pAUC)
- Examine the relation of drug concertation or pAUC to the probability of seizure cessation (at 60 minutes)
- Examine the relation of drug concentration or AUC to secondary endpoints
- Test the effect of variables such as weight, BMI, age, gender, on the drug exposure-response relationship

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Outcomes

- **Characterization of the exposure-response relationships.**
- **Provide guidance on how best to use FOS, LEV, and VPA for treatment of SE in children, adults, and elderly.**
- **Guide selection of optimal dose for future clinical trials.**

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Key Personnel

Personnel	Institution	Role
Lisa Coles, MS, PhD	Minnesota	PI, pharmacometric analysis
James Cloyd, PharmD	Minnesota	Co-PI, pharmacology core PI
Richard Brundage, PharmD, PhD	Minnesota	Pharmacometric consultant
Vijay Ivaturi, MS, PhD	Maryland	Pharmacometric analysis
Caitlyn Ellerbe, PhD	MUSC	Statistical analysis
Jaideep Kapur, MBBS, PhD	Virginia	ESETT PI
Robert Silbergleit, MD	Michigan	NETT PI
Jim Chamberlain, MD	Children's National	PECARN PI