ESETT PHARMACOKINETIC-PHARMACODYNAMIC (PK/PD) STUDY RESULTS

Lisa Coles - University of Minnesota

Established Status Epilepticus Treatment Trial

Outline

- Study overview
- Lessons
- Study Results
- Simulation Study

Established Status Epilepticus Treatment Trial

ESETT PK/PD Study

Aim: Relate drug exposure (area under the curve) with seizure cessation and the key secondary outcomes.

Established Status Epilepticus Treatment Trial

Study Timeline

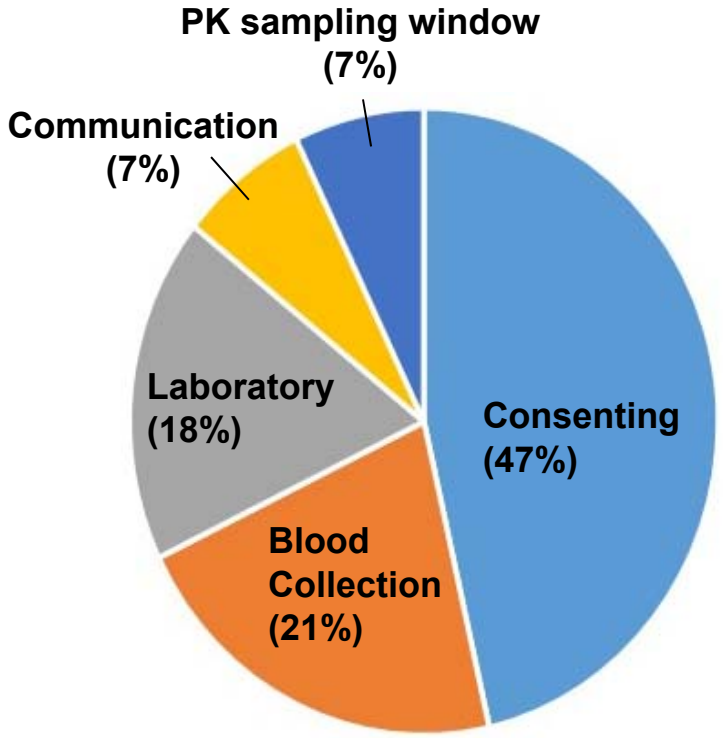
- ESETT started enrolling Nov. 2015
- Adult enrollment closed Oct. 2017
- ESETT closed – Dec. 2018

- PK-PD study funded – 8/15/2017
- 1st enrollment – 11/6/2017
- 27 children enrolled (~50% of eligible ESETT patients)
  - FOS -11
  - LEV – 7
  - VPA- 9

Established Status Epilepticus Treatment Trial

Lessons learned

- ***Challenges adding PK to ongoing study***
  - ***Potential ESETT patients lost because sites initiations were rolling***
  - ***Integrate blood sampling into the ESETT procedures***
  - ***Continuous communication with sites critical***
- ***Consent often required for children***
- ***Blood collection challenges***
  - ***Too restrictive blood sampling protocol***
  - ***If a first sample was collected, second was also obtained.***
  - ***Make PK sampling and sample processing procedures simple***
- ***Sites were committed to obtaining PK samples***

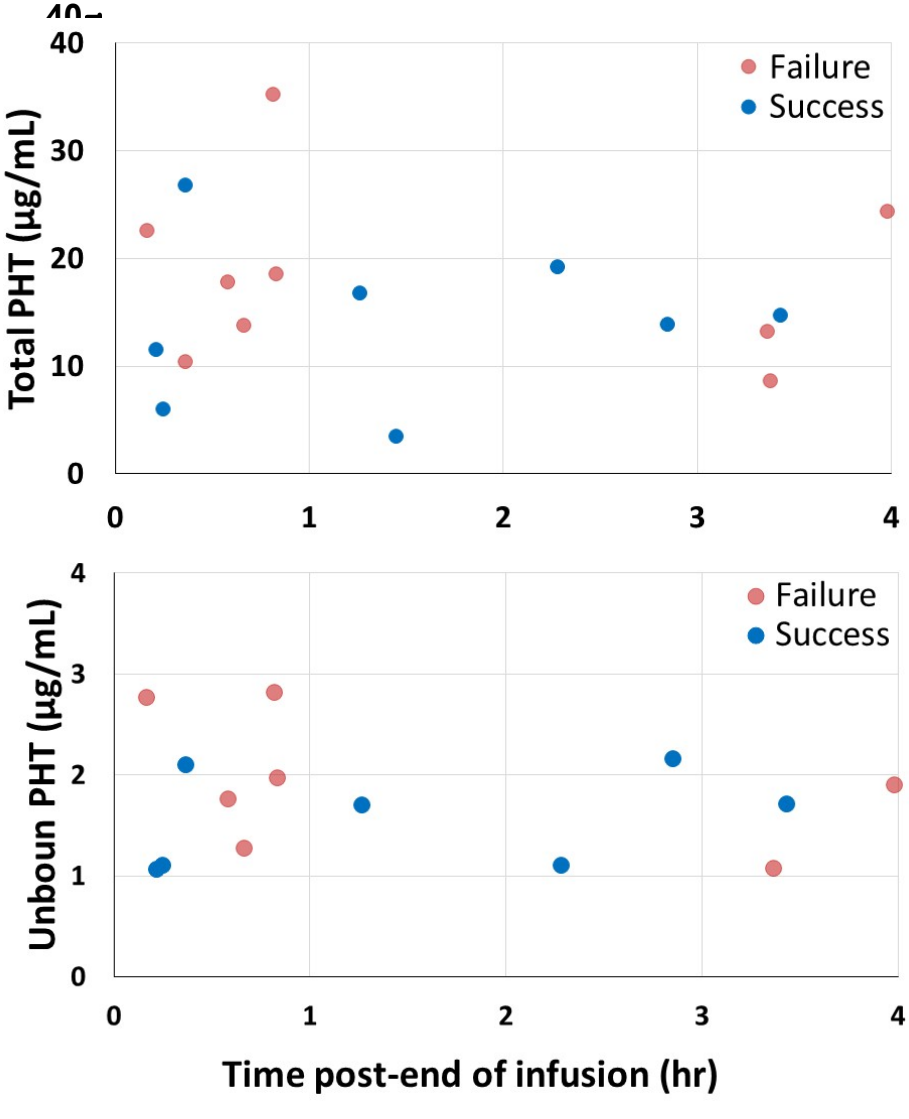


Reasons for Missed Enrollment (N=28)

Established Status Epilepticus Treatment Trial

PHT Concentrations

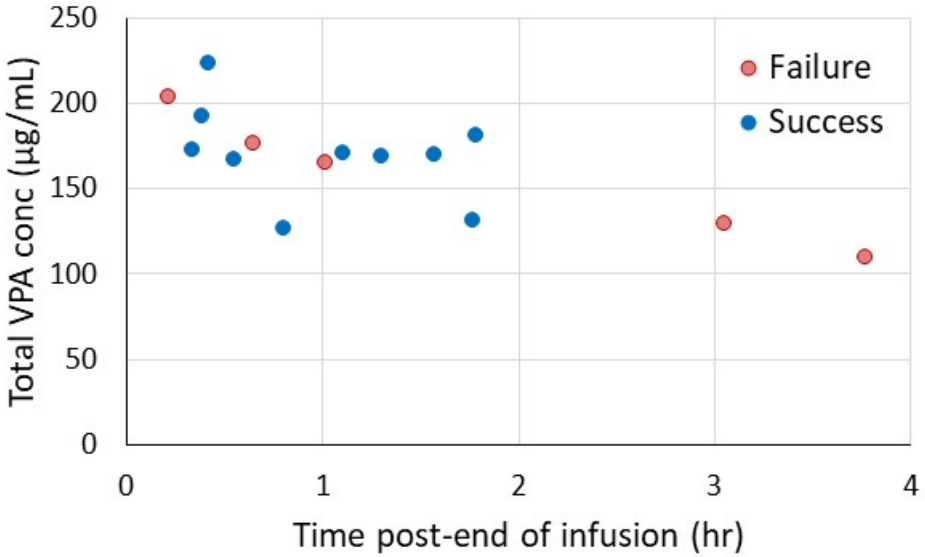
- N= 11
- Large intra-subject variability
- 81-94% bound

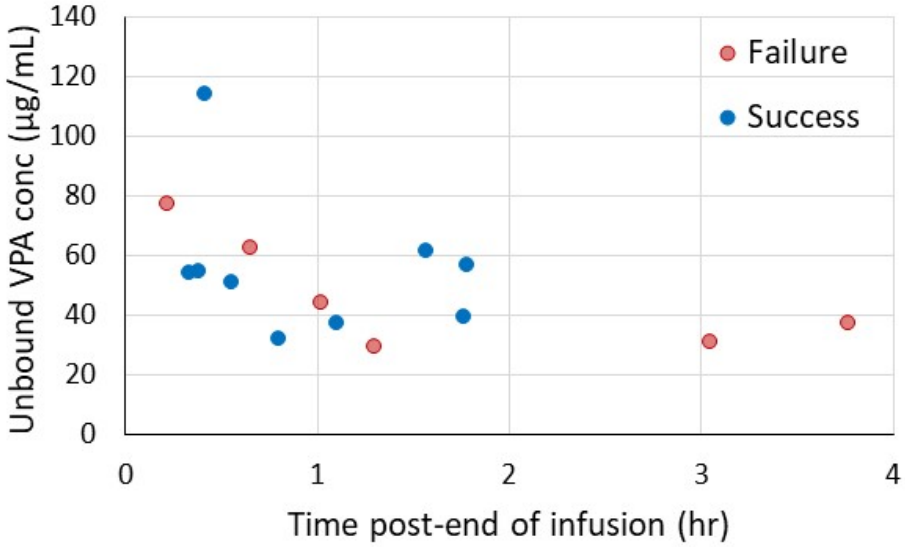


Established Status Epilepticus Treatment Trial

VPA Concentrations

- **N= 9**
- **48-82% bound**

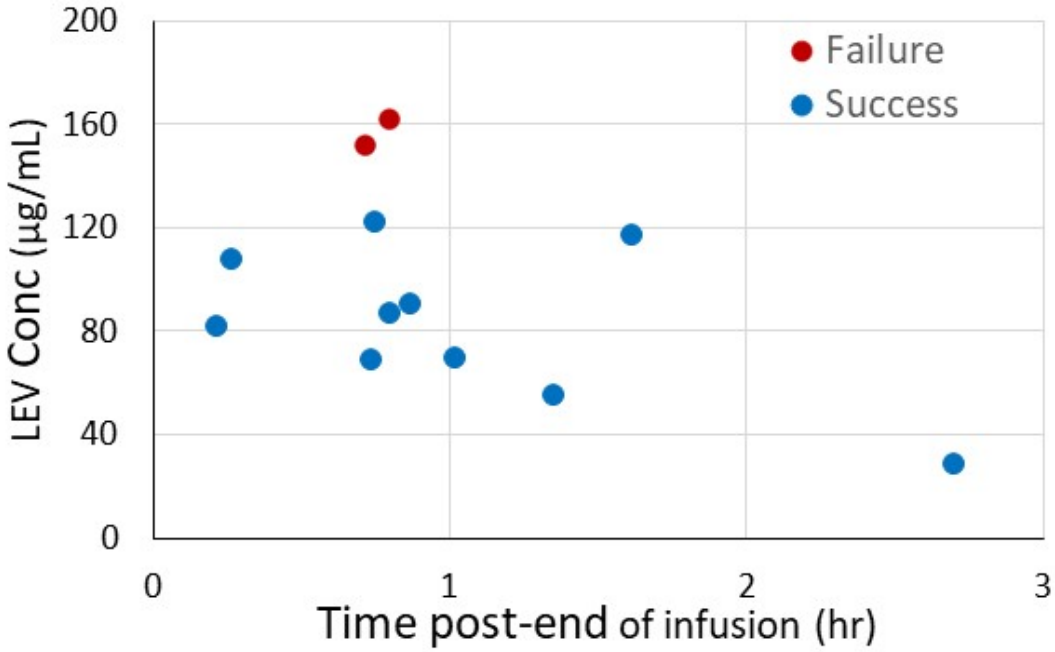




Established Status Epilepticus Treatment Trial

LEV Concentrations

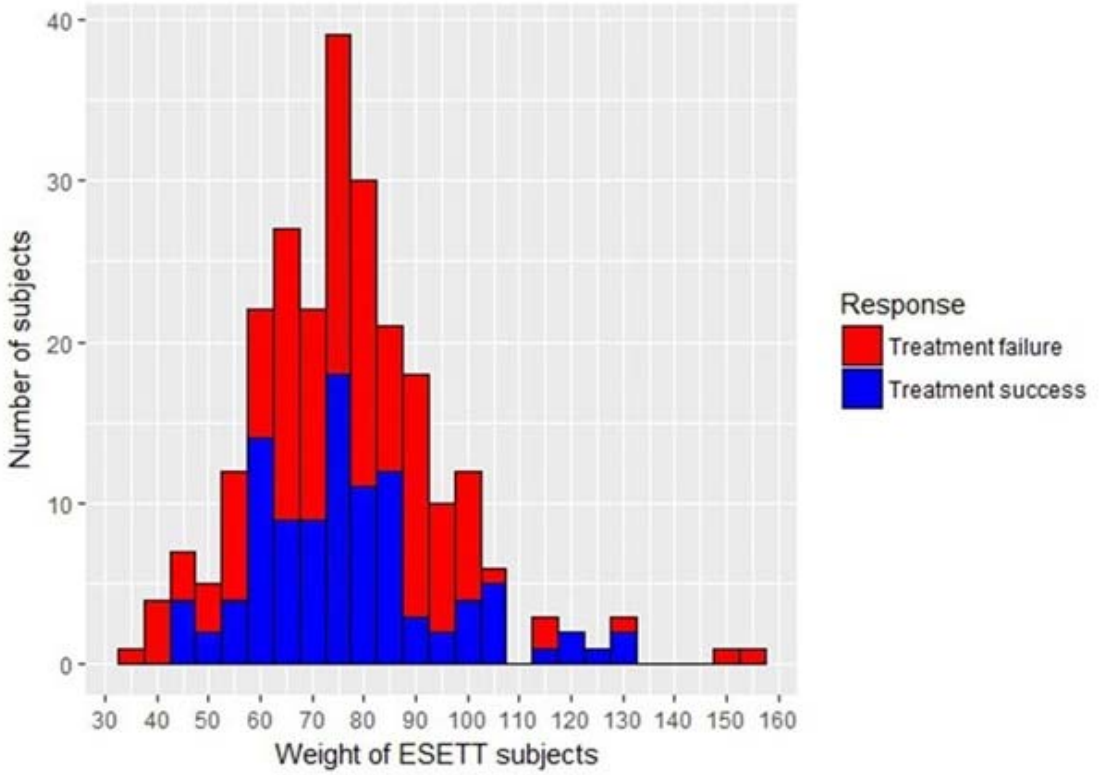
- **N= 7**
- **High between-subject variability**



Established Status Epilepticus Treatment Trial

Effect of Weight and Dose on Seizure Cessation

- **Weights of 247 adults: 36-157 kg**
- **122 weighed > 75 kg**
- **Overall success rate: ~43% in those < 75 kg ~39% in those >75 kg**
- **Success rates for LEV: 40% and 41%, VPA: 41% and 47%, and FOS: 40% and 41%**
- **No statistically significant differences in seizure cessation using dose/weight as primary predictor**



Distribution of weights and responses of adult subjects enrolled in ESETT

Established Status Epilepticus Treatment Trial

Summary of Findings

- **In children, no strong evidence that drug concentrations help explain treatment response**
- **In adults, weight-based dosing with a 75 kg cut-off did not appear to have an effect on treatment success**
- **Small sample size limits our ability to draw conclusions**

Established Status Epilepticus Treatment Trial

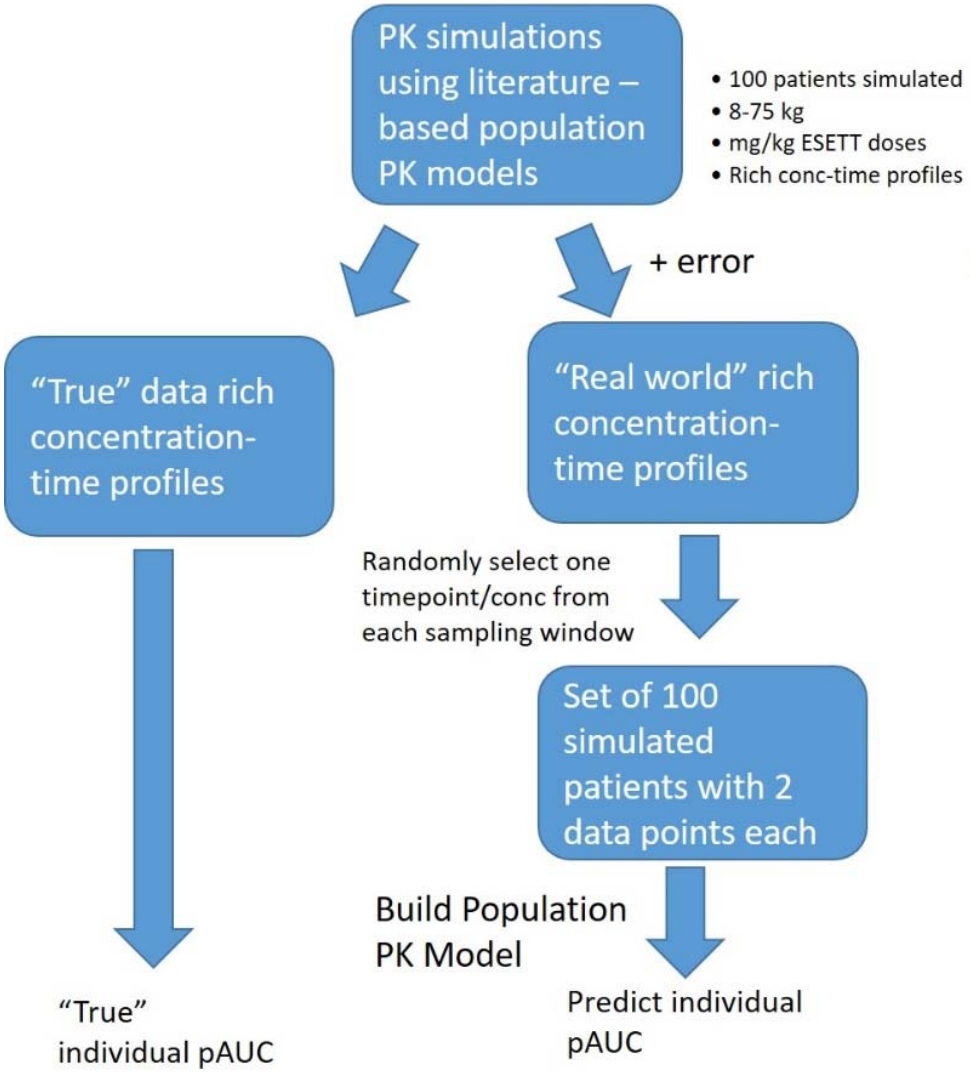
PK Simulation Study

- **PK/PD study objective was to relate early drug exposure (concentrations) with response**
- **Sparse sampling approach (20-50 min and the other within 60-120 min after the start of drug infusion)**

- **Objective: evaluate the performance of this sparse sampling approach to predict partial area under the curve from 20-120 min (pAUC) using a simulated patient population generated from literature-based models for PHT, LEV, and VPA.**

Established Status Epilepticus Treatment Trial

Simulation Study to Evaluate Feasibility of Sparse PK Sampling Approach

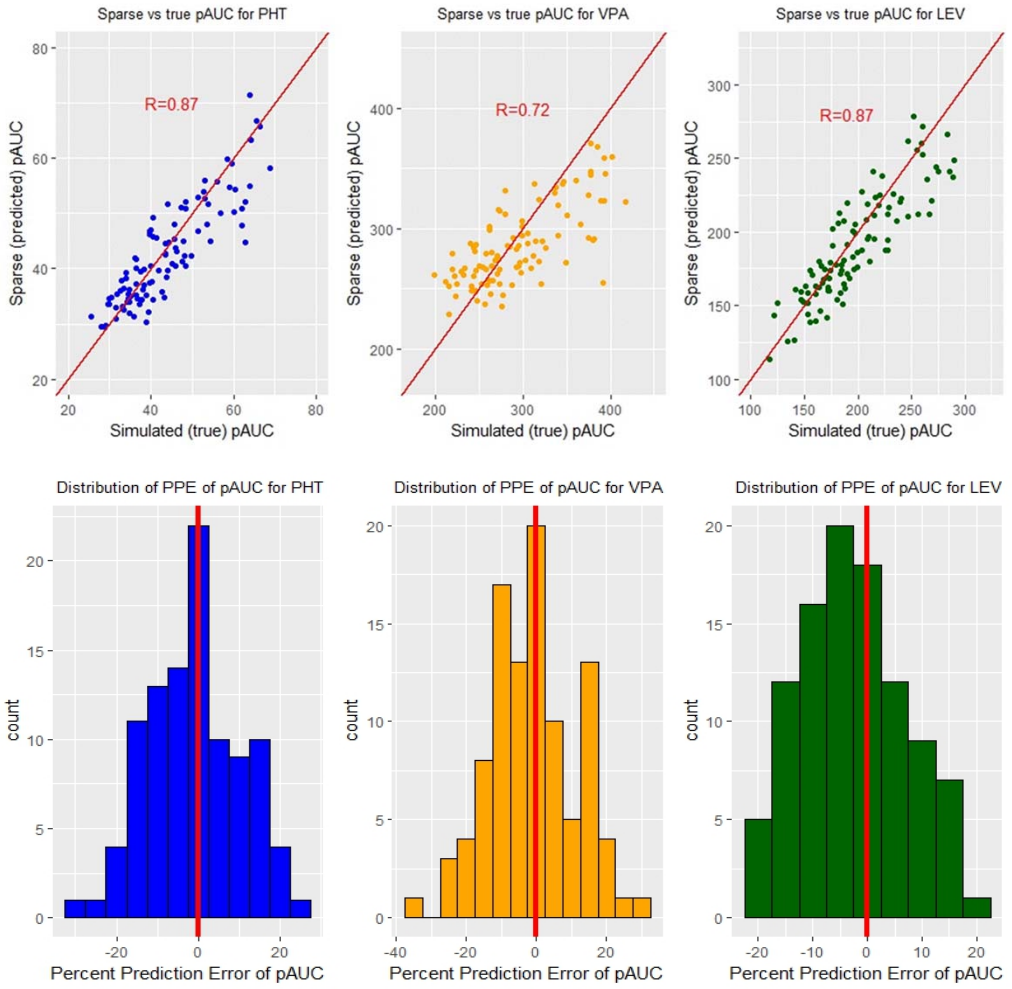


$$\text{PPE for pAUC} = \left(\frac{\text{Sparse pAUC} - \text{Simulated(true) pAUC}}{\text{Simulated(true) pAUC}} \right) \times 100$$

Established Status Epilepticus Treatment Trial

Simulation Results

- **Good correlation between "true" and predicted "sparse" drug exposure pAUCs.**
- **The percent prediction error was within ± 20% in most cases for all 3 drugs.**



Established Status Epilepticus Treatment Trial

Summary of Findings

- **Sparse sampling approach can accurately predict metrics of early drug exposure.**
- **Allow for exposure-response modeling to investigate factors affecting drug response.**
- **This approach can be explored in other emergent conditions and in children when blood sample limitations exist.**

Established Status Epilepticus Treatment Trial

Thank you from the ESETT PK-PD Study Team!!

Established Status Epilepticus Treatment Trial