CE Trials: Pragmatic, but Simple?

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Comparative Effectiveness

- Head-to-head comparisons of active treatments
- Generalized study populations
- Facilitate informed decision-making in the health care environment

Pragmatic Trial
Pragmatic Trial

- Large = Generalizability
- Simple = Feasibility
- Trial = Validity
A large simple trial….

“What is written without effort is in general read without pleasure.”

Samuel Johnson

Or…..

Simple ≠ Easy
When Large, make it look simple!
Neurological Emergencies Treatment Trials (NETT)

Intramuscular midazolam v. intravenous lorazepam in the pre-hospital treatment of status epilepticus: the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART)

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NIH/NINDS funded clinical trial network (entering 8th year)

Goal: to conduct confirmatory trials in acute neurological emergencies

Multidisplinary collaboration focusing on earlier interventions

MUSC – NETT SDMC and clinical site

UMICH – NETT CCC

Clinical Centers across the US participating
RAMPART

Importance to clinical practice:

- 200,000 cases of status epilepticus in the US every year resulting in as many as 55,000 deaths (40K/patient)
- Standard treatment is intravenous (IV) benzodiazepine
- Existing prehospital treatments are suboptimal
  - IV starts difficult/dangerous in the convulsing patient
  - Impractical for EMS so using non-IV routes
- IM treatment may be faster and easier but needs to be tested
Hypotheses

Primary Hypothesis

- IM midazolam is non-inferior to IV lorazepam at stopping convulsions prior to ED arrival

Secondary Hypotheses

- Convulsions stop more rapidly with treatment with IM midazolam versus IV lorazepam
- There is no difference in safety between the two treatments
Primary Outcome

- Proportion of subjects with termination of clinically evident seizure determined at arrival in the Emergency Department (ED) after a single dose of study medication (i.e., without rescue treatment).
Population

Inclusions
- Convulsive seizure activity for > 5 minutes
- Patient is still convulsing
- Estimated weight > 13 kg

Exclusions
- Major trauma precipitating seizure
- Hypoglycemia
- Known allergy to midazolam or lorazepam
- Sensitivity to benzodiazepines
- Cardiac arrest or heart rate < 40 beats/minute
- Known pregnancy
- Prisoner
Study Intervention
Study materials
Design Aspects

- 1023 enrollments (893 subjects)
- Assume 70% success rate for IV route
- Non-Inferiority Margin: 10% (IM is <10% less successful than IV)
- Simple randomization in ambulance
- Patient followed until ED or hospital discharge
Design Aspects

Benefits
- Both arms are accepted therapy
- Potential for direct benefit to subjects

Challenges
- Exception to Informed Consent
- IRB approval at all receiving hospitals
- Training of EMS
- Randomization and Time data collection in the field
Exception from Informed Consent

- Community Consultation / Public Notification
- Local Outreach – attend community meetings
- Patient Focus Groups – survivors and clinics

- 225 activities at 17 clinical hubs
- ~23,898 participants
- ~6,842 of whom provided direct feedback

- 43 IRBs for 321 sites reviewed and approved (median time=11months)
EMS Training and Deployment

- 4,314 medics trained
- 40 EMS Services in 14 States
  - Fire Service (67%)
  - Third Service or Hospital Based (33%)
- Wide ranging EMS system sizes
  - >100,000 runs/year (20%)
  - <5,000 runs/year (27%)
- Ambulances, Supervisor Units, Engines
Close-Out Performance

Last enrollment
1/14/2011

Last subject to reach end-of-study
4/10/2011

Database locked
4/22/2011
“Intramuscular midzolam is non-inferior to intravenous lorazepam in stopping seizures before arrival in the emergency department in patients with status epilepticus.”

“Use of an autoinjector is safe and maximized the speed and ease of intramuscular delivery … and reduced delays in initiating intravenous access.”
Results

Summary – accompanying editorial

“...the findings in this study should lead to a systematic change in the way patients in status epilepticus are treated en route to the hospital.”

Lawrence Hirsch
Pragmatic, but simple?

- Large = Generalizable to the EMS community
- Simple = Very few data points; minimal follow up
- Trial = Randomized, double-blind

LST ≠ Easy
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Our subjects &
Thousands of medics

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