Challenges in the Design and Analysis of Non-Inferiority Trials: A Case Study

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Key Points from FDA Guidance

• Active Control
• Non-Inferiority Margin
• Assay Sensitivity
• Single historical studies
• Alternative Designs

Draft Guidance for Industry Non-Inferiority Clinical Trials March 2010
Neurological Emergency Treatment Trials Network

- Funded by NINDS Fall 2006
- Mission:
  - Phase III
  - Multicenter clinical trials
  - Acute injuries/illnesses affecting the brain, spinal cord and peripheral nervous system.
- Unique Multidisciplinary collaboration

NETT Coordinating and Hub Sites

- Texas
- OHSU
- NYU
- VCU
- MD
- Stanford
- UCSF San Francisco General
- Hennepin County
- Medical College of Wisconsin
- Wayne State University
- Temple University
- University of Michigan Clinical Coordinating Center
- University of Cincinnati
- University of Kentucky
- Emory University
- Medical University of South Carolina Statistical & Data Management Center
- Texas
- Coordinating Centers
- Hub Sites
Current Trials

- ALIAS – ischemic stroke
- PROTECT – traumatic brain injury
- POINT – TIA or minor ischemic stroke
- SHINE – ischemic stroke
- RAMPART – status epilepticus

RAMPART

- Status Epilepticus (SE)
  - Seizure activity persisting for >5mins or patient not regaining consciousness between seizures;
  - 120,000 - 200,000 cases of SE in this country each year resulting in as many as 55,000 deaths.

- Duration of seizure ≡ Neurological Outcome.

- Goal: Rapid seizure cessation.
  - Pre-hospital treatment
Why RAMPART?

- Current standard treatment:
  - IV Lorazepam in ED (FDA approved)
  - One pre-hospital study (Alldredge et al NEJM 2001)

- Difficult to administer pre-hospital.

- Choice of other administration method?

Primary Question

- Is IM administration ‘no worse than some clinically relevant amount’ when compared to IV at stopping seizures?

- ‘Better’ is not the primary question.

- Willing to ‘give up’ some amount of the number of seizures we stop in order to gain in other aspects of treatment.
RAMPART Study Design

• Non-inferiority Design

• Randomized Parallel Arm
  – Active Control Arm = IV Lorazepam
  – Experimental Arm = IM Midazolam

• Double-Blind (Double Dummy)
  – Active Control Arm: IV Lorazepam/IV Placebo
  – Experimental Arm: IM Midazolam/IM Placebo

Primary Outcome

• Proportion of subjects with termination of clinically evident seizure determined at arrival to the ED after a single dose of study medication ($p_{IM}$ and $p_{IV}$).
**Trial Features**

- NI Margin = Absolute difference of 10%
- N = 1024 subjects (512 per treatment arm)
- EFIC (Exception From Informed Consent)
- IND (Investigational New Drug Application)

**FDA Clinical Hold**

1. Consider including a placebo arm.

2. Concern that there may be inadequate controlled experience with lorazepam to establish a predictable minimum treatment effect.

3. Consider designing a superiority trial on an appropriate outcome measure such as time interval from paramedic arrival to termination of seizure.
1. Including a Placebo in RAMPART

- Consider alternative designs
  – add-on studies; subpopulation studies; or rescue treatment design

- Life-threatening condition

- Unethical

2. Choice of Active Control

- The primary potential problem is that the investigational treatment could be proven to be within the non-inferiority margin of the active control, but that the active control itself may not be reliably better than placebo.
Choice of Active Control

- Widely used treatment;
- Established efficacy in well-designed and documented superiority trials; and,
- Expected to exhibit similar efficacy in the proposed active control trial (constancy assumption).

Systematic Review

- Twelve studies of IV lorazepam in the acute treatment of SE (11ED; 1 prehospital; 1 placebo-controlled).
- In total 1,439 subjects with acute treatment of SE were included in randomized, quasi-experimental, and prospective observational studies of IV lorazepam combined.
- Efficacy was consistently defined as termination of seizure within a specified short period of time, averaging 10 minutes.
### Primary Clinical Question:

Does the proposed practical IM treatment work as well in terms of termination of seizure and as safely as the FDA-approved, preferred ED treatment?

### Table: Efficacy of Different Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Responders n/N</th>
<th>Efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV lorazepam 2-4 mg</td>
<td>39/66</td>
<td>0.59 (0.47-0.71)</td>
</tr>
<tr>
<td>IV diazepam 5-10 mg</td>
<td>29/68</td>
<td>0.49 (0.31-0.55)</td>
</tr>
<tr>
<td>IV placebo</td>
<td>15/71</td>
<td>0.21 (0.12-0.31)</td>
</tr>
<tr>
<td>IV lorazepam 4 mg</td>
<td>11/17</td>
<td>0.65 (0.38-0.86)</td>
</tr>
<tr>
<td>IV diazepam 10 mg</td>
<td>28/46</td>
<td>0.61 (0.45-0.75)</td>
</tr>
<tr>
<td>IV lorazepam 0.1 mg/kg</td>
<td>20/31</td>
<td>0.65 (0.45-0.81)</td>
</tr>
<tr>
<td>IV diazepam 0.3 mg/kg</td>
<td>11/17</td>
<td>0.65 (0.38-0.86)</td>
</tr>
<tr>
<td>IV lorazepam 0.05 mg/kg</td>
<td>8/12</td>
<td>0.67 (0.35-0.9)</td>
</tr>
<tr>
<td>IV lorazepam 0.1 mg/kg</td>
<td>67/100</td>
<td>0.67 (0.57-0.76)</td>
</tr>
<tr>
<td>IV diazepam / phenytoin 0.15 mg/kg/18 mg/kg</td>
<td>59/59</td>
<td>0.60 (0.49-0.85)</td>
</tr>
<tr>
<td>IV lorazepam 0.05-0.1 mg/kg</td>
<td>19/27</td>
<td>0.70 (0.50-0.86)</td>
</tr>
<tr>
<td>IV diazepam 0.3-0.4 mg/kg</td>
<td>22/34</td>
<td>0.65 (0.47-0.85)</td>
</tr>
<tr>
<td>PR diazepam 0.3-0.4 mg/kg</td>
<td>7/19</td>
<td>0.37 (0.16-0.62)</td>
</tr>
<tr>
<td>IV lorazepam 0.1 mg/kg</td>
<td>160/211</td>
<td>0.76 (0.70-0.82)</td>
</tr>
<tr>
<td>IV diazepam 0.19/199</td>
<td>56 (0.49-0.61)</td>
<td></td>
</tr>
<tr>
<td>B lorazepam</td>
<td>82/183</td>
<td>0.45 (0.38-0.52)</td>
</tr>
<tr>
<td>IV lorazepam 4-6 mg</td>
<td>29/37</td>
<td>0.78 (0.62-0.90)</td>
</tr>
<tr>
<td>IV diazepam 10-20 mg</td>
<td>19/33</td>
<td>0.58 (0.39-0.75)</td>
</tr>
<tr>
<td>IV lorazepam 0.05 mg/kg</td>
<td>18/22</td>
<td>0.82 (0.60-0.95)</td>
</tr>
<tr>
<td>IV diazepam 0.1-0.15 mg/kg</td>
<td>11/16</td>
<td>0.69 (0.41-0.89)</td>
</tr>
<tr>
<td>IV lorazepam 4 mg</td>
<td>19/22</td>
<td>0.86 (0.65-0.97)</td>
</tr>
<tr>
<td>IV lorazepam 1-2 mg</td>
<td>33/53</td>
<td>0.62 (0.45-0.75)</td>
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<tr>
<td>IV lorazepam 4-8 mg</td>
<td>22/25</td>
<td>0.88 (0.69-0.98)</td>
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<tr>
<td>IV lorazepam 4 mg</td>
<td>15/17</td>
<td>0.83 (0.64-0.99)</td>
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<tr>
<td>IV diazepam 10 mg</td>
<td>8/14</td>
<td>0.57 (0.29-0.82)</td>
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<tr>
<td>IV lorazepam</td>
<td>427/587</td>
<td>0.73 (0.69-0.76)</td>
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<tr>
<td>Active comparators</td>
<td>420/781</td>
<td>0.54 (0.51-0.56)</td>
</tr>
<tr>
<td>IV placebo</td>
<td>15/71</td>
<td>0.21 (0.12-0.32)</td>
</tr>
</tbody>
</table>
Superiority trial in terms of Time to Event?

• no data to suggest exactly how much of a difference in time to termination represents a clinically relevant difference within the 10 minute window we are studying.

Superiority Endpoints (Secondary)

To assess the rapidity of IM midazolam versus IV lorazepam by comparing intervals from:

• paramedic arrival to the termination of clinically evident seizure; and,

• initiation of treatment to the termination of clinically evident seizure.
Choosing the Non-Inferiority Margin

Non-inferiority Margin

Combination of Statistical & Clinical Judgment.

- Clinical Perspective – what will change practice
- Statistical Perspective – takes into account the variability of the control’s effect.
**Noninferiority Margin**

Statistical: Retains at least a certain amount (e.g., at least 50%) of the superiority of the active control over placebo.

PHTSE Placebo Controlled Trial:
- Treatment effect: 0.38 (95% CI: 0.23, 0.52)
- Fraction of the lower limit: \( M_2 \leq X(.23) \) where \( X=(1-.5) \).

\[
\text{Placebo} = 0.211 \quad \text{IV} = 0.591
\]

**NI Margin**

\[
(p_{IM} - p_{IV}) = \text{NI} = -10\%
\]
Additional safeguard.....

RAMPART was designed to mirror the setting and study population of the referenced studies but.....

• there is still a risk that the chosen active control could have poor performance in RAMPART which could make a finding of non-inferiority misleading.

Criteria for Claiming Non-inferiority

1. If the primary hypothesis test rejects the null,

2. Then the active control must also maintain superiority over the historical placebo as determined by a 2-sided 95% confidence interval for the point estimate of the $p_{IV}$
   - if the lower limit of the interval exceeds the lower limit of that seen in the PHTSE (lower limit = 0.47), then non-inferiority of the IM arm cannot be claimed for the RAMPART Trial.
RAMPART

• Started enrollment June 2009

• ~800 paramedic units in over 40 EMS units across the US

• Recently completed enrollment

Summary

• Draft guidance very helpful

• Outstanding NI design and analysis issues:
  – Impact of no placebo control
  – Impact of interim analyses
  – NIs place in adaptive designs
Acknowledgements

• Clinical PIs
  – Robert Silbergleit, MD, UMICH
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• RAMPART DSMB Members