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Draft Guidance for Industry Non-Inferiority Clinical Trials March 2010

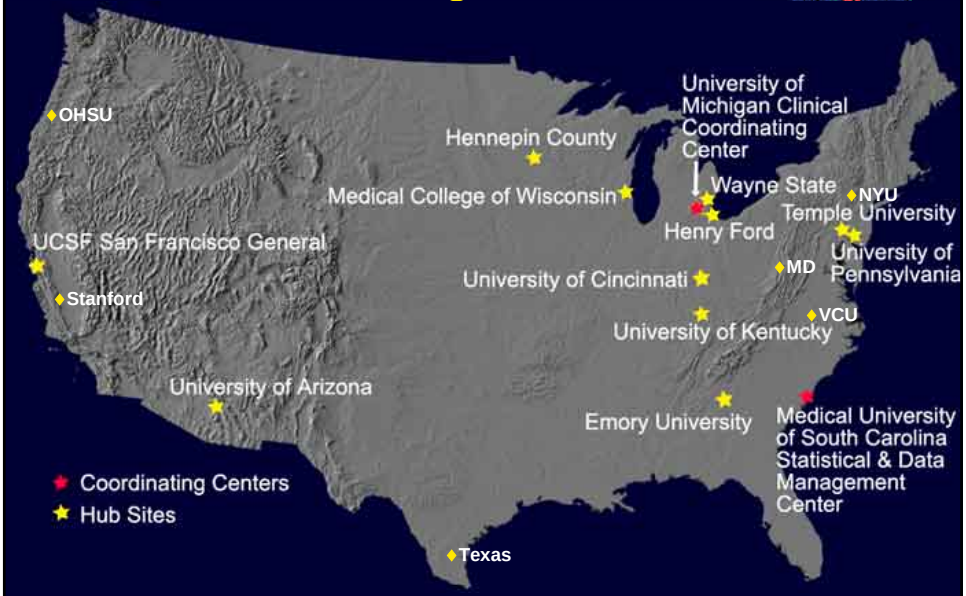
Neurological Emergency Treatment Trials Network

❖Funded by NINDS Fall 2006

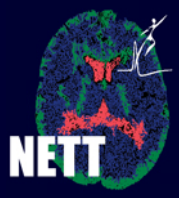
❖Mission:
- Phase III
- Multicenter clinical trials
- Acute injuries/illnesses affecting the brain, spinal cord and peripheral nervous system.

❖Unique Multidisciplinary collaboration

NETT Coordinating and Hub Sites

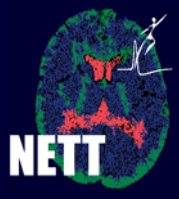


Current Trials



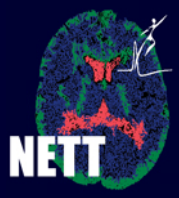
- ALIAS – ischemic stroke
- PRoTECT – traumatic brain injury
- POINT – TIA or minor ischemic stroke
- SHINE – ischemic stroke
- RAMPART – status epilepticus

RAMPART



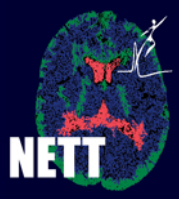
- Status Epilepticus (SE)
  - Seizure activity persisting for >5mins or patient not regaining consciousness between seizures;
  - 120,000 - 200,000 cases of SE in this country each year resulting in as many as 55,000 deaths.
- Duration of seizure ≡ Neurological Outcome.
- Goal: Rapid seizure cessation.
  - Pre-hospital treatment

Why RAMPART?



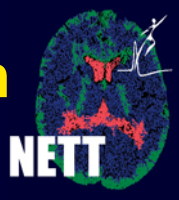
- Current standard treatment:
  - IV Lorazepam in ED (FDA approved)
  - One pre-hospital study (*Alldredge et al NEJM 2001*)
- Difficult to administer pre-hospital.
- Choice of other administration method?

Primary Question



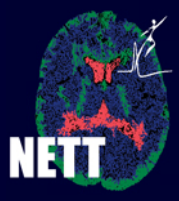
- Is IM administration 'no worse than some clinically relevant amount' when compared to IV at stopping seizures?
- 'Better' is not the primary question.
- Willing to 'give up' some amount of the number of seizures we stop in order to gain in other aspects of treatment.

RAMPART Study Design



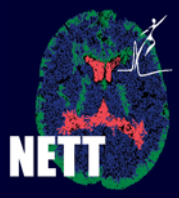
- Non-inferiority Design
- Randomized Parallel Arm
  - Active Control Arm = IV Lorazepam
  - Experimental Arm = IM Midazolam
- Double-Blind (Double Dummy)
  - Active Control Arm: IV Lorazepam/IV Placebo
  - Experimental Arm: IM Midazolam/IM Placebo

Primary Outcome



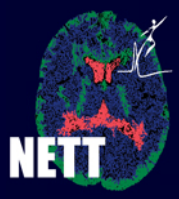
- Proportion of subjects with termination of clinically evident seizure determined at arrival to the ED after a single dose of study medication (p_{IM} and p_{IV}).

Trial Features



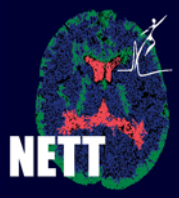
- NI Margin = Absolute difference of 10%
- N = 1024 subjects (512 per treatment arm)
- EFIC (Exception From Informed Consent)
- IND (Investigational New Drug Application)

FDA Clinical Hold



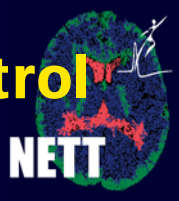
1. Consider including a placebo arm.
2. Concern that there may be inadequate controlled experience with lorazepam to establish a predictable minimum treatment effect.
3. Consider designing a superiority trial on an appropriate outcome measure such as time interval from paramedic arrival to termination of seizure.

1. Including a Placebo in RAMPART



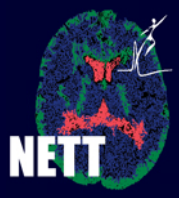
- Consider alternative designs
  - add-on studies; subpopulation studies; or rescue treatment design
- Life-threatening condition
- Unethical

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

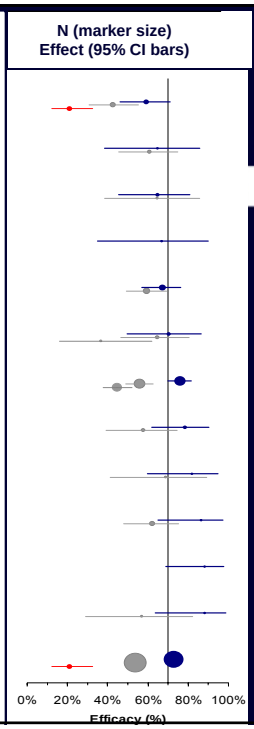


- Widely used treatment;
- Established efficacy in well-designed and documented superiority trials; and,
- Expected to exhibit similar efficacy in the proposed active control trial (constancy assumption).

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.

Intervention	Responders n/N	Efficacy (95% CI)
IV lorazepam 2-4 mg	**39/66**	**0.59 (0.47-0.71)**
IV diazepam 5-10 mg	29/68	0.43 (0.31-0.55)
IV placebo	15/71	0.21 (0.12-0.31)
IV lorazepam 4 mg	**11/17**	**0.65 (0.38-0.86)**
IV diazepam 10 mg	28/46	0.61 (0.45-0.75)
IV lorazepam 0.1mg/kg	**20/31**	**0.65 (0.45-0.81)**
IV diazepam 0.3 mg/kg	11/17	0.65 (0.38-0.86)
IV lorazepam 0.05 mg/kg	**8/12**	**0.67 (0.35-0.9)**
IV lorazepam 0.1mg/kg	**67/100**	**0.67 (0.57-0.76)**
IV diazepam / phenytoin 0.15 mg/kg /18 mg/kg	59/99	0.60 (0.49-0.69)
IV lorazepam 0.05-0.1 mg/kg	**19/27**	**0.70 (0.50-0.86)**
IV diazepam 0.3-0.4mg/kg	22/34	0.65 (0.47-0.80)
PR diazepam 0.3-0.4 mg/kg	7/19	0.37 (0.16-0.62)
IV lorazepam 0.1 mg/kg	**160/211**	**0.76 (0.70-0.82)**
IN lorazepam	111/199	.56 (0.49-0.63)
B lorazepam	82/183	0.45 (0.38-0.52)
IV lorazepam 4-8 mg	**29/37**	**0.78 (0.62-0.90)**
IV diazepam 10-20 mg	19/33	0.58 (0.39-0.75)
IV lorazepam 0.05mg/kg	**18/22**	**0.82 (0.60-0.95)**
IV diazepam 0.1-0.15 mg/kg	11/16	0.69 (0.41-0.89)
IV lorazepam 4 mg	**19/22**	**0.86 (0.65-0.97)**
IV lorazepam 1-2 mg	33/53	0.62 (0.48-0.75)
IV lorazepam 4-8 mg	**22/25**	**0.88 (0.69-0.98)**
IV lorazepam 4 mg	**15/17**	**0.88 (0.64-0.99)**
IV diazepam 10 mg	8/14	0.57 (0.29-0.82)
IV lorazepam	**427/587**	**0.73 (0.69-0.76)**
Active comparators	420/781	0.54 (0.51-0.58)
IV placebo	15/71	0.21 (0.12-0.32)

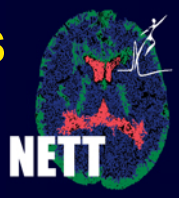


3. FDA: Superiority vs Non-inferiority

Primary Clinical Question:

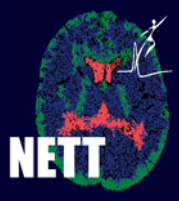
– Does the proposed practical IM treatment work as well in terms of termination of seizure and as safely as the FDA-approved, preferred ED treatment?

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

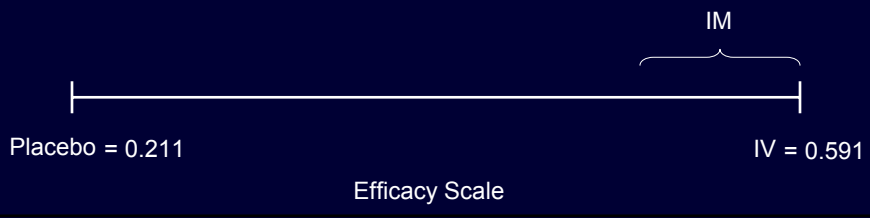
Combination of Statistical & Clinical Judgment.

- Clinical Perspective – what will change practice
- Statistical Perspective – takes into account the variability of the control's effect.

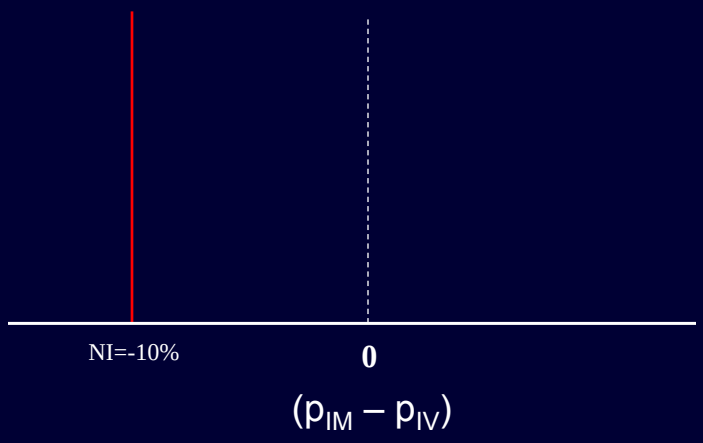
Noninferiority Margin

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

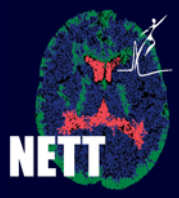
PHTSE Placebo Controlled Trial:
Treatment effect: 0.38 (95% CI: 0.23, 0.52)
Fraction of the lower limit: M2 ≤ X(.23) where X=(1 -.5).



NI Margin



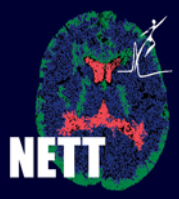
Additional safeguard…..



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.

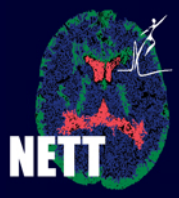
Criteria for Claiming Non-inferiority



1. If the primary hypothesis test rejects the null,

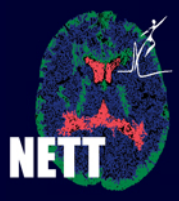
2. Then the active control must also maintain superiority over the historical placebo as determined by a 2-sided 95% confidence interval for the point estimate of the p_{IV}
   - if the lower limit of the interval exceeds the lower limit of that seen in the PHTSE (lower limit = 0.47), then non-inferiority 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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- NETT Network and EMS units
- NINDS and CounterAct (sponsors)
- FDA
- RAMPART DSMB Members