A Bayesian Adaptive Trial for CER: Case Study in Status Epilepticus

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DESIGN-IT 2013

Adaptive Clinical Trial Design: Beyond Theory into Reality

Disclosures / Acknowledgements

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- No financial disclosures relevant to presentation

Status Epilepticus (SE)

- Seizure activity persisting > 5 minutes
- Mortality ranges from 17-26%
- Mortality predictors
  - Age
  - Etiology
  - Severity of underlying disease
  - ***Duration of SE***
- Many are left with permanent neuro deficits

Management of SE

- First line therapy
  - Benzodiazepines (BDZ)
- "Established" SE
  - fosPhenytoin
  - Valproate
  - Levitiracetam
- "Refractory" SE
  - General anesthesia

Established SE

- Most effective treatment is unclear
- Phenytoin is the standard
  - If BZP fails, few patients respond to phenytoin
- Comparison studies have been limited and not definitive
- Other drugs may have a better safety profile

Study Population

- Adults and children > 2 years old
- SE not responsive to adequate doses of BZP
- Exclusions
  - Intubated patients
  - Sz secondary to trauma, anoxia, high or low BS
  - Pregnancy

Study Objectives

- Determine which of 3 agents are more or least effective in controlling seizures without need for further anticonvulsants and without life threatening hypotension or arrythmias at 2 hours post presentation
  - fosPhenytoin
  - Valproate
  - Levitiracetam

Outcomes

- Primary
  - Cessation of Sz without additional medications or serious side effects maintained for 2 hours
- Secondary
  - Time to cessation of Sz
  - Need for intubation/anesthesia
  - Disposition
  - Outcome

Conflicts of Interest

- None for three drugs being discussed

- Consult with many other drug & device companies I won't discuss

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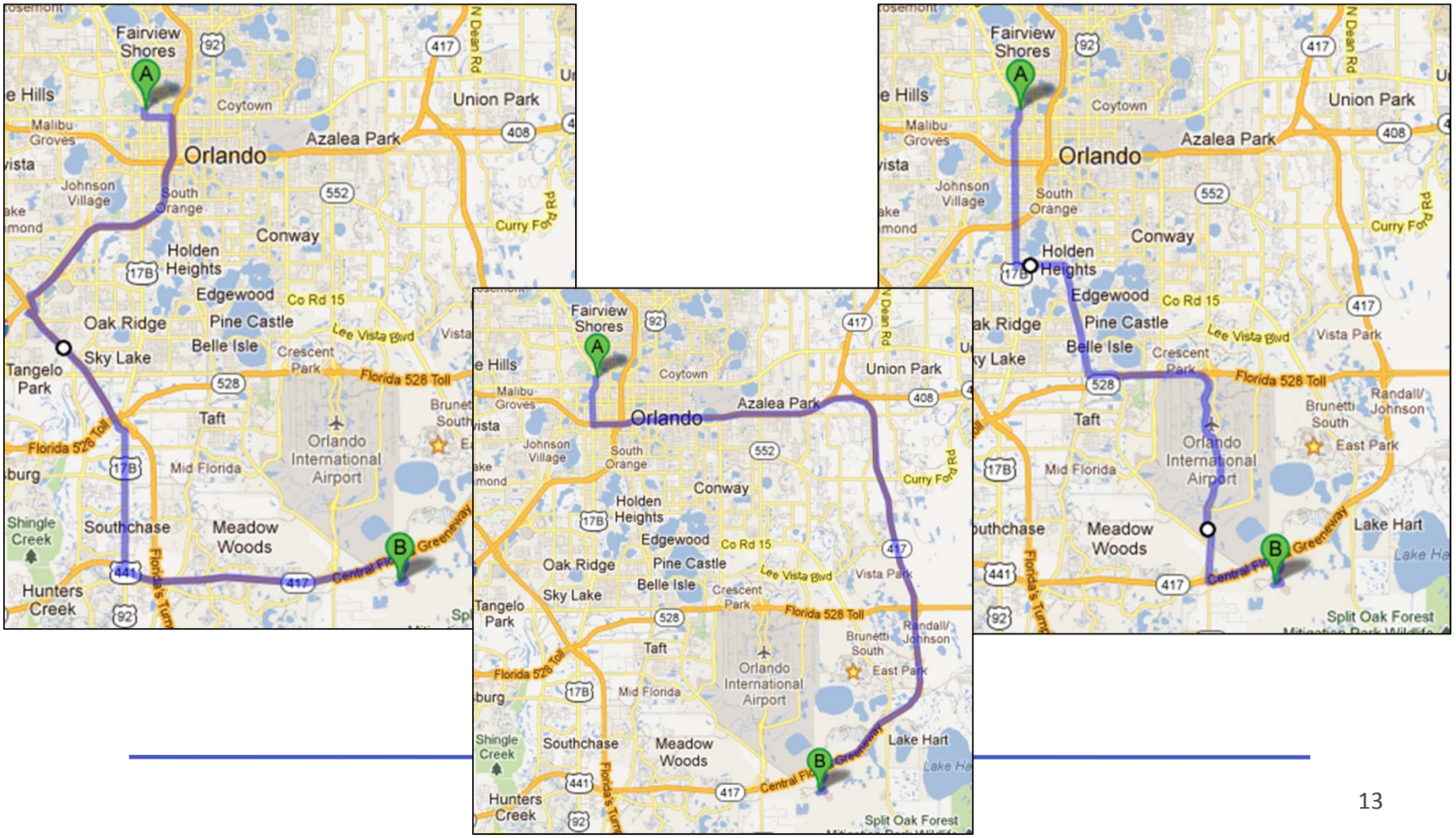
Research Question

- How to treat static epilepticus patients who've failed benzodiazapines?
  - fosphenytoin (fPHT)
  - levetiracetam (LVT)
  - valproic acid (VPA)
- Composite endpoint
  - Cessation of seizure with 20 minutes
  - No further treatment within 2 hours
  - No significant adverse event

Comparative Effectiveness

- No control group
  - Three drugs start out equal
  - Want to know which is best
- What is Type I error in CER?
  - Consequence of Type I error less in CER
- Really want to know
  - Which drug is best … with measure of certainty
  - Which drug is worst … with measure of certainty

A Common CER Trial



Bayesian Adaptive Design Features

- Adaptively allocate to favor better treatments
- Drop poor performing arms
  - Relative to one another
  - Relative to 25% goal
- Stop early if we know the answer
  or know we won't know
  - Efficacy stop if treatment clearly better
  - Futility stop if unlikely to ID a 'best' or 'worst'
    - Do not stop if 1 worse and other 2 equally good
  - Futility stopping if all arms bad

Adaptive Allocation

- Randomize 300 patients equally (Max is 795)
- At 300 & then every 100 adaptively allocate to
  - Favor better performing treatments
  - Favor treatments with greater uncertainty
  - Every 100 = About every 6 months | expected accrual

$$r_a \propto \sqrt{\frac{\Pr\left(p_a = \max_j p_j\right) Var\left(p_a\right)}{N_a}}$$

- If allocation probability < 5%, suspend accrual
- If Pr(p_a > 0.25) < 0.05 drop arm

Early Stopping

- Begins after 400 patients and every additional 100 patients accrued
- Early Success Stopping:
  - If arm has 97.5% probability of having highest success rate
    - i.e. Pr(Arm = Max Effective Trt) > 0.975
- Early Futility Stopping
  - If predicted probability of success (ID ‘winner’ or ‘loser’ at the max N=795) < 0.05
  - If all doses have Pr(Success > 0.25) < 0.05

Example Trial: 300-pt analysis

	N Enrolled Observed Response Rate			Pr(Max Effective Trt)			Pr(Allocation)			Pred Prob
Look	fPHT	LVT	VPA	fPHT	LVT	VPA	fPHT	LVT	VPA	
300	51/100 51%	55/100 55%	64/100 64%	0.025	0.092	0.88	0.12	0.22	0.66	0.71

Example Trial: 400-pt analysis

	N Enrolled Observed Response Rate			Pr(Max Effective Trt)			Pr(Allocation)			Pred Prob
Look	fPHT	LVT	VPA	fPHT	LVT	VPA	fPHT	LVT	VPA	
300	51/100 51%	55/100 55%	64/100 64%	0.025	0.092	0.88	0.12	0.22	0.66	0.71
Next 100	6/11 55%	19/26 73%	39/63 62%							
400	57/111 51%	74/126 59%	105/163 64%	0.01	0.16	0.83	0.09	0.34	0.57	0.50

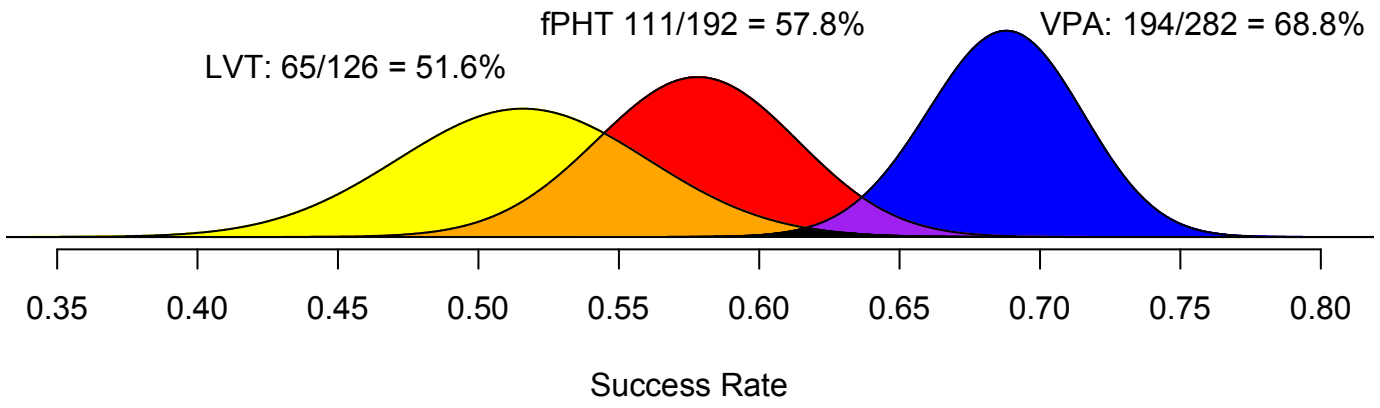
Example Trial: 500-pt analysis

	N Enrolled Observed Response Rate			Pr(Max Effective Trt)			Pr(Allocation)			Pred Prob
Look	fPHT	LVT	VPA	fPHT	LVT	VPA	fPHT	LVT	VPA	
300	51/100 51%	55/100 55%	64/100 64%	0.025	0.092	0.88	0.12	0.22	0.66	0.71
400	57/111 51%	74/126 59%	105/163 64%	0.01	0.16	0.83	0.09	0.34	0.57	0.50
Next 100	5/12 42%	20/38 53%	34/50 68%							
500	62/123 50%	94/164 57%	139/213 65%	0.004	0.056	0.94	0.08	0.23	0.69	0.59

Example Trial: 600-pt analysis

	N Enrolled Observed Response Rate			Pr(Max Effective Trt)			Pr(Allocation)			Pred Prob
Look	fPHT	LVT	VPA	fPHT	LVT	VPA	fPHT	LVT	VPA	
300	51/100 51%	55/100 55%	64/100 64%	0.025	0.092	0.88	0.12	0.22	0.66	0.71
400	57/111 51%	74/126 59%	105/163 64%	0.01	0.16	0.83	0.09	0.34	0.57	0.50
500	62/123 50%	94/164 57%	139/213 65%	0.004	0.056	0.94	0.08	0.23	0.69	0.59
Next 100	3/3 100%	17/28 61%	55/69 80%							
600	65/126 52%	111/192 58%	194/282 69%	0.000 0.87	0.008 0.13	**0.992** 0.00	Trial Stops Early for Identifying Best Treatment			

Example Trial: Final Evaluation



Treatment	Observed	%	95% CI	Pr(Best)	Pr(Worst)
VPA	194/282	68.8%	(.632, .739)	0.992	0.0005
LVT	111/192	57.8%	(.507, .646)	0.007	0.138
fPHT	65/126	51.6%	(.429, .601)	0.0005	0.862

Difference	Observed	95% CI	Pairwise Comparison
VPA – LVT	0.110	(0.022, 0.197)	Pr(VPA>LVT) = 0.993
VPA – fPHT	0.172	(0.069, 0.272)	Pr(VPA>fPHT) > 0.999
LVT - fPHT	0.062	(-0.049, 0.172)	Pr(LVT>fPHT) = 0.862

Comparison to without Adaptive Randomization

	Adaptive Randomization			Fixed Randomization		
Scenario 3 Efficacy Rates	**Power**	**Mean N**	**% to Best**	**Power**	**Mean N**	**% to Best**
Null 0.5 – 0.5 – 0.5	0.042	507		0.029	499	
One Good 0.5 – 0.5 – 0.65	0.94	483	48	0.88	497	33
Two Good 0.5 – 0.65 – 0.65	0.81	679	84	0.86	687	67
One Middle One Good 0.5 – 0.575 – 0.65	0.73	586	47	0.69	599	33
All Bad 0.25– 0.25 – 0.25	0.044	524		0.030	509	
All Very Bad 0.10 – 0.10 – 0.10	0.005	400		0.028	400	

Power = Pr(Identify Best or Worst with Pr>0.975)

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Summary

- Comparative Effectiveness is an ideal setting for Bayesian adaptive trials
- Interim analyses early & often
- Steer patients to better therapies
- Steer patients away from poorer therapies
- Increase power in 3+ arm trial with adaptive rand.
- Stop trial as soon as best treatment identified
- Natural way of learning & making decisions
- Paper accepted by *Journal of Clinical Epidemiology*