Simple Protocol & Bayesian Design: Established Status Epilepticus Treatment Trial (ESETT)

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Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1).
It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

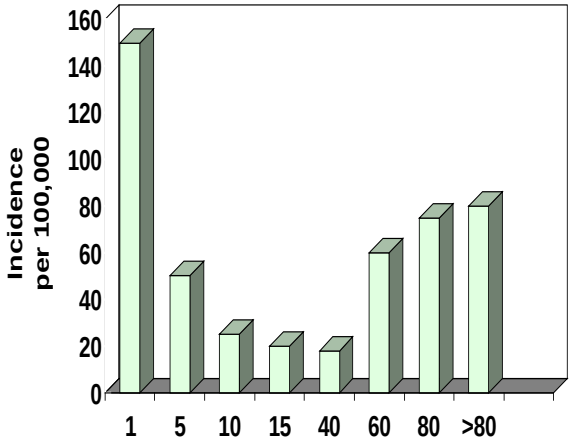
ILAE taskforce Epilepsia Oct 2015

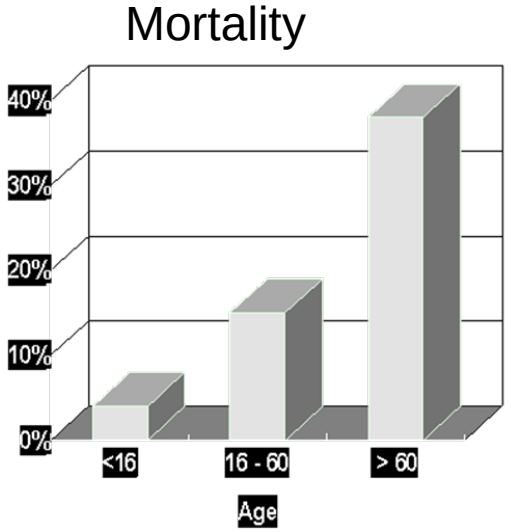
Status Epilepticus: Epidemiology

Incidence 41-61/100,000.

Episodes of status epilepticus in US in 2010: 120,000-188,459.

Mortality in patients with status epilepticus to 17%.
Mortality correlates with cause & duration of SE.





DeLorenzo et al. Neurology 1996
Towne et al. J. Clin. Neurophysiology 1994

Need for ESETT

- Four well-controlled studies demonstrate that benzodiazepines are effective and safe initial treatment of status epilepticus in adults and children.
- Episodes of SE in US in 2010: 41- 61/100,000 X 309 million = 120,000-188459
- 35-45 % of patients with convulsive SE do not respond to benzodiazepines i.e.42-72,000 ESE patient.
- There is no well-controlled prospective clinical trial to guide the treatment of SE in patients who fail benzodiazepines.
- Three drugs chosen for the trial, Fosphenytoin, Levetiracetam and Valproic acid are commonly used treat benzodiazepine-refractory status epilepticus.

ESETT

Established **S**tatus **E**pilepticus **T**reatment **T**rial (ESETT)

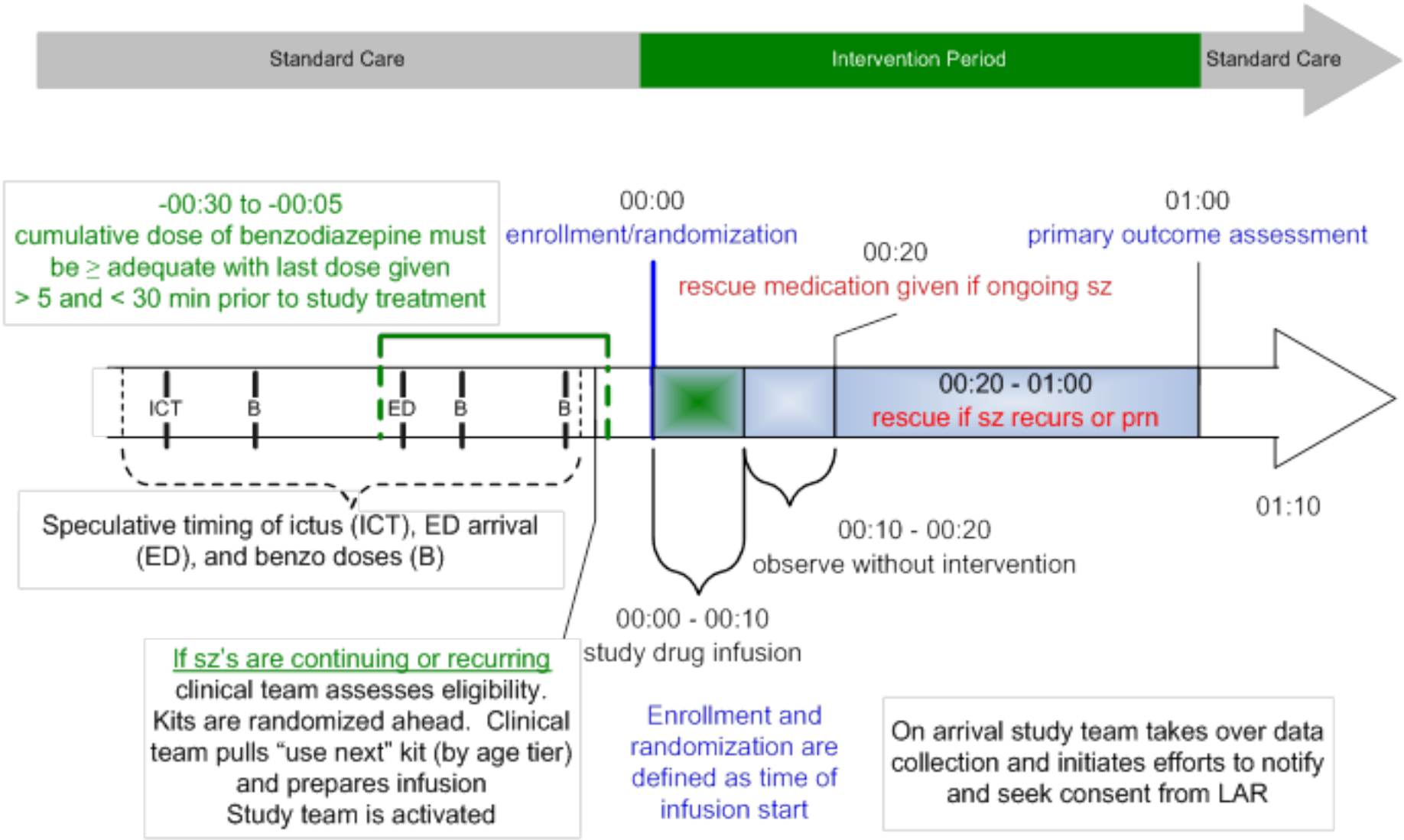
A multicenter, randomized, blinded, comparative effectiveness study of fosphenytoin, valproic acid, or levetiracetam in the emergency department treatment of patients with benzodiazepine-refractory status epilepticus.

Inclusion Criteria

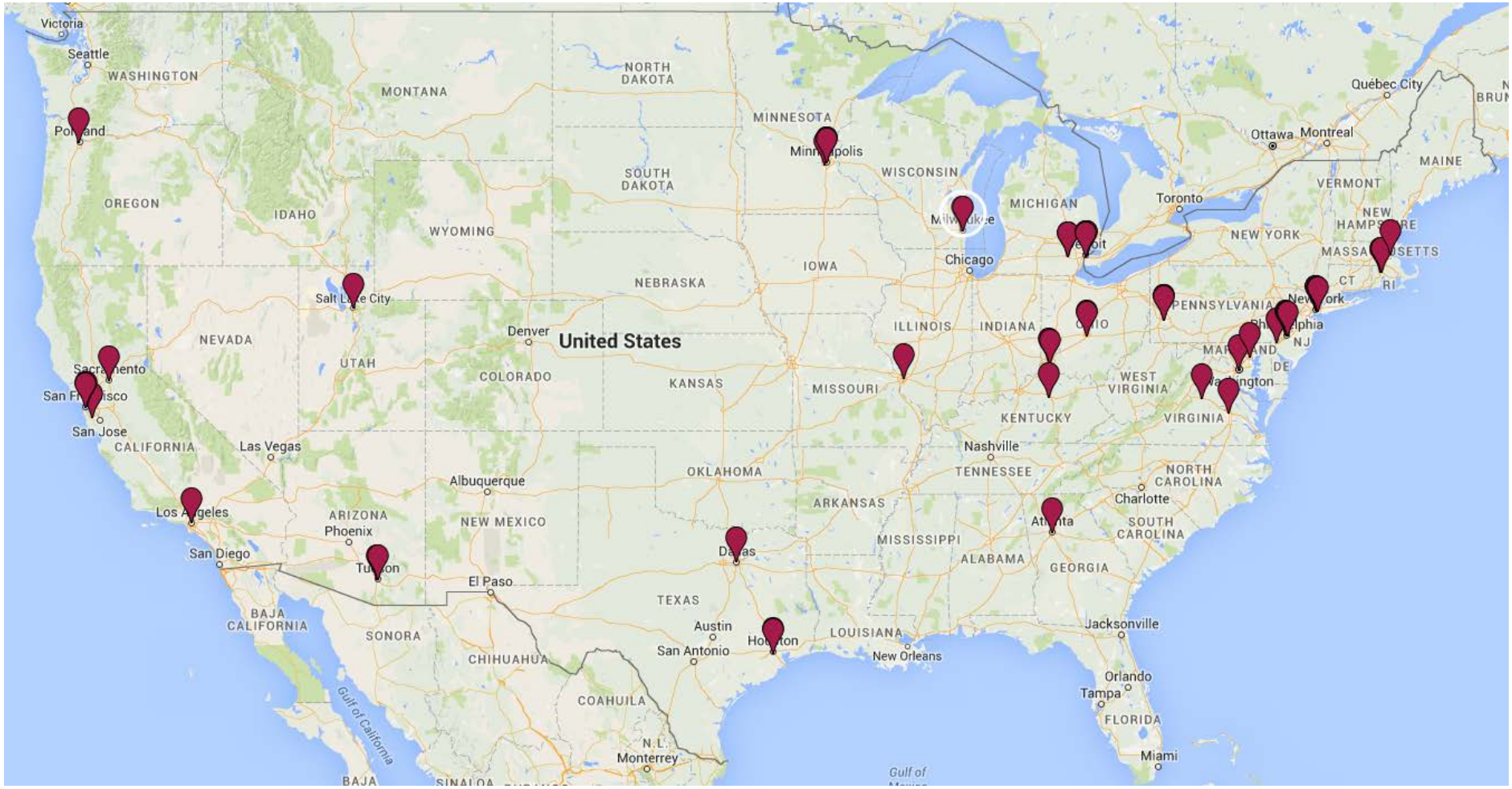
Inclusion criteria	Measure
Patient witnessed to have a seizure in the past 5-30 minutes.	Time of first seizure is when EMS personnel were called if eyewitness account available or first seizure witnessed by EMS personnel.
Patient received adequate dose of benzodiazepines in the past 5-30 minutes. The doses may be divided. Time is counted from the last dose.	EMS or ED record of treatment: For those > 40 kg--diazepam 10 mg IV or rectal, lorazepam 4 mg, IV, or midazolam 10 mg IM or IV. For those 10-40 Kg adequate doses are: diazepam 0.3 mg/kg IV or rectal, lorazepam 0.1 mg/kg IV or midazolam 0.3 mg/kg IM or 0.2 mg/Kg IV
Continueded seizure in the Emergency Department	Clinical observation
Age more than 2 years	Caretakers report the age or clinical observation

Exception From Informed Consent

- **Justification:**
  - Convulsive status epilepticus is a life threatening disease
  - Best available treatment is unproven
  - Clinical trials are needed
  - Obtaining prospective informed consent is not feasible
    - Subject altered (actively seizing and unconscious)
    - An acute seizing patient cannot be identified prospectively
    - LAR is often not available in the short time frame required. Even when an LAR is available, **meaningful informed consent is impossible to obtain** because of the time constraints and the emotional distress caused by witnessing convulsive SE.
  - Subjects may benefit from the research
  - Research could not be carried out without EFIC
  - Therapeutic window too short


Standard Care
Intervention Period
Standard Care
-00:30 to -00:05
cumulative dose of benzodiazepine must be ≥ adequate with last dose given
> 5 and < 30 min prior to study treatment
00:00
enrollment/randomization
00:20
rescue medication given if ongoing sz
01:00
primary outcome assessment
ICT
B
ED
B
B
00:20 - 01:00
rescue if sz recurs or prn
01:10
Speculative timing of ictus (ICT), ED arrival (ED), and benzo doses (B)
00:10 - 00:20
observe without intervention
00:00 - 00:10
study drug infusion
If sz's are continuing or recurring
clinical team assesses eligibility.
Kits are randomized ahead. Clinical team pulls "use next" kit (by age tier) and prepares infusion
Study team is activated
Enrollment and randomization are defined as time of infusion start
On arrival study team takes over data collection and initiates efforts to notify and seek consent from LAR

ESETT: NETT &PECARN 51 sites



Primary Outcome

Clinical cessation of status epilepticus, determined by the absence of clinically apparent seizures and improving responsiveness, at 60 minutes after the start of study drug infusion, without the use of additional anti-seizure medication.

(*Note if patient is intubated within 60 minutes of enrollment, it is failure to meet primary outcome, because sedatives are used)

Study Design

- Bayesian Adaptive Design (extensive simulation study)
- Maximum sample size is N=795 total (using pairwise comparisons).
- Primary endpoint at 60 minutes
- Followed until discharge/30 days
- Randomization will be stratified by three age groups
  - 2-18 years
  - 19-65 years
  - 66 years and older

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

1st Interim Analysis: N = 300 Subjects

Only Adaptive Allocation Allowed

Look	N Enrolled Observed Response Rate			Pr(Max Effective Trt)			Pr(Allocation)			Pred Prob
	LVT	fPHT	VPA	LVT	fPHT	VPA	LVT	fPHT	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

2nd Interim Analysis: N = 400 Subjects

Adaptive Allocation AND Early Stopping Allowed

Look	N Enrolled Observed Response Rate			Pr(Max Effective Trt)			Pr(Allocation)			Pred Prob
	LVT	fPHT	VPA	LVT	fPHT	VPA	LVT	fPHT	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

3rd Interim Analysis: N = 500 Subjects

Adaptive Allocation AND Early Stopping Allowed

Look	N Enrolled Observed Response Rate			Pr(Max Effective Trt)			Pr(Allocation)			Pred Prob
	LVT	fPHT	VPA	LVT	fPHT	VPA	LVT	fPHT	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

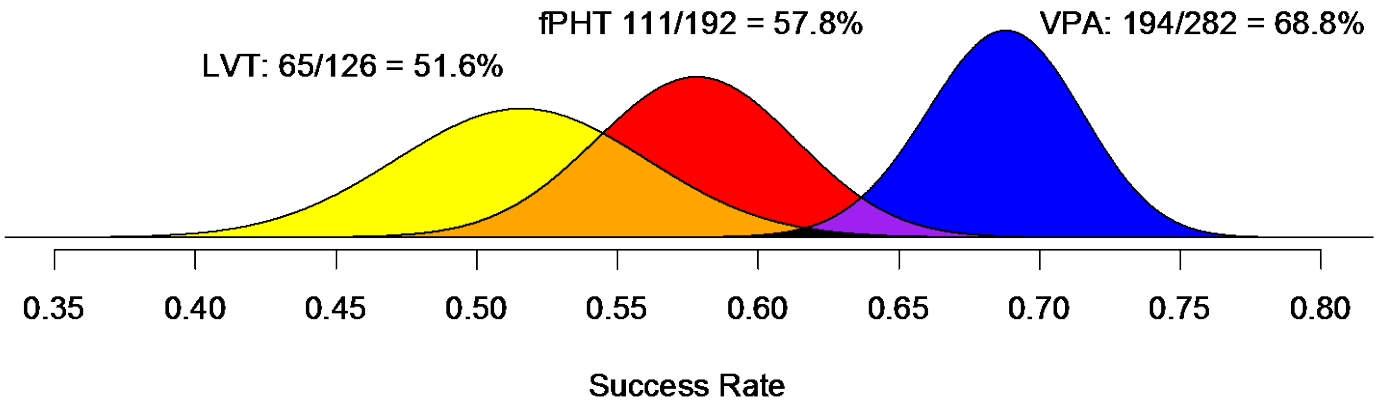
4th Interim Analysis: N = 600 Subjects

Adaptive Allocation AND Early Stopping Allowed

Look	N Enrolled Observed Response Rate			Pr(Max Effective Trt)			Pr(Allocation)			Pred Prob
	LVT	fPHT	VPA	LVT	fPHT	VPA	LVT	fPHT	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

Final Analysis: N = 600 Subjects



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

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

Scenarios

	fPHT	LVT	VPA
Null	50%	50%	50%
One Good	50%	50%	65%
Two Good	50%	65%	65%
One Middle One Good	50%	57.5%	65%
All Bad	25%	25%	25%
All Really Bad	10%	10%	10%

Connor, Elm &ESETT planning group

Operating Characteristics
Max N = 720

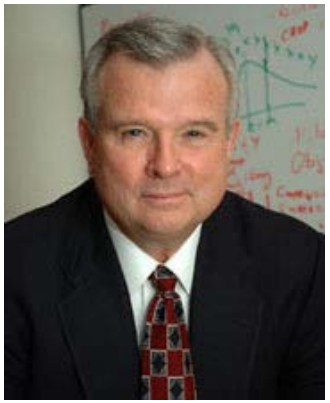
Scenario 3 Efficacy Rates	Mean N	Pr(ID Worst) Early-End	Pr(ID Best) Early-End	Pr(Randomize To Best)	Pr(Best Or Worst)
Null 0.5 – 0.5 – 0.5	507	0.018	0.013 0.012 0.001	100%	0.031
One Good 0.5 – 0.5 – 0.65	483	0.033	0.89 0.88 0.01	48%	0.90
Two Good 0.5 – 0.65 – 0.65	679	0.67	0.12 0.48 0.02	84%	0.76
1 Middle 1 Good 0.5 – 0.575 – 0.65	586	0.25	0.50 0.48 0.02	47%	0.68
All Bad 0.25 – 0.25 – 0.25	524	0.030	0.017 0.016 0.001	100%	0.044
All Really Bad 0.10 – 0.10 – 0.10	400	0.000	0.006 0.006 0.000	100%	0.006

ESETT planning group &NIH

Bleck

Cock

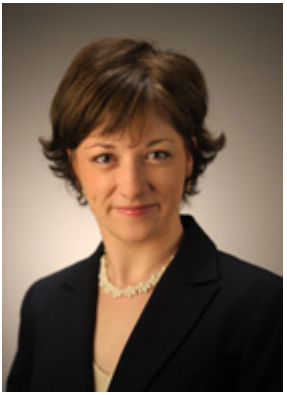
Chamberlain



Cloyd

Elm

Fountain



Fureman

Lowenstein

Shinnar

Silbergleit

Treiman

Trinka