ESETT

Established Status Epilepticus Treatment Trial (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.

Established
Status
Epilepticus
Treatment
Trial

History of the trial

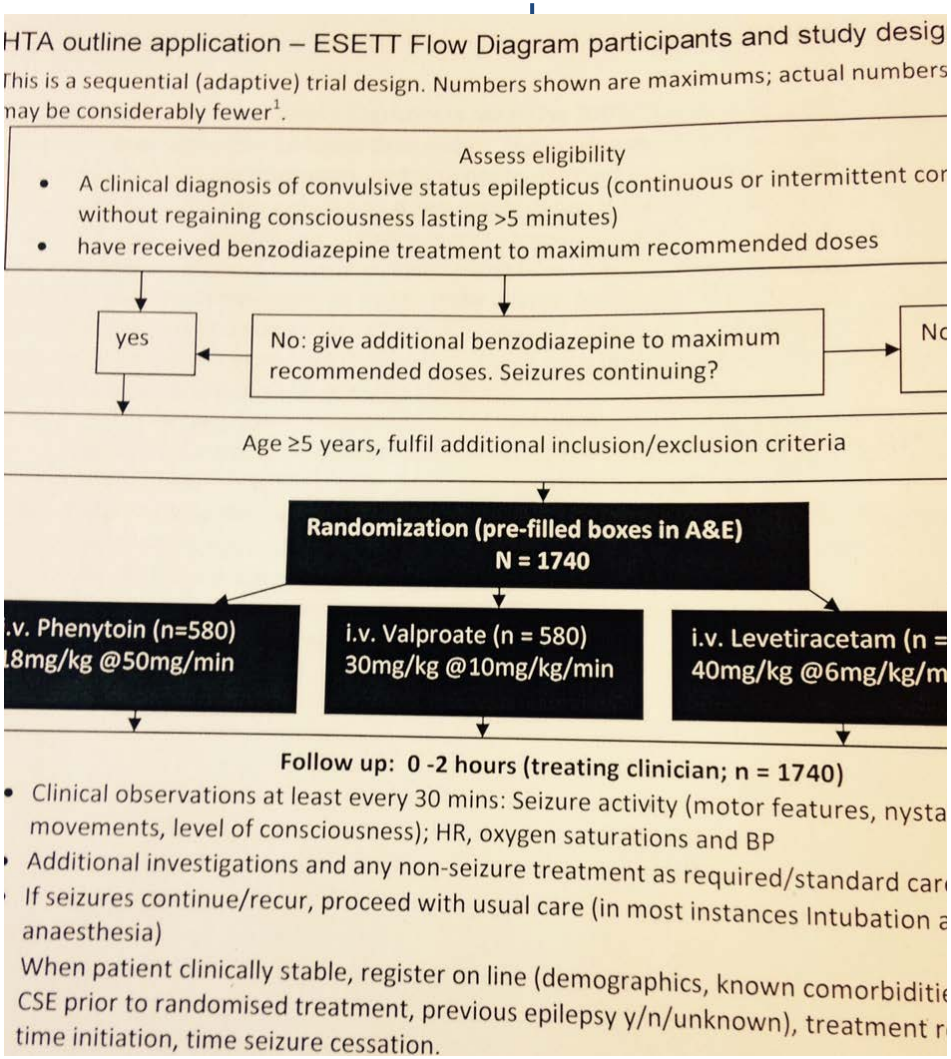
14:00-14:30 What is the relative value of the standard anticonvulsants: phenytoin and fosphenytoin, valproate, phenobarbital, levetiracetam? Eugen Trinka (Innsbruck, Austria)

14:30-15:00 Pharmacodynamic and pharmacokinetic characteristics of intravenous drugs in status epilepticus Meir Bialer (Jerusalem, Israel)

15:30-18:00 Clinical trials in SE
Chairs: Michel Baulac (Paris, France)
Matthew Walker (London, United Kingdom)

ESETT: Europe & US 2009-2010

Hannah Cock



Established Status Epilepticus Treatment Trial

ESETT: Europe & US 2009-2010

E-mail from DHL

2. Our colleagues in Europe (including Hannah Cock, Simon Shorvon and Tim Coats from the U.K. and Eugen Trinka from Austria) are making definite progress with their plans for ESETT (European Status Epilepticus Treatment Trial). **Based on discussions we had at the last SE Colloquium held in Innsbuck in April, there was a strong consensus that it would be best if the European trial was carried out jointly with centers in the U.S., given the likely number of study subjects and the desire to complete the study as rapidly as possible.** The Europeans have already determined there is a reasonably good chance they can find funding for the study from within the U.K., but rules on indemnification will prevent any funds going to the U.S.

Established Status Epilepticus Treatment Trial

ESETT: Europe & US 2009-2010

E-mail from DHL

3. The RAMPART (Rapid Anticonvulsant Medications Prior to Arrival Trial) study, which has been implemented within the NINDS-supported **Neurology Emergency Treatment Trials (NETT) network, is enrolling patients at a faster than expected rate and may well be completed within 12-18 months. The NETT is therefore looking for opportunities to support the next SE study sooner than later.**

Established Status Epilepticus Treatment Trial

ESETT: Europe & US 2009-2010

E-mail from DHL

4. Preliminary discussions with NINDS leadership have indicated that the institute **is very interested** in supporting a SE study of the type we are considering.

Established Status Epilepticus Treatment Trial

ESETT planning group

Bleck

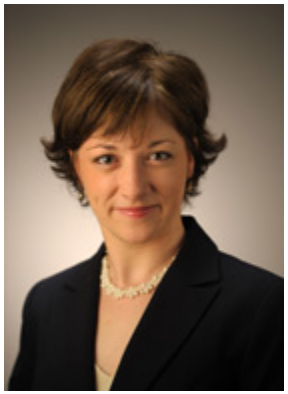
Cock

Chamberlain

Cloyd

Elm

Fountain



Fureman

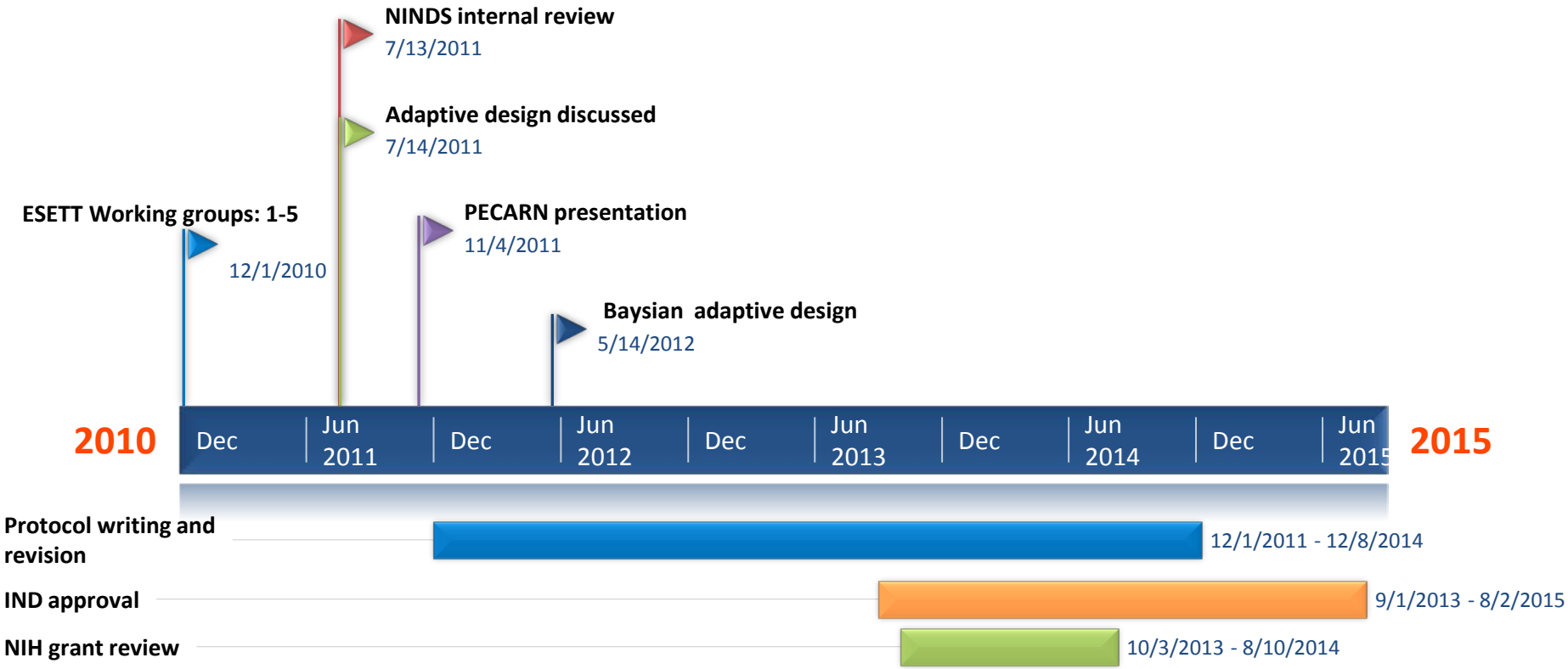
Lowenstein

Shinnar

Silbergleit

Treiman

Trinka



Established Status Epilepticus Treatment Trial

Rationale

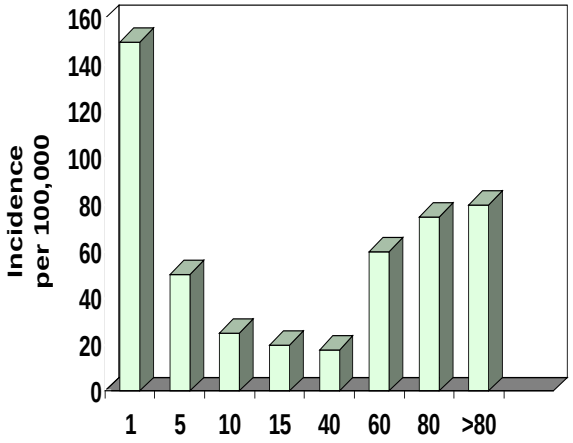
Status Epilepticus: Epidemiology

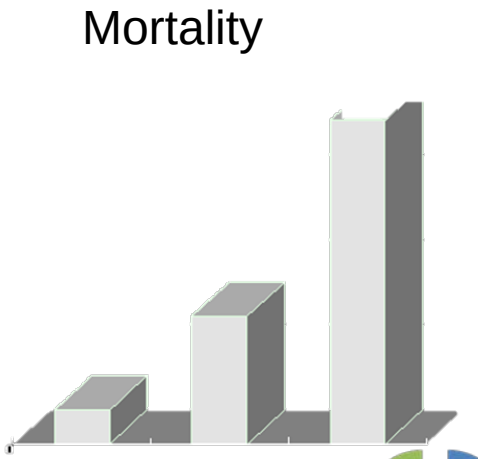
Status epilepticus: a prolonged self-sustaining seizure or recurrent seizures without recovery of consciousness.

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.





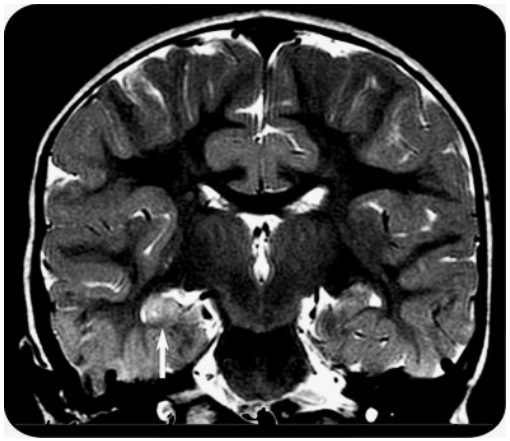
DeLorenzo et al. Neurology 1996
Towne et al. J. Clin. Neurophysiology 1994

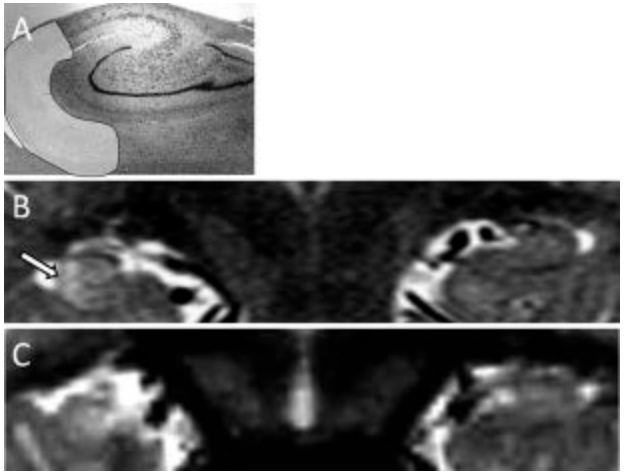
Established Status Epilepticus Treatment Trial

Effects of Fever Associated Status Epilepticus in Children: FEBSTAT

1) 11% incidence of Hippocampal injury (T2 signal increase) compared to 0% in control (febrile seizures).

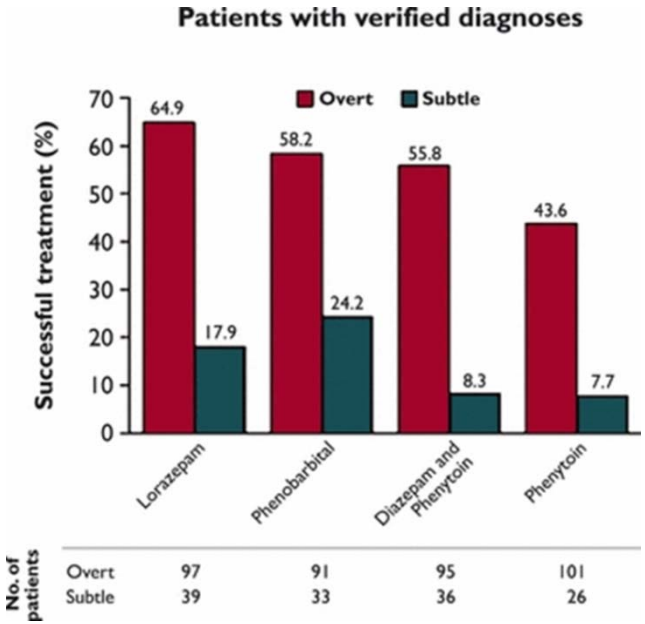
2) Hippocampal T2 hyperintensity after FSE represents acute injury often evolving to a radiological appearance of HS after 1 year.



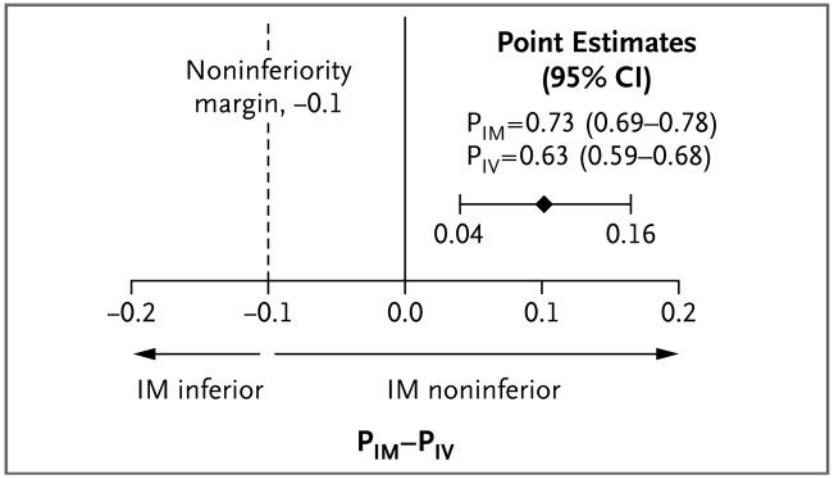


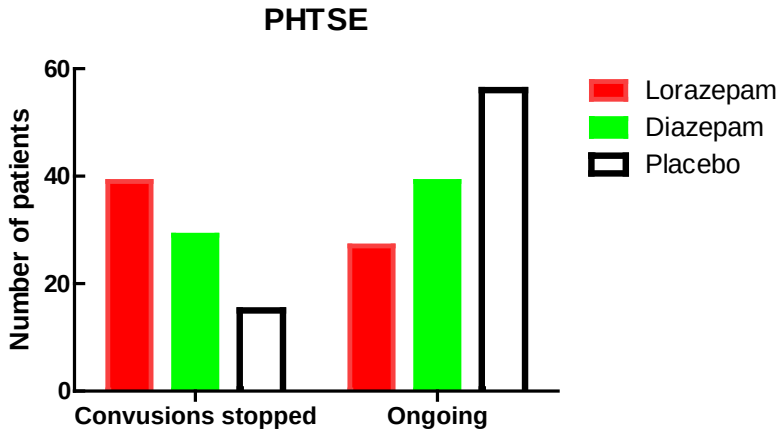
Shinnar et al. Neurology 2012
Lewis et al. Annals of Neurology 2014

Benzodiazepines: Initial Treatment

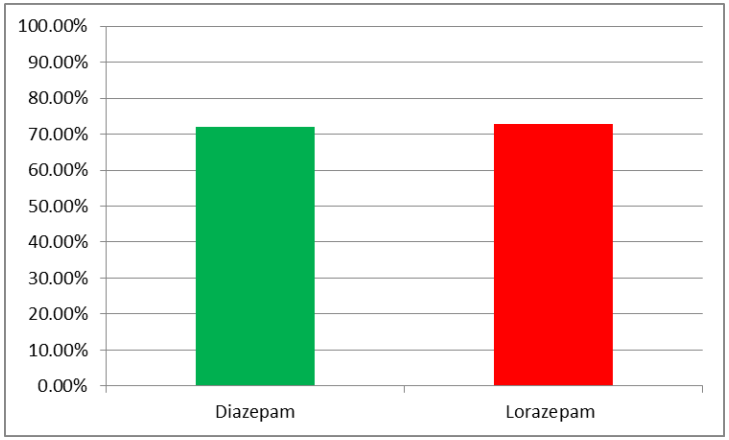


IM midazolam vs IV lorazepam





Lorazepam vs diazepam for pediatric status epilepticus



Need for Trial

- There is no well-controlled prospective clinical trial to guide the treatment of SE in patients who fail benzodiazepines.
- SE not responding to benzodiazepines is called Established Status Epilepticus (ESE).
- 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.

Established Status Epilepticus Treatment Trial

Therapy of Established SE: Real world choices

Property/AED	Fosphenytoin	Levetiracetam	Valproic Acid
Popularity of use in the US	Most commonly used (60-65%)	Used often (20-30)	Least often
Ease of administration	Slow	Fast	Fast
Speed of action	Slow administration	Enters brain Slowly, acts slowly	Yes
Action last long	Yes	Yes	Yes
Efficacious in animal models	Least effective	In combination with diazepam	Very effective
Terminates seizures	Partial seizures	Partial and generalized	Partial and generalized
Safe	Hypotension, cardiac arrhythmia.	safe	Safe for acute use

EFIC

- **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

Established Status Epilepticus Treatment Trial

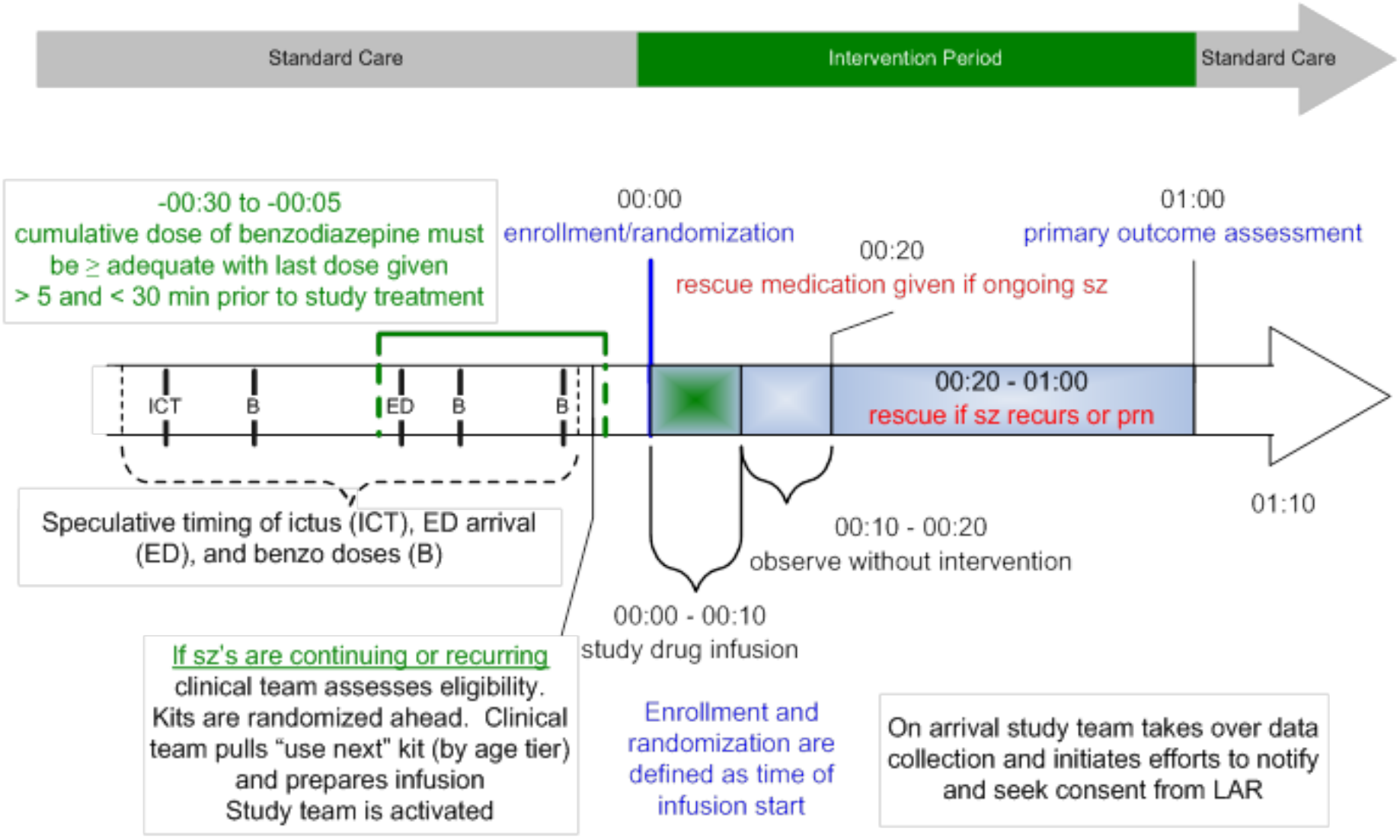
Inclusion Criteria

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

Established Status Epilepticus Treatment Trial

Intervention

Drug	Dose	Comments	Supporting References
FOS	20 mg /kg (PE) with maximum 1500 mg	Viewed as standard dose.	PDR: Package insert
LEV	60 mg/kg with max 4500 mg	Highest approved dose for children, Published reports suggest safety of 4500 mg.	
VPA	40 mg/kg with max 3,000 mg	Doses ranging between 15-45 mg/kg have been reported.	Limdi, et al (2007)



Established Status Epilepticus Treatment Trial

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)

Established Status Epilepticus Treatment Trial

Recording Prospective Data: Primary & Back up

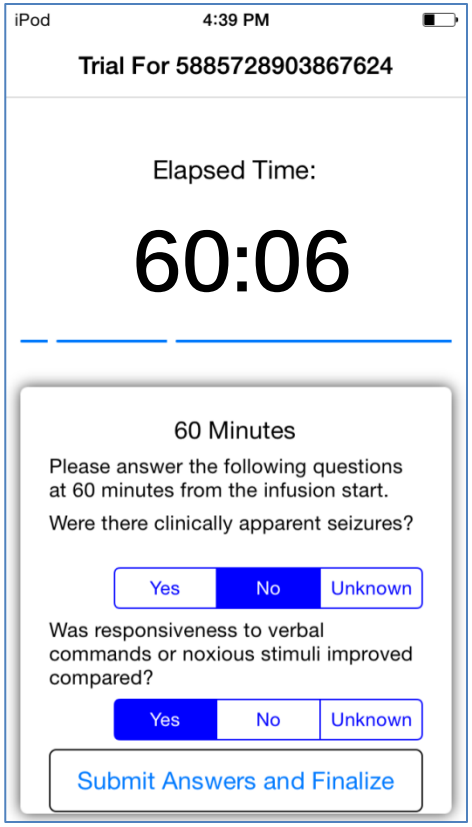
Primary record

Paper record produced by the clinical coordinator

Based on review of the chart, interviews with clinical care team.

However…coordinator could be late, team busy, shifts may change and there is potential for lost data

Back up data recording device



Established Status Epilepticus Treatment Trial

Safety Outcomes at T0 +60

- **Life-threatening hypotension:** Within 1 hour of start of infusion of the study drug, systolic blood pressure remains below specified levels on two consecutive readings at least 10 minutes apart and remains below specified levels for more than 10 minutes despite reduced drug infusion rate or its termination and a fluid challenge.
  - "Specified levels" for systolic blood pressure are 90 mmHg in adults and children older than 13 years old, 80 mmHg in children 7 to 12 years old, and 70 mmHg in children 2 to 6 years of age.
- **Life-threatening cardiac arrhythmia:** Any arrhythmia that occurs within 1 hour of start of infusion of the drug that persists despite reducing rate of drug infusion, or that requires termination with chest compressions, pacing, defibrillation, or use of an anti-arrhythmic agent or procedure.

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Secondary Outcomes

- Occurrence of life threatening Hypotension or cardiac arrhythmia,
- Richmond agitation and sedation score at primary outcome determination
- Time to termination of seizures
- Intubation,
- Admission to ICU
- Seizure recurrence
- Length of stay in the ICU and hospital,
- Mortality

Established Status Epilepticus Treatment Trial

STUDY DESIGN

Primary Objective

- To determine the most effective and/or the least effective treatment of benzodiazepine-refractory status epilepticus (SE) among patients older than 2 years.

- Three active treatment arms:
  - fosphenytoin (FOS)
  - levetiracetam (LEV)
  - valproic acid (VPA)

Established Status Epilepticus Treatment Trial

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.

Established Status Epilepticus Treatment Trial

Study Design by Berry Consultants (Jason Connor, PhD)

- Bayesian Adaptive Design (extensive simulation study)
- Maximum sample size is N=795 total.
- Power of 90% when best has 65% response rate (vs 50% other arms)
- Primary endpoint at 60 minutes
- Followed until discharge/30 days
- Randomization will be stratified by three age groups
  - 2 - <18 years
  - 18-65 years
  - 66 years and older

Established Status Epilepticus Treatment 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

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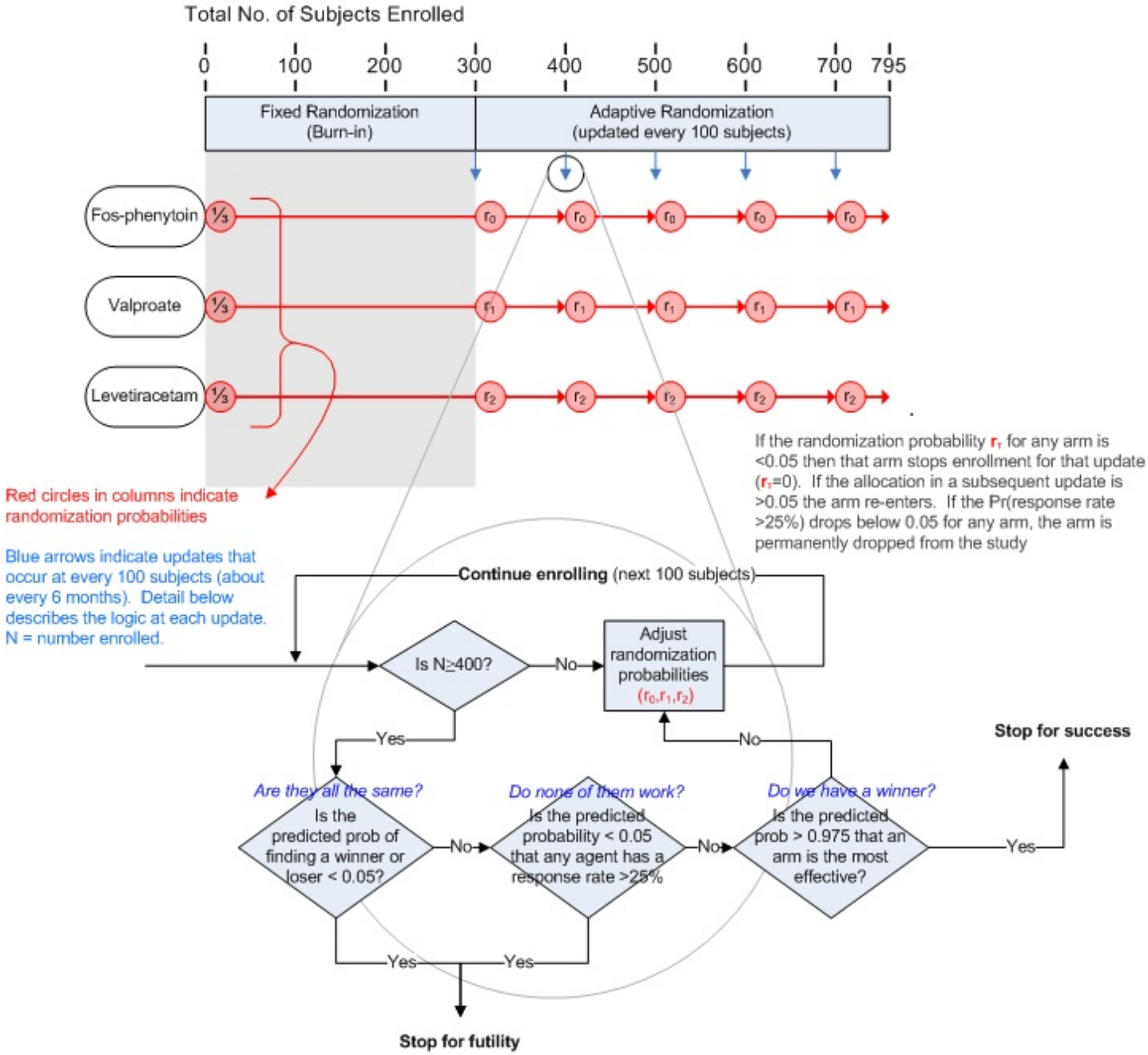

Total No. of Subjects Enrolled
0
100
200
300
400
500
600
700
795
Fixed Randomization (Burn-in)
Adaptive Randomization (updated every 100 subjects)
Fos-phenytoin
Valproate
Levetiracetam
1/3
r0
r1
r2
Red circles in columns indicate randomization probabilities
Blue arrows indicate updates that occur at every 100 subjects (about every 6 months). Detail below describes the logic at each update. N = number enrolled.
If the randomization probability rT for any arm is <0.05 then that arm stops enrollment for that update (rT=0). If the allocation in a subsequent update is >0.05 the arm re-enters. If the Pr(response rate >25%) drops below 0.05 for any arm, the arm is permanently dropped from the study
Continue enrolling (next 100 subjects)
Is N≥400?
No
Adjust randomization probabilities (r0,r1,r2)
Yes
No
Are they all the same?
Is the predicted prob of finding a winner or loser < 0.05?
No
Do none of them work?
Is the predicted probability < 0.05 that any agent has a response rate >25%
No
Do we have a winner?
Is the predicted prob > 0.975 that an arm is the most effective?
Yes
Stop for success
Yes
Yes
Stop for futility

Adaptive Allocation

- Randomize N=300 patients equally
  - At N=300 begin adaptive allocation
  - Update allocation probability after every 100 subjects (N = 300, 400, … , 700)
- Adaptive allocations after every 100 subjects equates to approx. every 6 months given expected accrual
- Adaptively allocate to
  - Favor better performing treatments
  - Favor treatments with greater uncertainty

$$r_t \propto \sqrt{\frac{Pr(p_t = max(p))Var(p_t)}{n_t}}$$

- If allocation probability(r_t) < 5%, suspend accrual
  - Allocation probability increased in remaining arms
- If $\Pr(p_t \geq 0.25) < 0.05$, drop arm

Established Status Epilepticus Treatment Trial

Early Stopping

- Begins after 400 patients
  - Evaluated after every additional100 patients accrued to coincide with adaptive allocation assessments (i.e. N= 400, 500, 600, 700)

- Early Success Stopping:
  - If arm has 97.5% probability of having highest success rate
    - i.e. $Pr(p_t = max(p)) \geq 0.975$

- Early Futility Stopping
  - If predicted probability of success (ID 'winner' or 'loser' at the max N=795) < 0.05
  - If all arms have been permanently dropped
    - i.e. $\Pr(p_t \geq 0.25) < 0.05$ for all arms

Established Status Epilepticus Treatment Trial

SAMPLE TRIAL

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

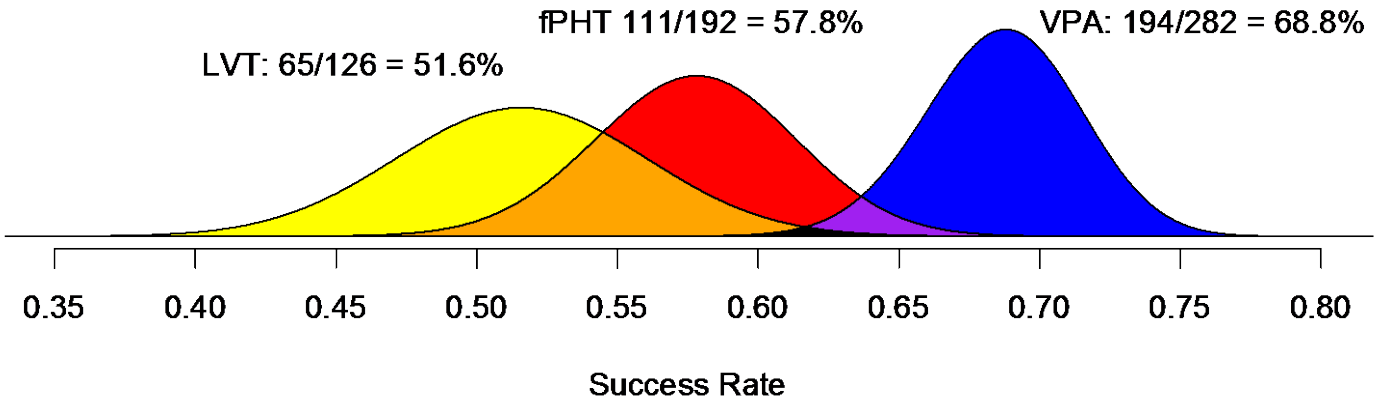
4th Interim Analysis: N = 600 Subjects

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

ORGANIZATION AND CULTURE

Why

How

What

Simon Sinek

Start with Why

http://www.ted.com/talks/simon_sinek

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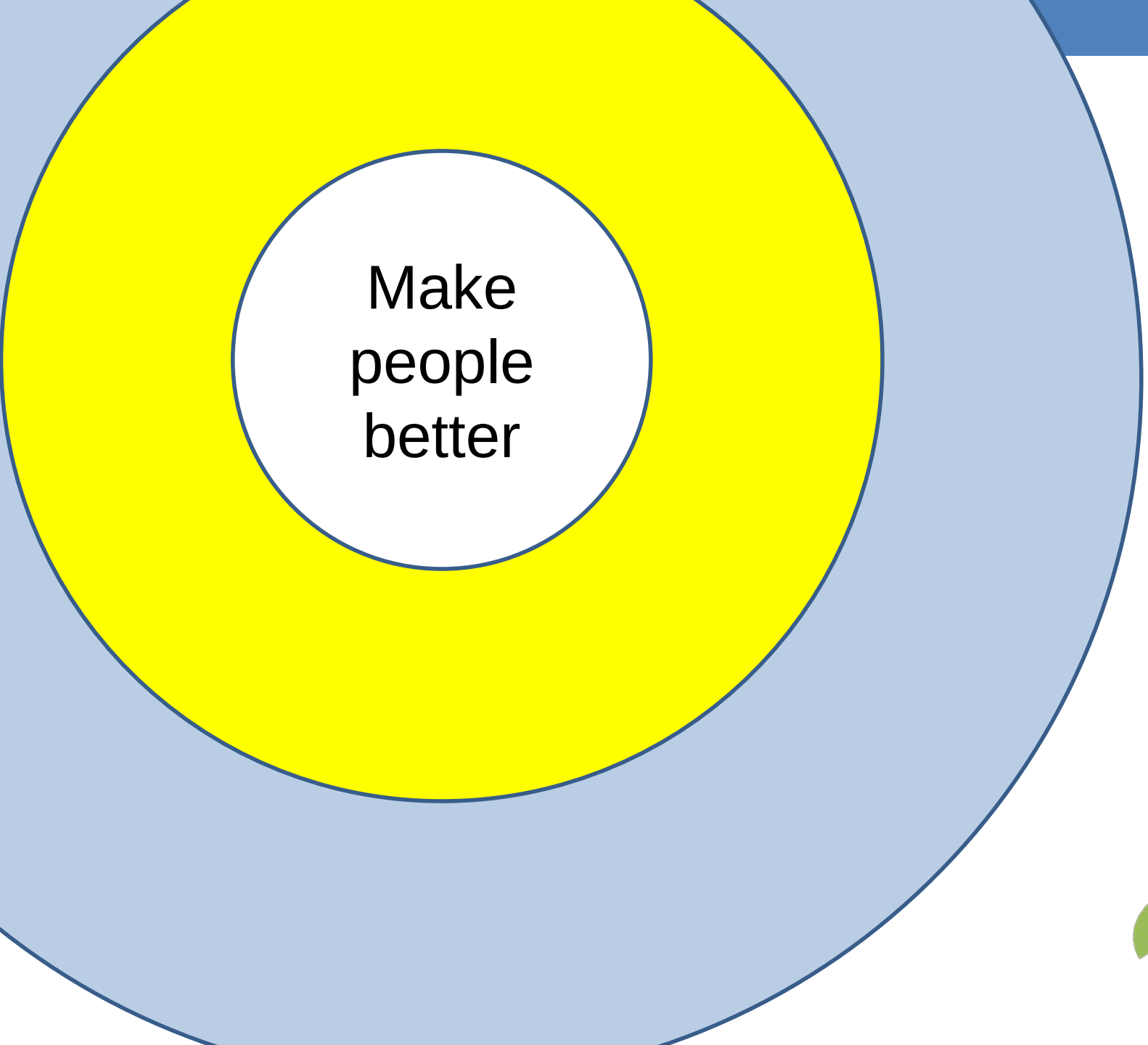

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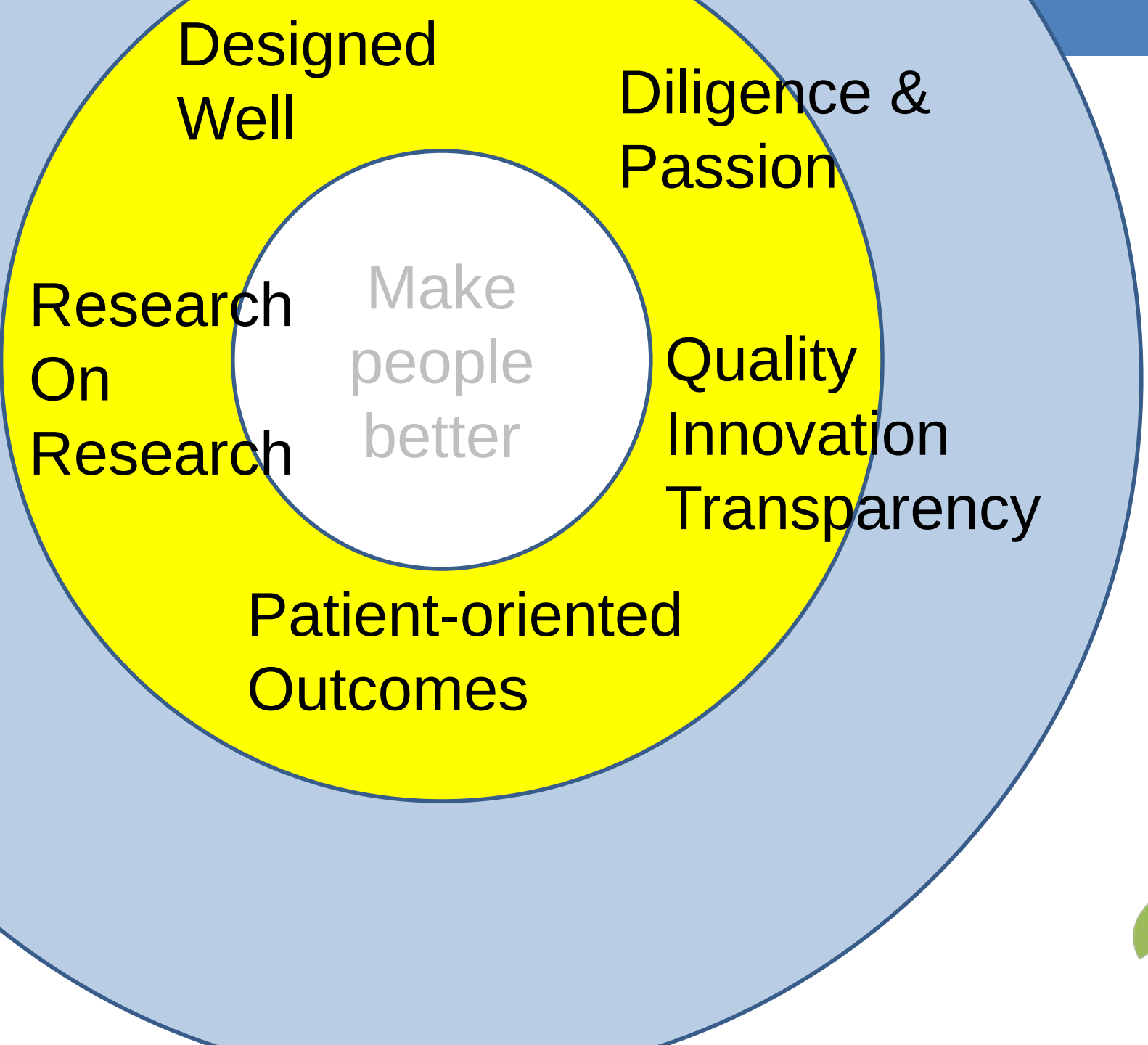

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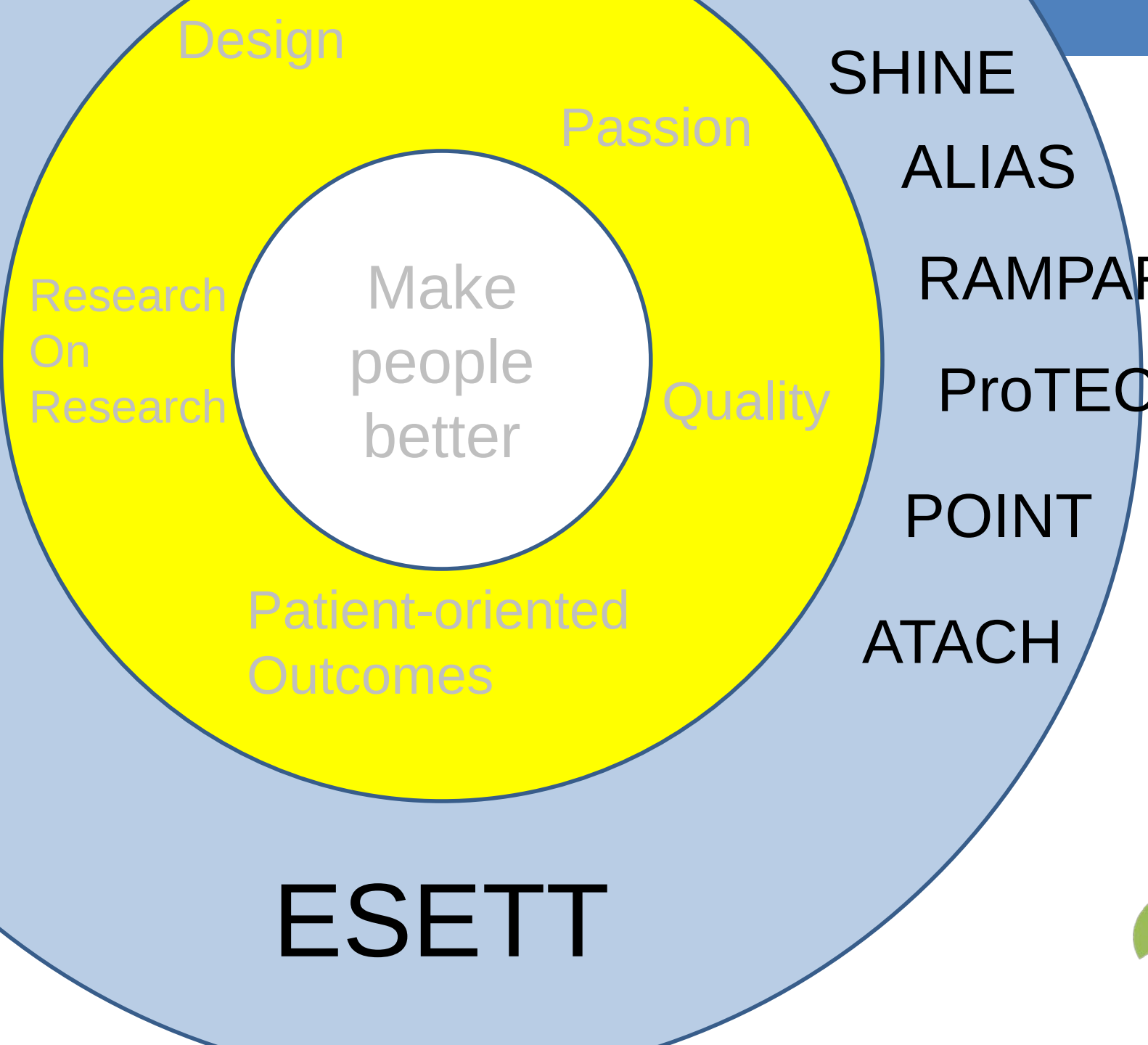

SHINE

ALIAS

RAMPART

ProTECT

POINT

ATACH

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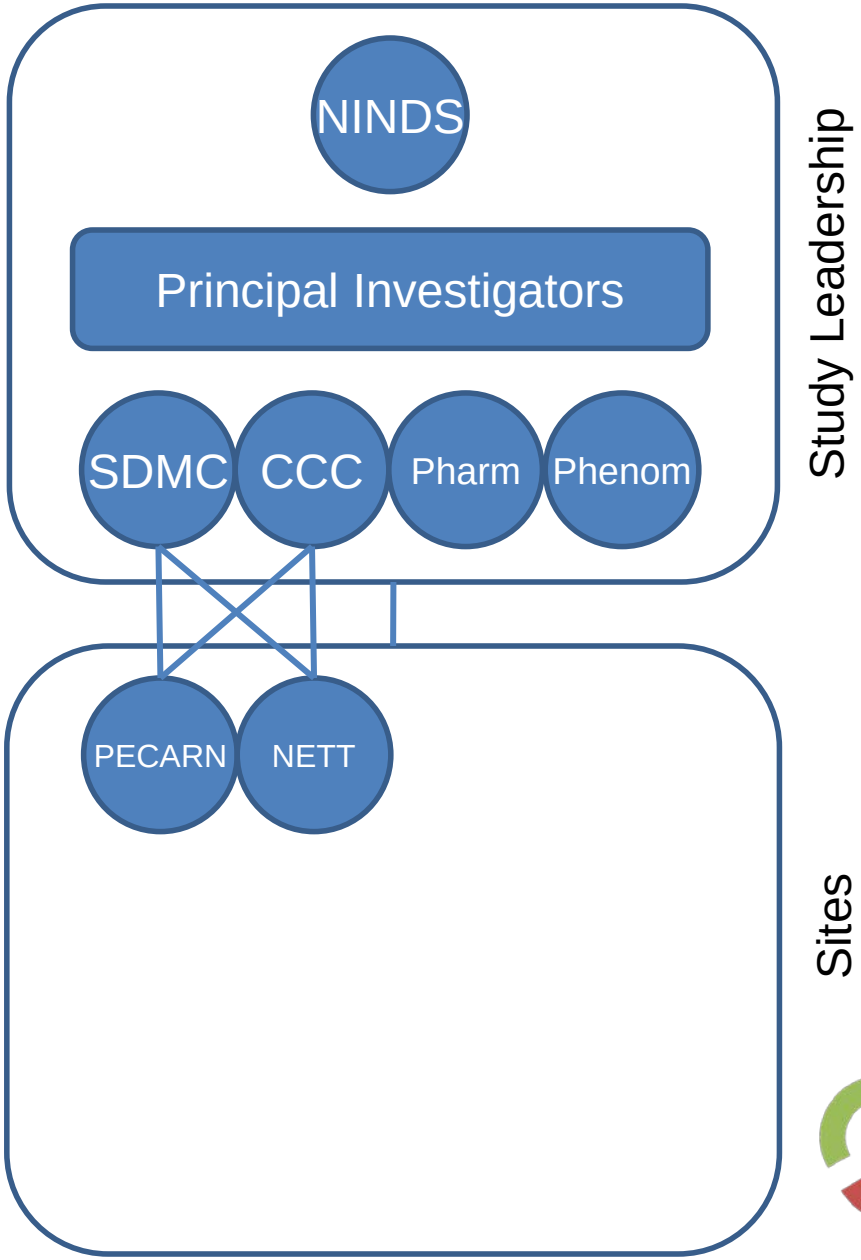
Epilepticus
Treatment
Trial

Organization



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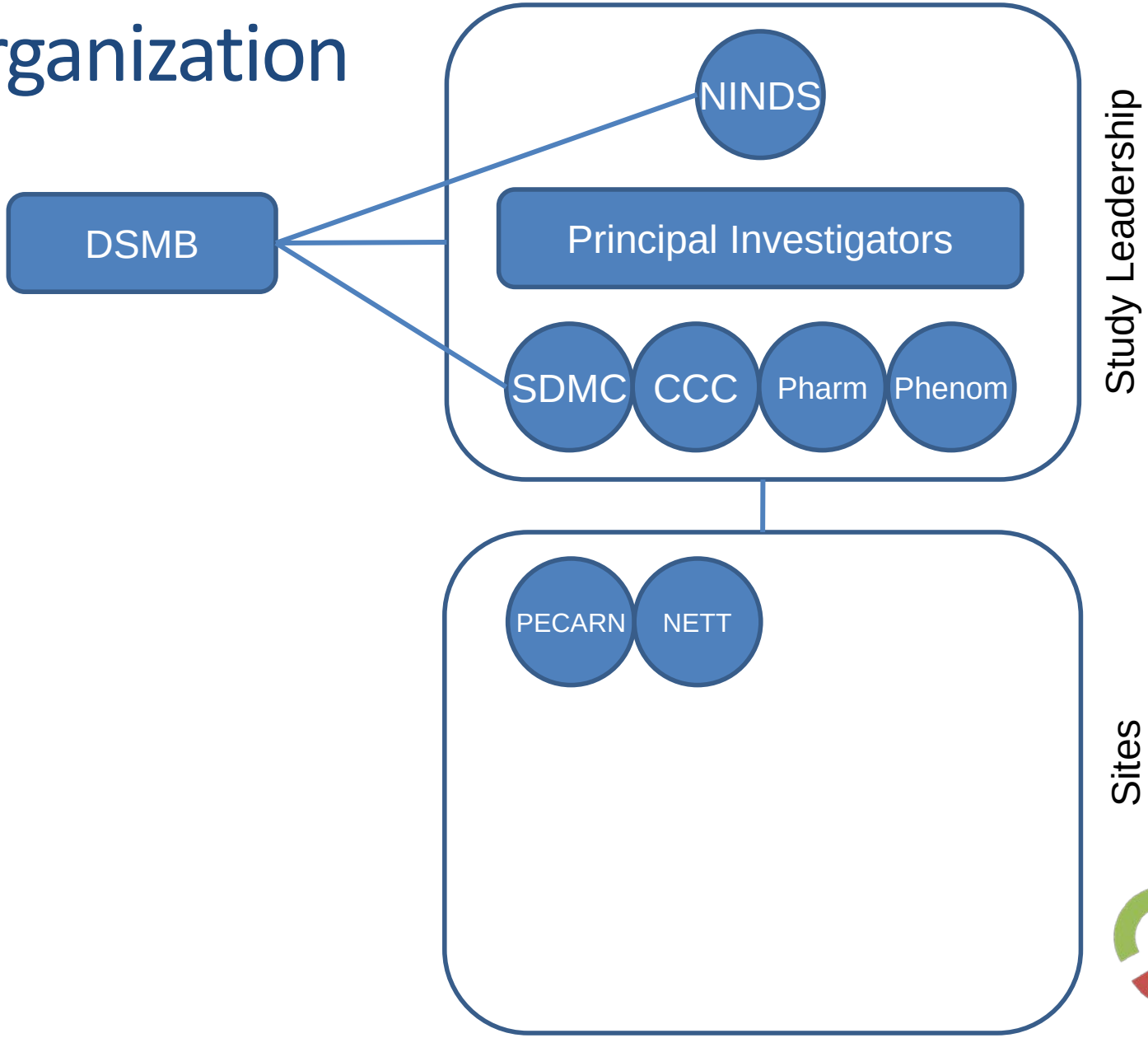

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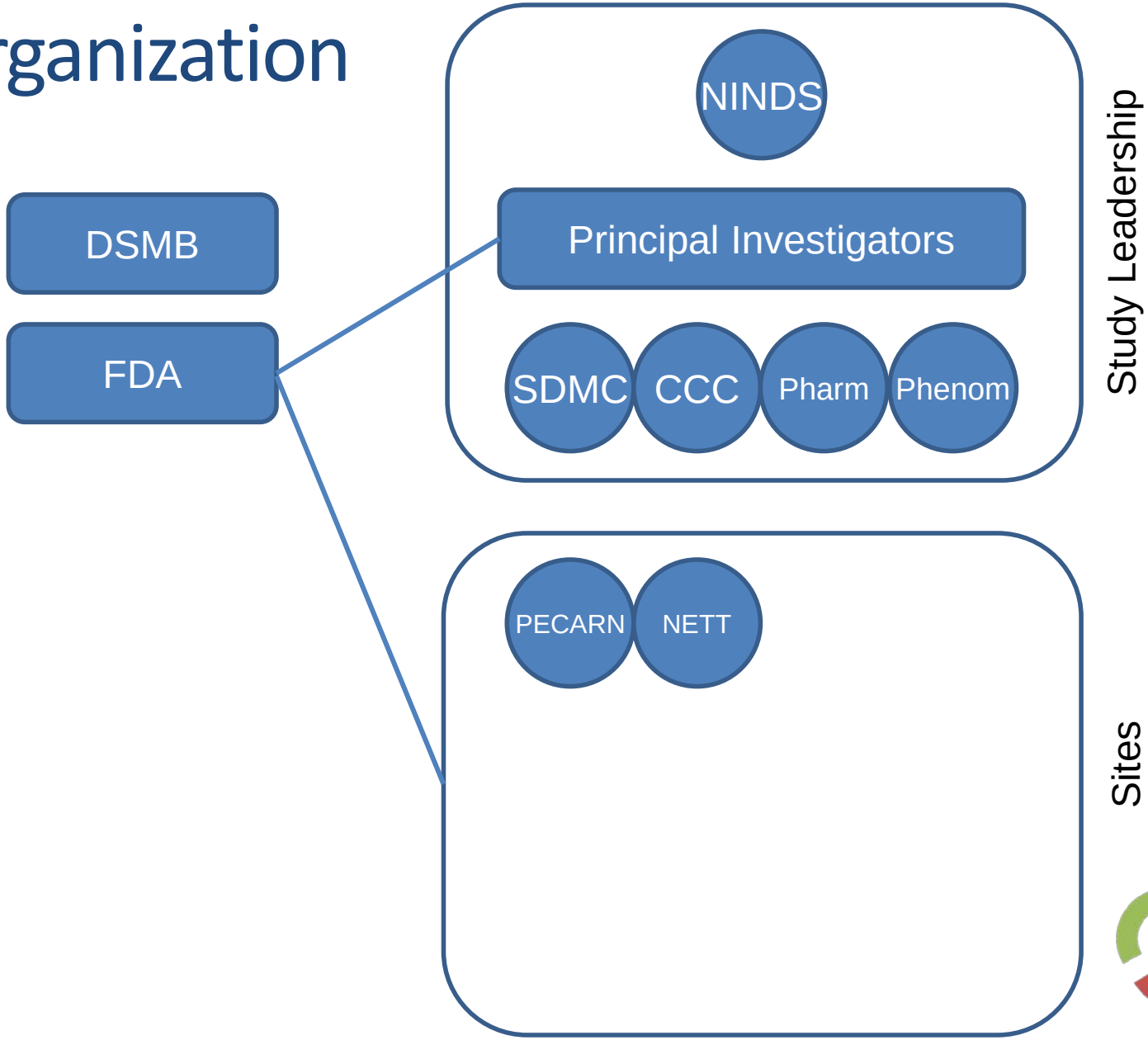

Established Status Epilepticus Treatment Trial

Can't tell the players without a program…

- NINDS — Brandy Fureman, Robin Conwit, Scott Janis
- Prime (U Virginia) — Jaideep Kapur, Amy Fansler, Emily Gray
- CCC (Michigan) — Robert Silbergleit, Valerie Stevenson, Erin Bengelink, Arthi Ramakrishnan, Deneil Harney, Joy Black
- SDMC (S Carolina) — Jordan Elm, Caitlin Ellerbe, Catherine Dillon, Cassidy Conner, Kristina Hill
- PECARN — Jim Chamberlain, Kate Shreve
- Pharm (Minnesota) — Jim Cloyd, Lisa Coles
- Phenomenology — Dan Lowenstein, Shlomo Shinnar

Established Status Epilepticus Treatment Trial

Prime – University of Virginia

- Overall Grant Management
- Organize and Direct Leadership
- FDA and IND Sponsorship
- Publications

Established Status Epilepticus Treatment Trial

CCC

- Management of protocol and MoP
- Site Monitoring
- Internal safety review
- EFIC oversight
- Regulatory management
- Adjudication core support
- Protocol assist device data collection

UNIVERSITY OF MICHIGAN

Established Status Epilepticus Treatment Trial

SDMC

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

- Biostatistical support and study design
- Randomization programming (RAR)
- Data management and validation
- CTMS WebDCU (data, regulatory, site management, invoicing, drug tracking)
- DSMB Report generation
- Publication support

Established Status Epilepticus Treatment Trial

Pharmacology Core

- Pharmacology core oversees acquisition, manufacturing and testing of drugs.
- Assist with preparing and maintaining IND
- Manufacturing facility: UC Davis GMP facility
- Testing UC Davis facility and Analytical Research Laboratories, Oklahoma

- Pharmacology core team members:
  - Minnesota - Jim Cloyd, Lisa Coles
  - UC Davis – Gerhard Bauer, Brian Fury
  - ARL – Jessica Munson

College of Pharmacy

UCDAVIS

GMP Facility
Good Manufacturing Practice *at* UC Davis

ARL
Analytical Research Labs

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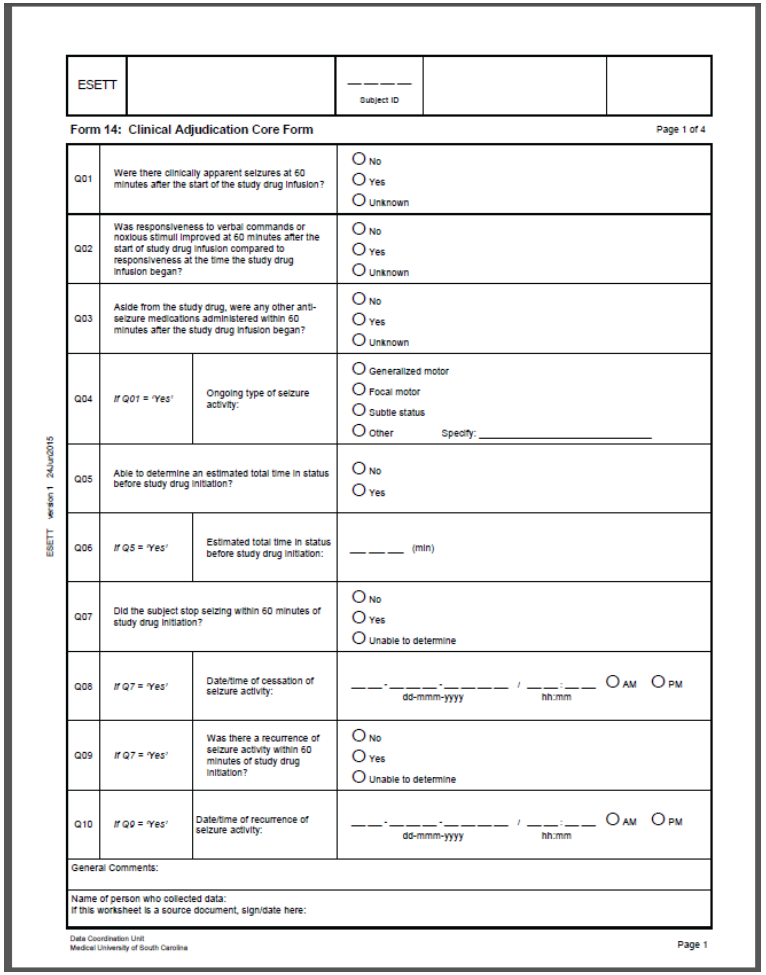
Phenomenology Core

- The Core will monitor the consistency of primary outcomes determined locally.
- Adjudicate secondary outcomes.

- Adjudication Core Members – Dan Lowenstein, Shlomo Shinnar, Hannah Cock, Nathan Fountain



ESETT | ____ Subject ID | Page 1 of 4

Form 14: Clinical Adjudication Core Form

Q01	Were there clinically apparent seizures at 60 minutes after the start of the study drug infusion?		○ No ○ Yes ○ Unknown
Q02	Was responsiveness to verbal commands or noxious stimuli improved at 60 minutes after the start of study drug infusion compared to responsiveness at the time the study drug infusion began?		○ No ○ Yes ○ Unknown
Q03	Aside from the study drug, were any other anti-seizure medications administered within 60 minutes after the study drug infusion began?		○ No ○ Yes ○ Unknown
Q04	*If Q01 = 'Yes'*	Ongoing type of seizure activity:	○ Generalized motor ○ Focal motor ○ Subtle status ○ Other Specify: _____
Q05	Able to determine an estimated total time in status before study drug initiation?		○ No ○ Yes
Q06	*If Q5 = 'Yes'*	Estimated total time in status before study drug initiation:	___ ___ ___ (min)
Q07	Did the subject stop seizing within 60 minutes of study drug initiation?		○ No ○ Yes ○ Unable to determine
Q08	*If Q7 = 'Yes'*	Date/time of cessation of seizure activity:	___-___-___ / ___:___ ○ AM ○ PM (dd-mmm-yyyy / hh:mm)
Q09	*If Q7 = 'Yes'*	Was there a recurrence of seizure activity within 60 minutes of study drug initiation?	○ No ○ Yes ○ Unable to determine
Q10	*If Q9 = 'Yes'*	Date/time of recurrence of seizure activity:	___-___-___ / ___:___ ○ AM ○ PM (dd-mmm-yyyy / hh:mm)

General Comments:

Name of person who collected data:
If this worksheet is a source document, sign/date here:

Data Coordination Unit
Medical University of South Carolina

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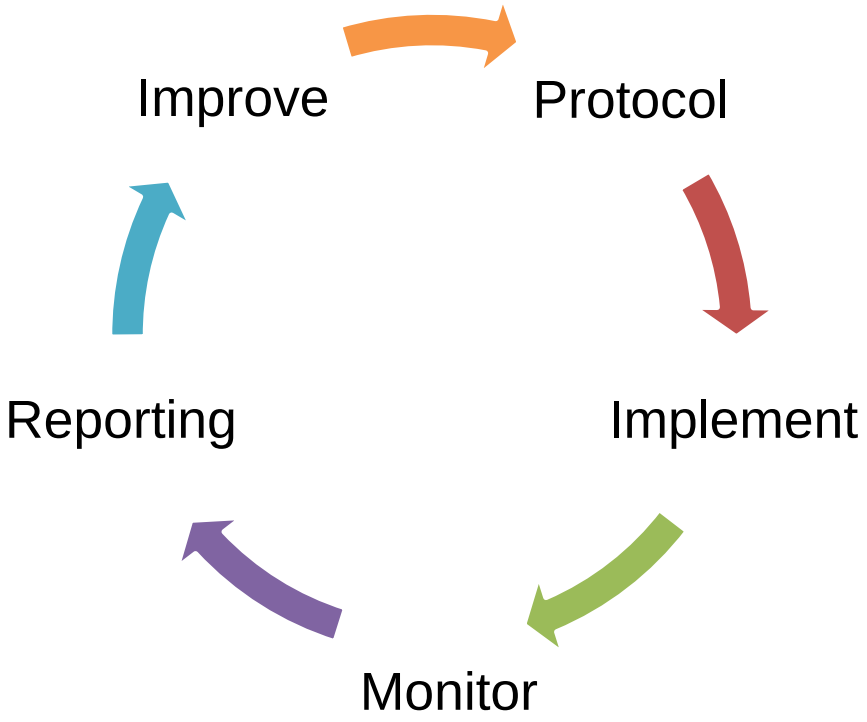
Established Status Epilepticus Treatment Trial

Quality

- Quality by Design
- Focused efforts on “errors that matter”



Established Status Epilepticus Treatment Trial

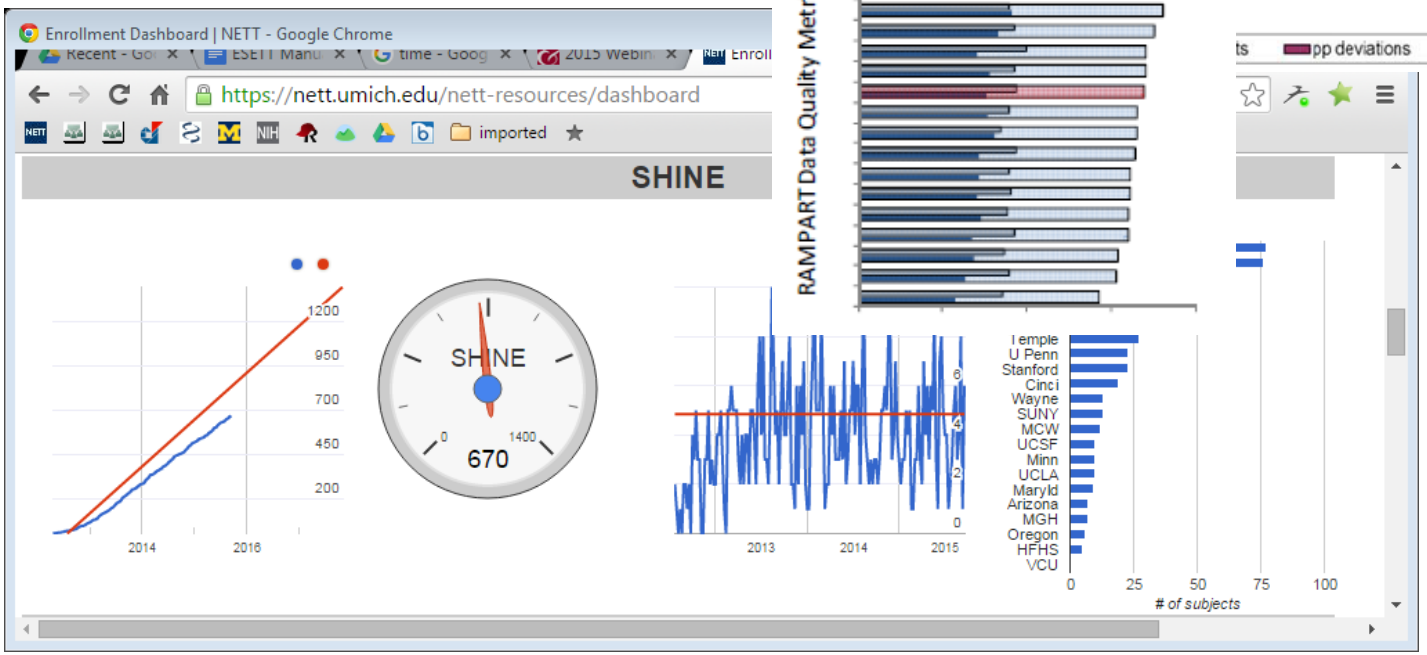
Monitoring

- Central Data Monitoring
- Source Document Verification (Site and Remote)
- Risk-based Allocation
- Site Monitoring

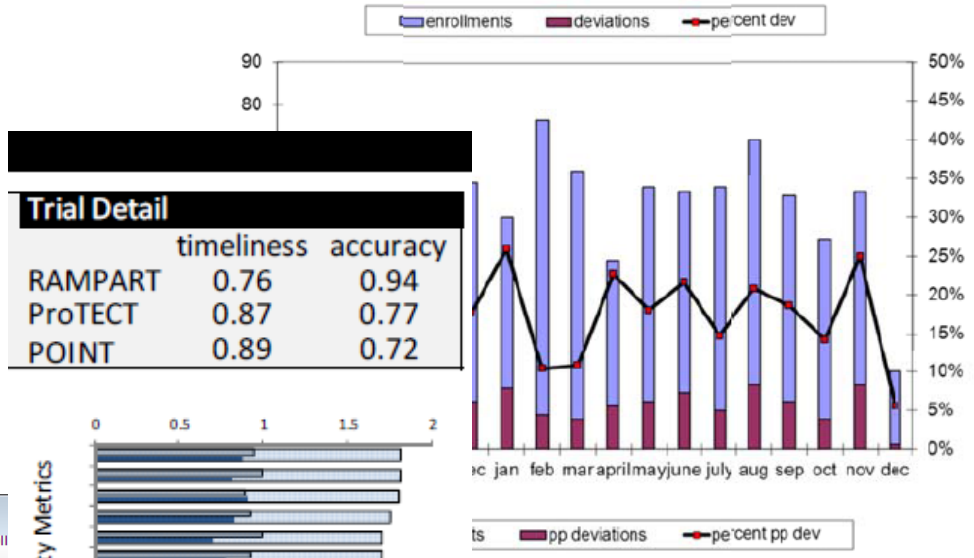
Established Status Epilepticus Treatment Trial

Performance

- Enrollment
- Deviations
- Timeliness
- Compliance



Protocol Deviation Tracking in RAMPART



Trial Detail

	timeliness	accuracy
RAMPART	0.76	0.94
ProTECT	0.87	0.77
POINT	0.89	0.72

Established Status Epilepticus Treatment Trial

Culture

- Electronic platforms
- Transparency
- Research on Research
- Ancillary studies

Established Status Epilepticus Treatment Trial

ESETT 2 Year Timeline