

ESETT: The Established Status Epilepticus Treatment Trial

A Bayesian Adaptive Comparative
Effectiveness Trial

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ADAPT-IT Grant: Analyzing the Process of Bayesian Adaptive Clinical Trial Design

*Adaptive Designs Accelerating Promising Trials
Into Treatments*



University of Michigan
Health System



ADAPT-IT - Objective

- *“To illustrate and explore how best to use adaptive clinical trial designs to improve the evaluation of drugs and medical devices and to use mixed methods to characterize and understand the beliefs, opinions, and concerns of key stakeholders during and after the development process.”*

Specific Tasks

- Design five clinical trials
 - Glycemic control in stroke
 - Status Epilepticus (Refractory)
 - Spinal cord trauma
 - Post cardiac arrest hypothermia
 - Neuroprotection across ischemic and hemorrhagic stroke

- Learn about process
 - Surveys
 - Focus Groups
 - Observation
 - Key Stakeholder Interviews
 - Thematic analysis

- Educate
 - Clinicians
 - Statisticians

Research Question

- How to treat patients who've failed benzodiazapines?
 - fosphenytoin (fPHT)
 - levetiracetam (LVT)
 - valproic acid (VPA)

Comparative Effectiveness

- No control group
 - Horse race between the three drug
- Really want to know
 - Which drug is best ... with measure of certainty
 - Which drug is worst ... with measure of certainty

Trial Overview

- Primary endpoint
 - cessation of seizure within 5 minutes
 - no further intervention within 2 hours
 - no significant adverse event
- Powered to identify 15% difference in response rate
 - 400 – 795 Patients
- Stratify randomization by age

Bayesian Adaptive Design Features

- Adaptively allocate to favor better treatments
- Drop poor performing arms
- Stop early if we know the answer
or know we won't know

Adaptive Allocation

- Randomize 300 patients equally
- At 300 & then every 100 adaptively allocate to
 - Favor better performing treatments
 - Favor treatments with greater uncertainty
 - Every 100

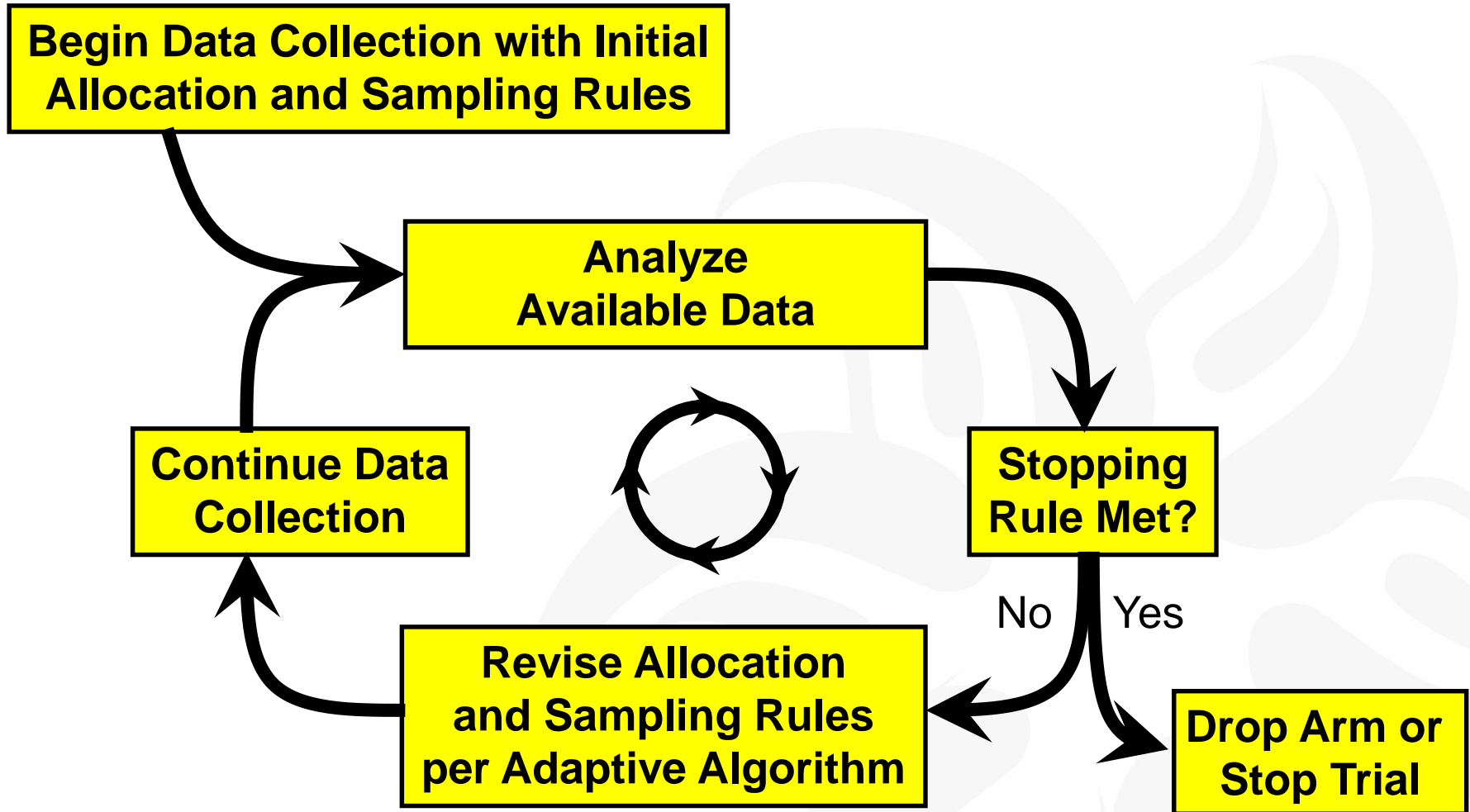
Arm Dropping

- Suspension:
 - If allocation probability $< 5\%$
- Terminal Drop
 - If $\Pr(\text{Response Rate} > 0.25) < 0.05$

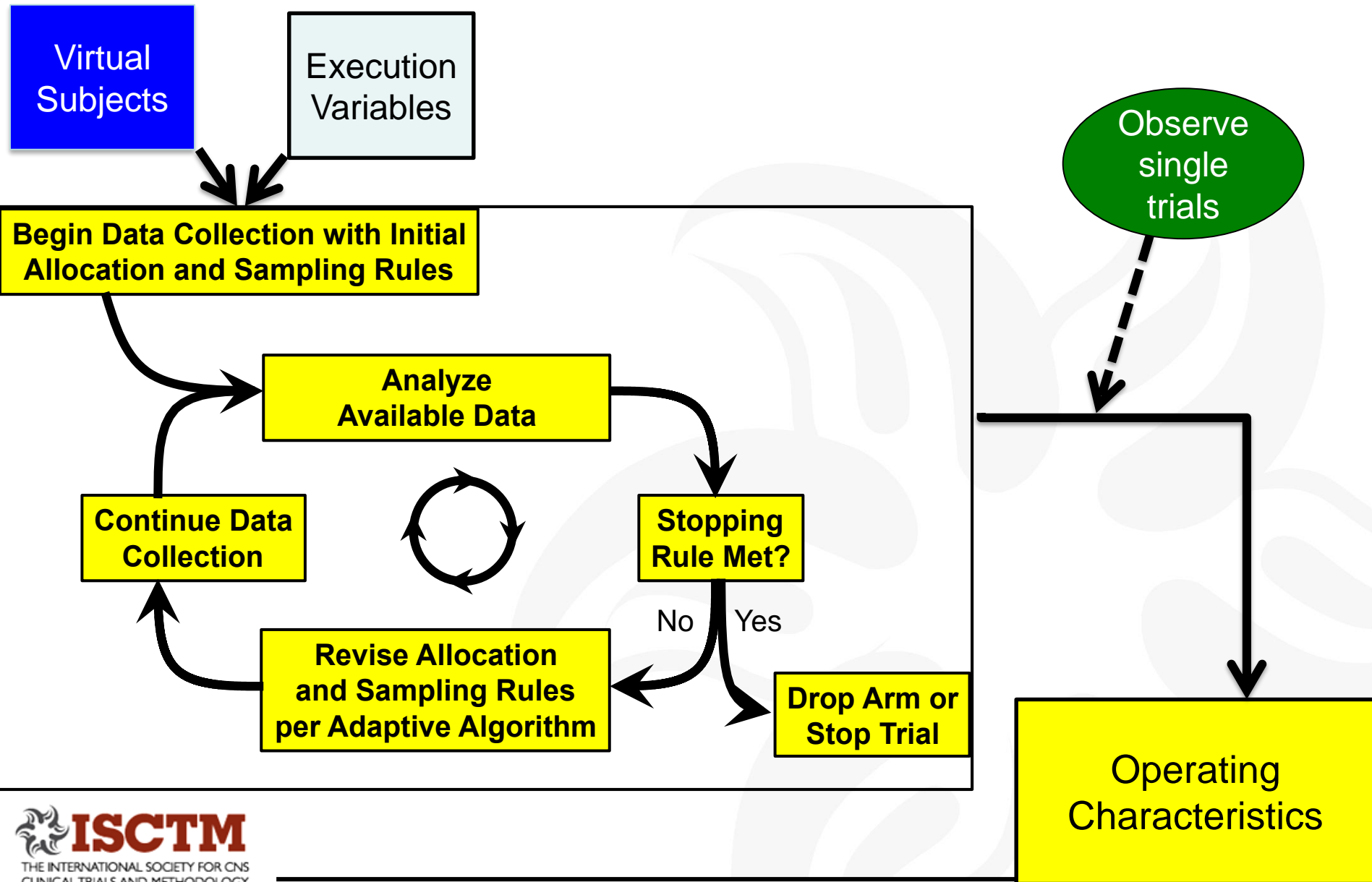
Early Stopping

- 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. $\Pr(\text{Arm} = \text{Max Effective Trt}) > 0.975$
- Early Futility Stopping
 - If predicted probability of success (ID 'winner' or 'loser' at the max $N=795$) < 0.05
 - If all arms have $\Pr(\text{Success} > 0.25) < 0.05$

The Adaptive Process



The Adaptive Process



Example Trial: 300 pt analysis

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

Example Trial: 400 pt analysis

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

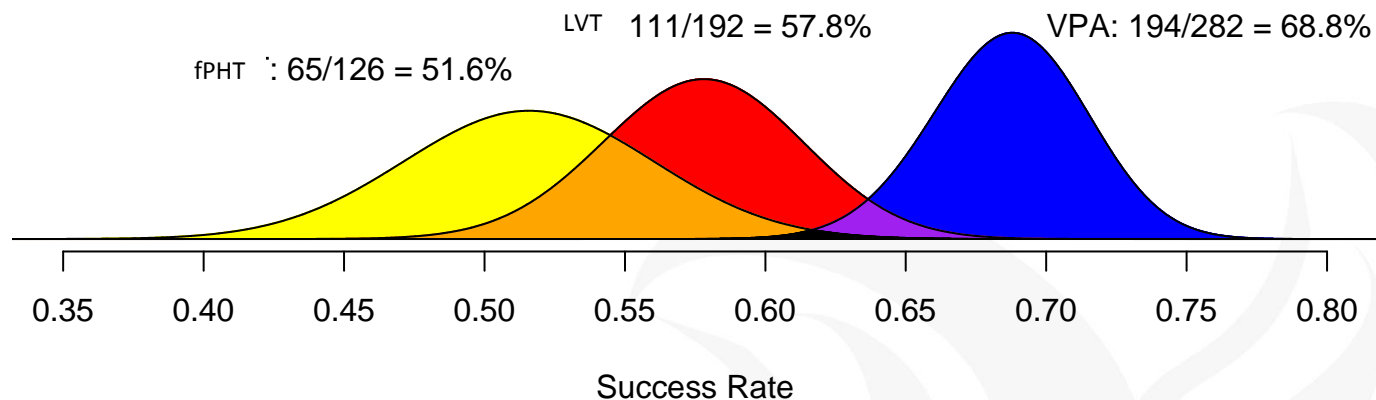
Example Trial: 500 pt analysis

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

Look	N Enrolled Observed Response Rate			Pr(Max Effective Trt)			Pr(Allocation)			Pred Prob
	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	
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	0.008	0.992	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



Operating Characteristics

Adaptive Randomization

Fixed Randomization

Scenario	Power Best	Mean N	% to Best	Power Best	Mean N	% to Best
3 Efficacy Rates						
Null 0.5 – 0.5 – 0.5	0.013	507		0.023	499	
One Good 0.5 – 0.5 – 0.65	0.89	483	48	0.87	497	33
Two Good 0.5 – 0.65 – 0.65	0.11	679	84	0.10	687	67
One Middle One Good 0.5 – 0.575 – 0.65	0.50	586	47	0.44	599	33
All Bad 0.25– 0.25 – 0.25	0.011	524		0.023	509	
All Very Bad 0.10 – 0.10 – 0.10	0.006	400		0.008	400	

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Adaptive Design Challenges

- The definitions and nomenclature of adaptive designs are incompletely understood in the broader medical and statistical communities
- Understanding the rationale for clinical trial simulations
- Presenting, interpreting, and grasping the results of clinical trial simulations
- Communicate the trial design and its validity to external audiences, eg, study sections, IRBs

Adaptive Design Challenges

- What pros/cons for using a more complex design compared to a traditional design?
- Lack of direct evidence of ACTs – Flexible adaptive designs and traditional trial designs have not been compared directly

Conclusion

- Roger Perlmutter (Merk Executive): “We do 21st century biology in our laboratories and then do clinical trials that Hippocrates would have been quite comfortable with.”