

Patient-Centered Randomized Clinical Trials for Parkinson's Disease

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Aim 3 Session Outline

- Patient value model
- Bayesian decision analysis
- Assumptions for trial design
- Neurostimulator case study
- The regulatory, patient, and industry perspective
 - Martin Ho (FDA), Kevin Kwok (MJFF), Edward Karst (Abbott)

	Approve	Reject
Effective	Wait	Type II error
Ineffective	Type I error	0

- Asymmetry between Type I and Type II error
- Patients prefer treatment today over treatment tomorrow

Value Lost (L_0) = Additional Risk

Additional Risk = ω_1 Depression Risk + ω_2 Brain Bleed Risk
+ Mortality Risk

- 6:1 ratio between depression to mortality risk
- 3:2 ratio between brain bleed to mortality risk

Value Lost (L_1) = Value of Additional Benefit – Additional Risk

Value of Benefit = $\beta \times \text{Benefit} + \gamma_1 \text{DBS} + \gamma_2 \text{Dyskinesia} + \gamma_3 \text{Motor symptom}$
 $+ \gamma_4 \text{Non-ambulatory} + \gamma_5 \text{Cognitive symptom}$

- Additional benefits include:
 - increases in on-time
 - reduction in medication burden
 - improvements in cognitive, motor, and pain symptoms

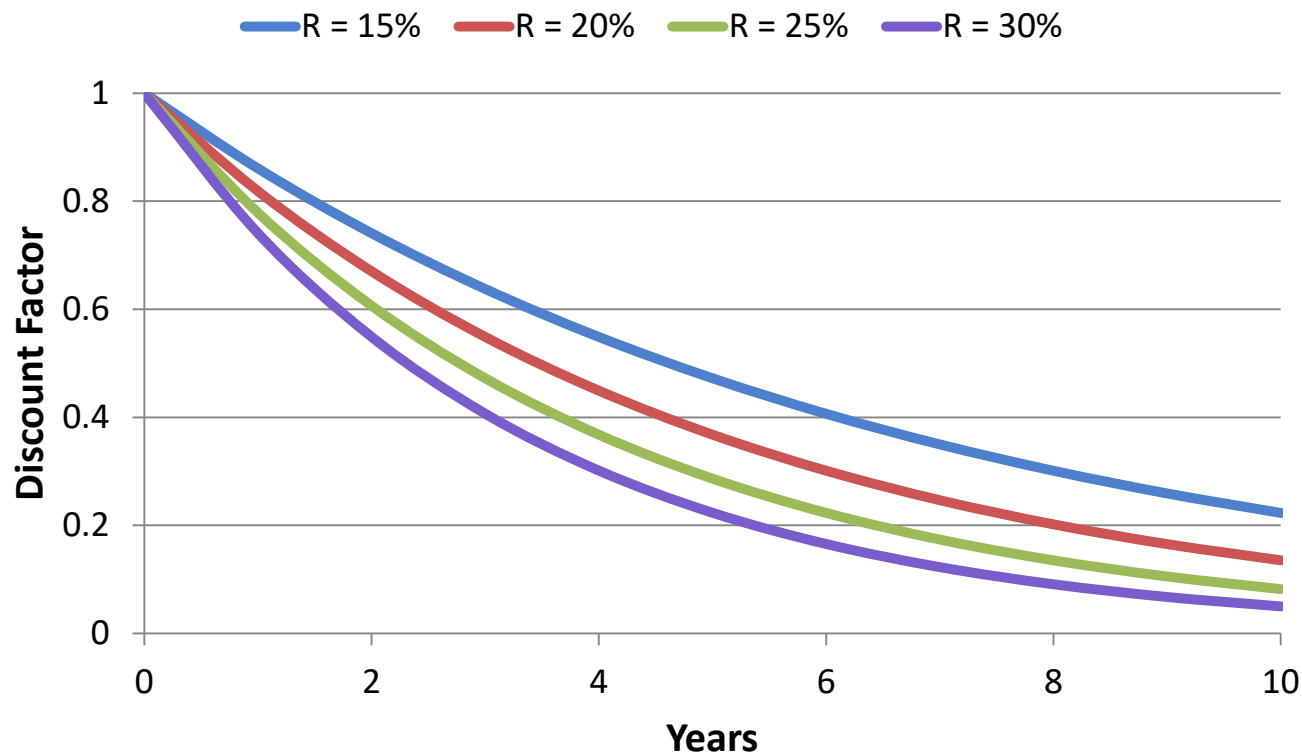
- If you could eat *one* cookie right now, or *two* cookies after waiting 15 minutes, which one would you pick?

Discount rate (R) > 4.6% per min



Patient Value Model: Wait Time

$$\text{Discount factor } (DF_t) = e^{-R \times t}$$

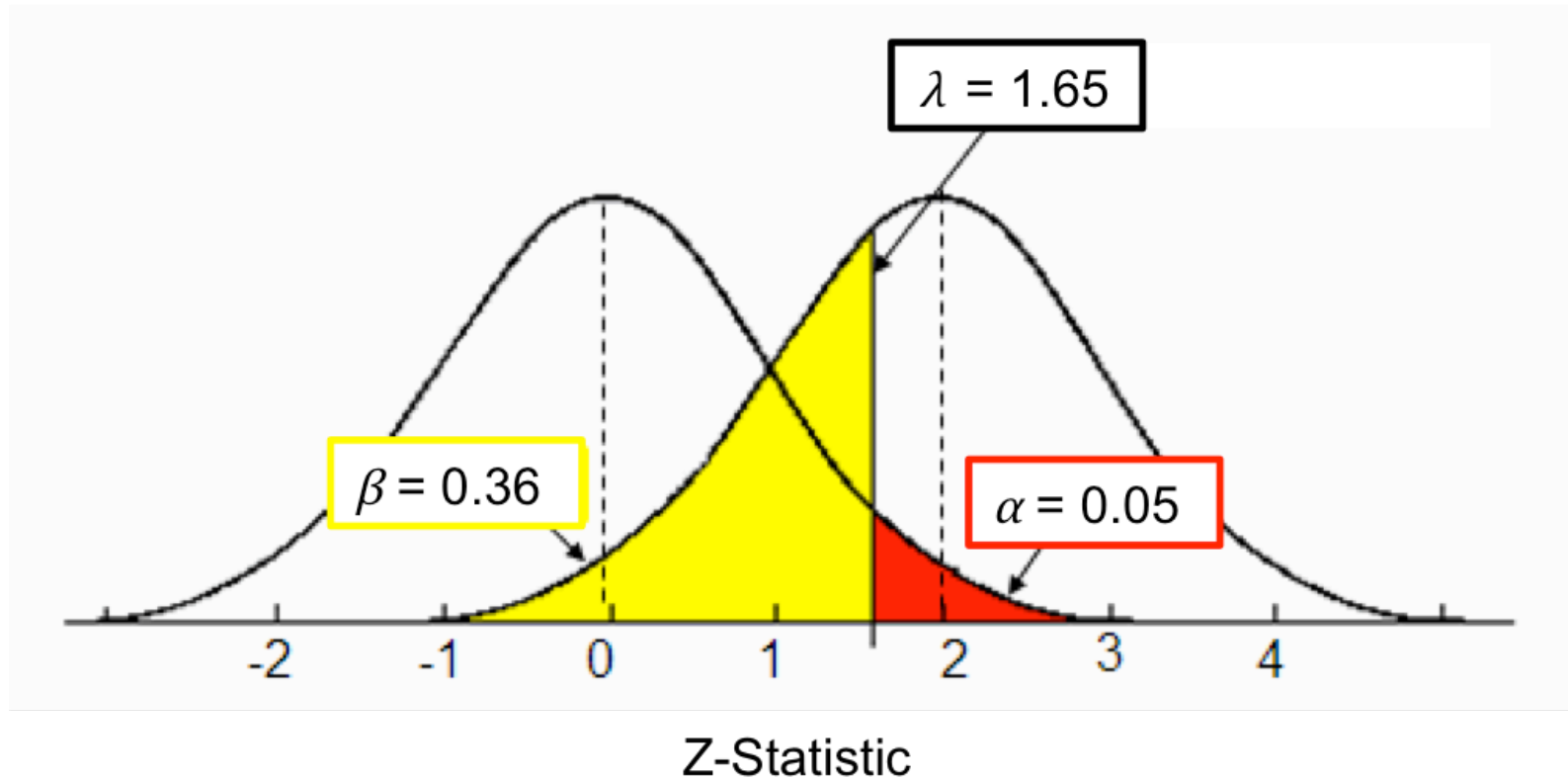


- Trial length \approx number of patients / accrual rate

	Approve	Reject
Effective	$(1-DF_t) \times L_1$	L_1
Ineffective	$DF_t \times L_0$	0

- Weight each scenario by its probability to calculate the expected value lost

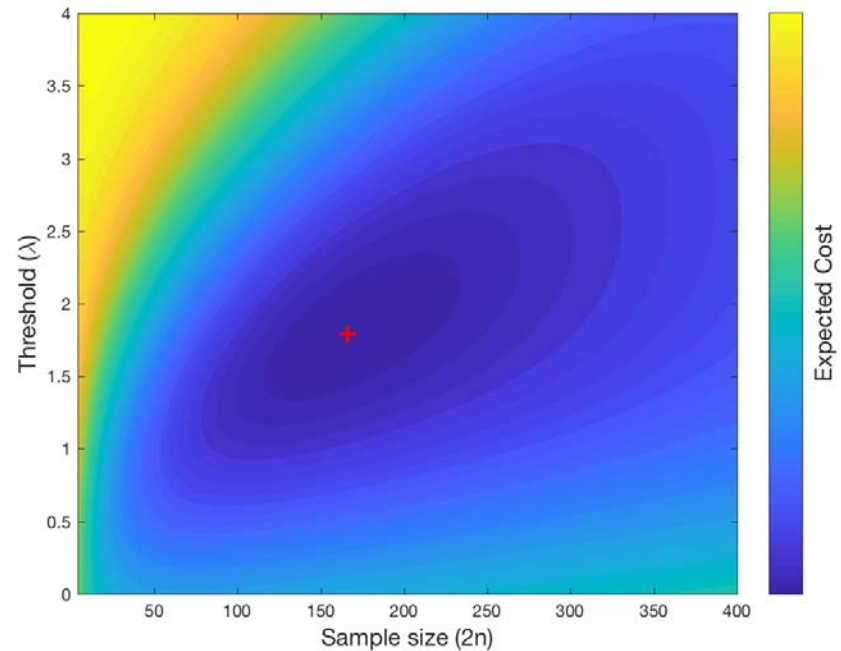
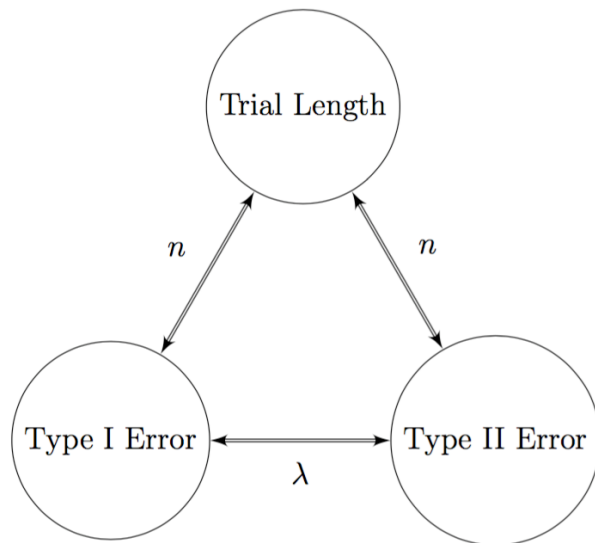
Statistical Significance and Power



	Approve	Reject
Effective	$1-\alpha$	α
Ineffective	β	$1-\beta$

- Assume prior probability p for ineffective scenario

$$(n^*, \lambda^*) = \arg \min_{n, \lambda} \left(p_0 \cdot E[\text{Cost} \mid H = 0] + (1 - p_0) \cdot E[\text{Cost} \mid H = 1] \right)$$



- BDA-optimal decision **maximizes** expected value to patients

Assumptions for trial design

Parameter	Assumed Value
Prior probability that treatment is effective	50%
Patient accrual rate	200 patients per year
Motor symptom score standard deviation	2 out of 10

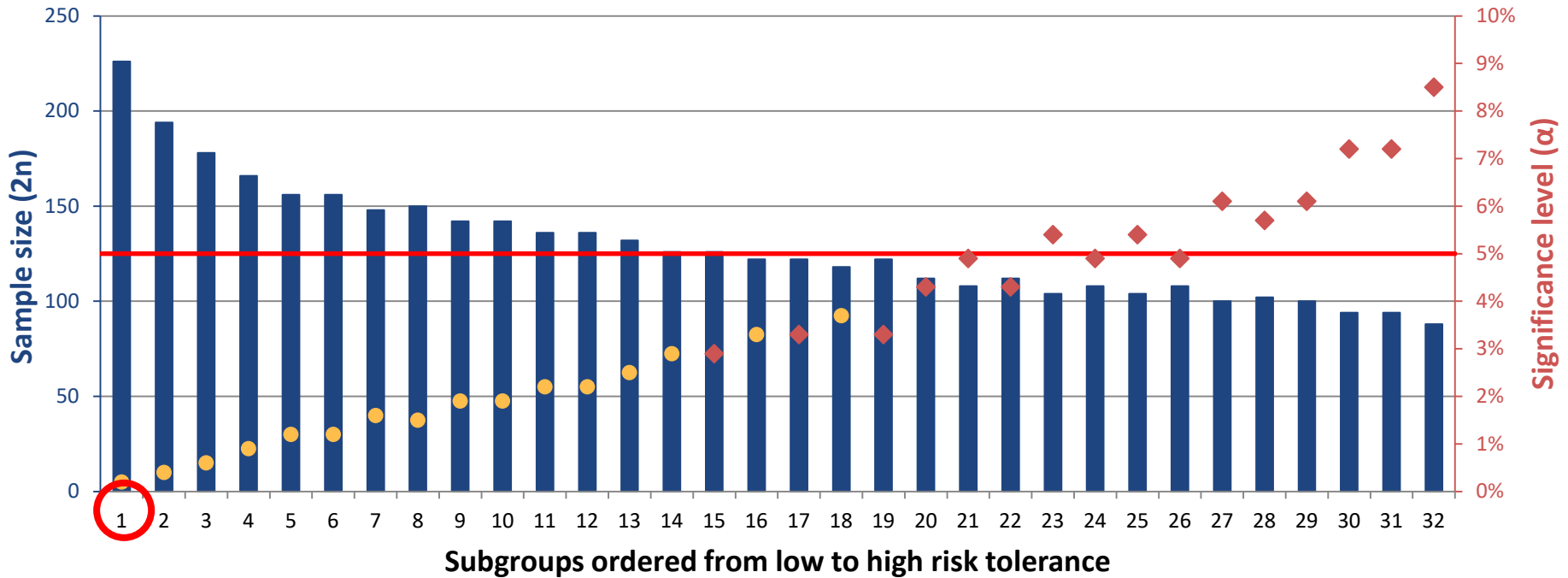
Motor symptom score mean difference	1.14 out of 10
On-time mean difference	4.6 hours
Reduction in pain symptoms mean difference	0.72 out of 10
Reduction in cognitive symptoms mean difference	0.37 out of 10
Reduction in medication mean difference	1.48 pills per day

Depression risk	3%
Brain bleed risk	1.6%
Mortality risk	0.8%

Attribute	Description
Deep brain stimulation	Patients have previously received deep brain stimulation
Non-ambulatory	Patients have problems with balance or walking
Cognitive impairment	Patients have difficulty thinking clearly
Motor impairment	Patients have impaired motor function
Dyskinesia	Patients experience dyskinesia as side effect of medication

- $2^5 = 32$ possible combinations
- Order subgroups by risk-tolerance

“Patient”-Values for Neurostimulator



**Mild symptoms,
No DBS**

**Severe symptoms,
DBS**

- A fixed significance level of 5% does not maximize patient value
- For risk-tolerant subpopulations (DBS, severe cognitive and motor function impairment), lengthy clinical trials are overprotective of the type I error rate
- For patients with less severe symptoms, traditional thresholds of 5% may be too permissive

Thank You!