BASS XXIII
Monday, Oct. 24, 2016
4:00 PM – 4:45 PM

Innovative Designs and Analyses for Pediatric Drug Development

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Overview of Talk

- Application of Bayesian methods and Adaptive Design to Pediatric Trial Design
- Setting: pediatric plan lags behind an adult indication
  - More information in adults, but comparatively less data in pediatrics, and the
  - Primary goal of the pediatric trials is to provide definitive efficacy and safety evidence to impact product labeling
  - Pediatric indication is rare, and difficult to enroll

Opportunities for the use of Bayesian modeling and simulation in Pediatric Drug Development

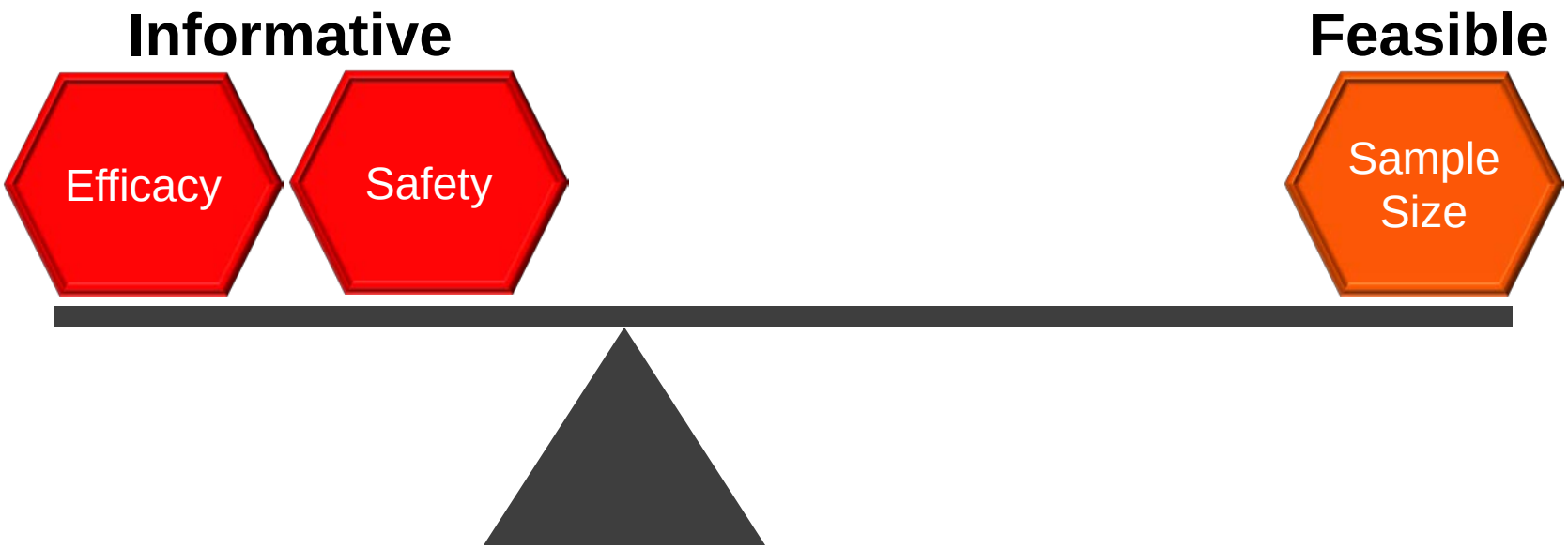
The Typical Problem

fosinopril. essential hypertension in children and adolescents.[5]

Adult study: 220 patients, 9 US sites, 5 mo. to complete

Pediatric study: 253 patients (6 -16y), 70 sites, 3countries,1y to complete

Finding balance

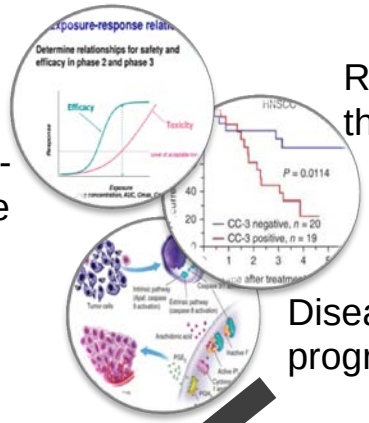


"Need to minimize number of subjects enrolled in pediatric clinical trials and the need to maximize the usefulness of the data obtained, while ensuring that the trials are **feasible**, **robust**, and **interpretable**." – Dunne et al. (2011)[6]

Extrapolation

We are thinking about extrapolation early in our drug development programs.

Weights of these factors determine **extent of extrapolation**



Exposure-Response

Response to therapy

Disease progression

Adult trials efficacy outcome data

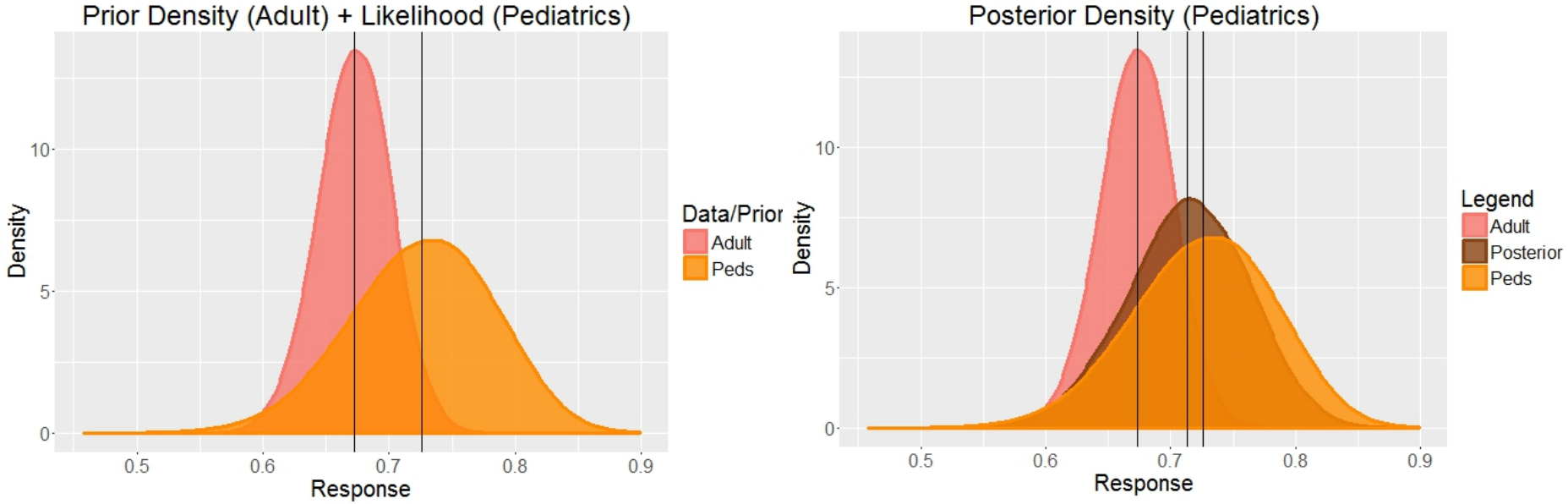
Bayesian extrapolation[7]

Pediatric trial efficacy outcome data

Bayesian extrapolation

Design Trial

- ❑ Specify a prior: **Adult Efficacy Data**
- ❑ Collect data + compute likelihood: **Pediatric Trial Efficacy data**
- ❑ Apply Bayes Theorem: **Posterior distribution**



Bayesian approach formalizes what pediatricians do when they combine the results from large adult trials with the results of smaller pediatric trials to make treatment decisions." - Schoenfeld et al. 2009[8]

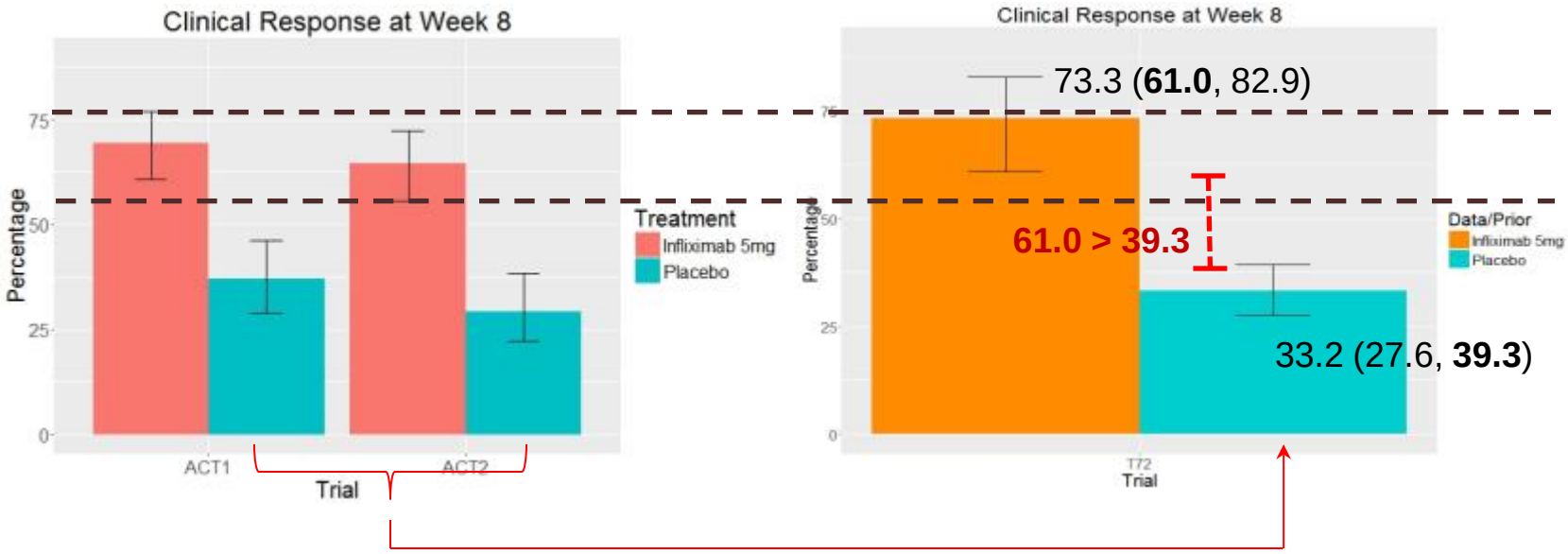
Example 1: Bayesian analysis

- Treatment: Infliximab 5mg/kg
- Indication: Ulcerative colitis
- Adult Trial design: 2 completed Placebo-Controlled
- Pediatric Trial design: Open-label

	ACT 1	ACT 2	T72
	Infliximab 5mg/kg	Infliximab 5mg/kg	Infliximab 5mg/kg
Endpoint	N = 121	N = 121	N = 60
Clinical response	**84 (69.4%)**	**78 (64.5%)**	**44 (73.3%)**
Clinical remission	47 (38.8%)	41 (33.9%)	24 (40.0%)
Mucosal healing	75 (62.0%)	73 (60.3%)	41 (68.3%)

Summary level data obtained from Rutgeerts et al, 2005[9], and Hyams, et al., 2012[10]. Placebo response not shown. Other information found Gastrointestinal AC meeting on this link: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM266697.pdf

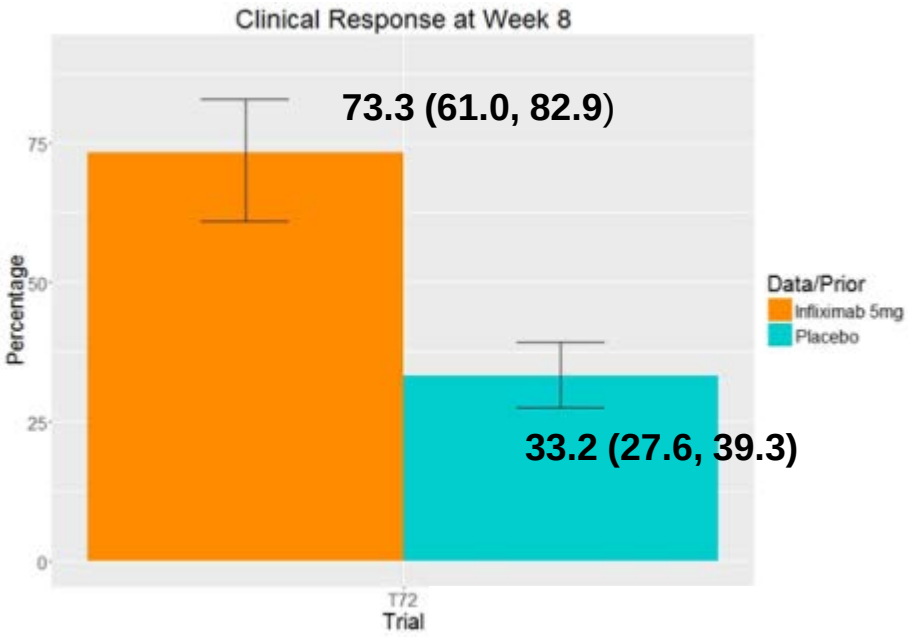
“Cursory” extrapolation



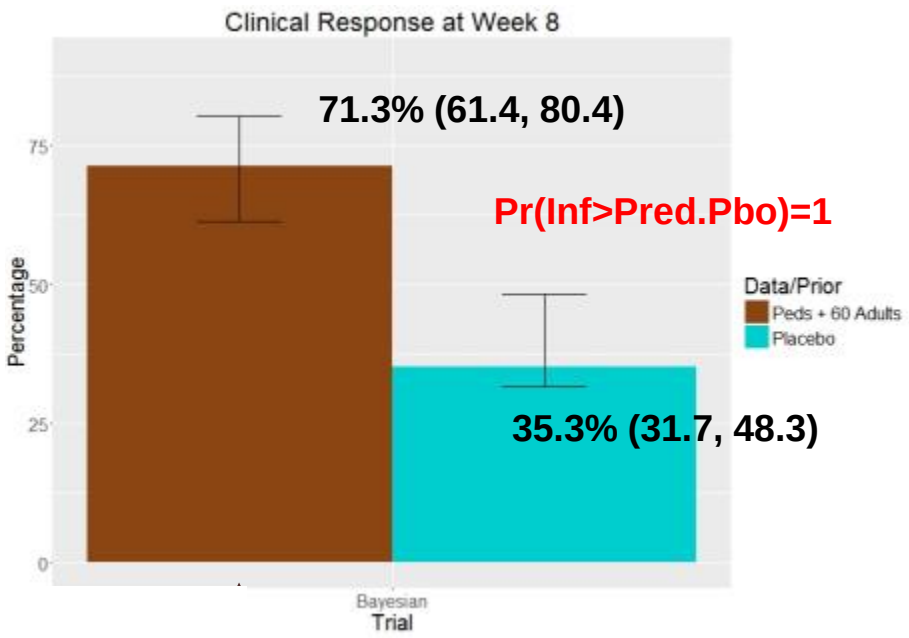
Step 1: **Assume** combined placebo response in adults is the same as placebo response in pediatrics.
Step 2: **Check** pediatric clinical response within reasonable range of adult response.
Step 2: Compare confidence interval limits.

Bayesian extrapolation

“Cursory”



Bayesian



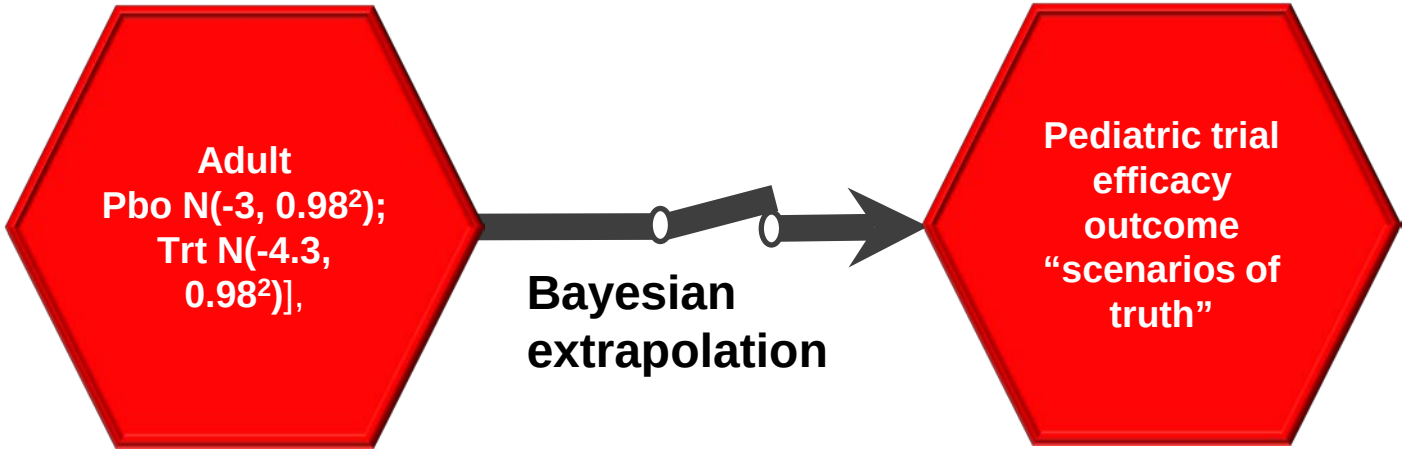
Bayesian extrapolation turns out more conservative!

Example 2: Bayesian Design

- **Treatment:** Trt
- **Indication family:** Analgesia
- **Objective**: Design Pbo-controlled Fixed Sample design in pediatrics borrowing results from adult data

Assumptions:

- **Partial extrapolation applicable**
- **Pediatric study uses the same endpoint/measurement and time of assessment**



Scenarios of Truth:
Effect sizes:
0, **0.15**, 0.30,
0.325, 0.35;
SD:3.789

Predicted Power

Effect Size	N=350 Informative Prior	N = 350 Discounted Prior*	N=400 Diffuse Prior	N=400 Informative Prior
0	**0.037**	0.026	**0.021**	0.034
0.15	**0.337**	0.288	**0.284**	0.348
0.30	**0.834**	0.788	**0.826**	0.866
0.325	**0.889**	0.855	**0.877**	0.912
0.35	**0.92**	0.899	**0.92**	0.943

- Success is defined as Pr(Trt > Placebo) > 0.975
- Simulated average conditional power can also be calculated given that treatment effect has a distribution over a certain range.
- Expected sample size can be further in either scenario (informative or diffuse) reduced using group sequential/adaptive designs.

***Discounted Prior Pbo N(-3, 0.98^2); Trt N(-3.65, 0.98^2) – this is a less optimistic informative prior**

Ensuring interpretability and robustness

- Alignment of adult and pediatric clinical trial
  - **Dose** needs to be correct!
  - Emphasis on **sufficient quality of data** from adult population, e.g., Study design, Data collection, Measurement

“Unquantifiable” sources of bias if there are differences in patient populations

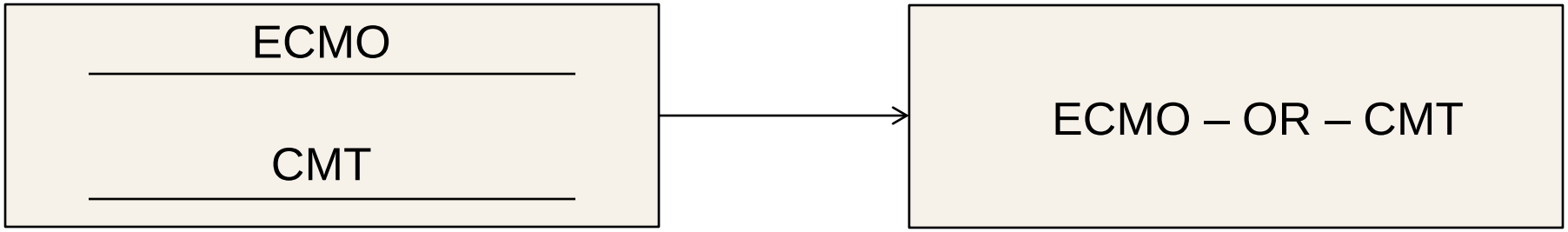
- Constrained/robust prior (avoid too much optimism!)

Example: ECMO Trial – Response Adaptive Randomization (RAR)

Two arm trial comparing Extracorporeal Membrane Oxygenation (ECMO) and Conventional Medical Therapy (CMT) for treatment of Persistent Pulmonary Hypertension in newborns (Bartlett, 1985)

Part 1: 1:1 randomization
Until 4 deaths on an arm

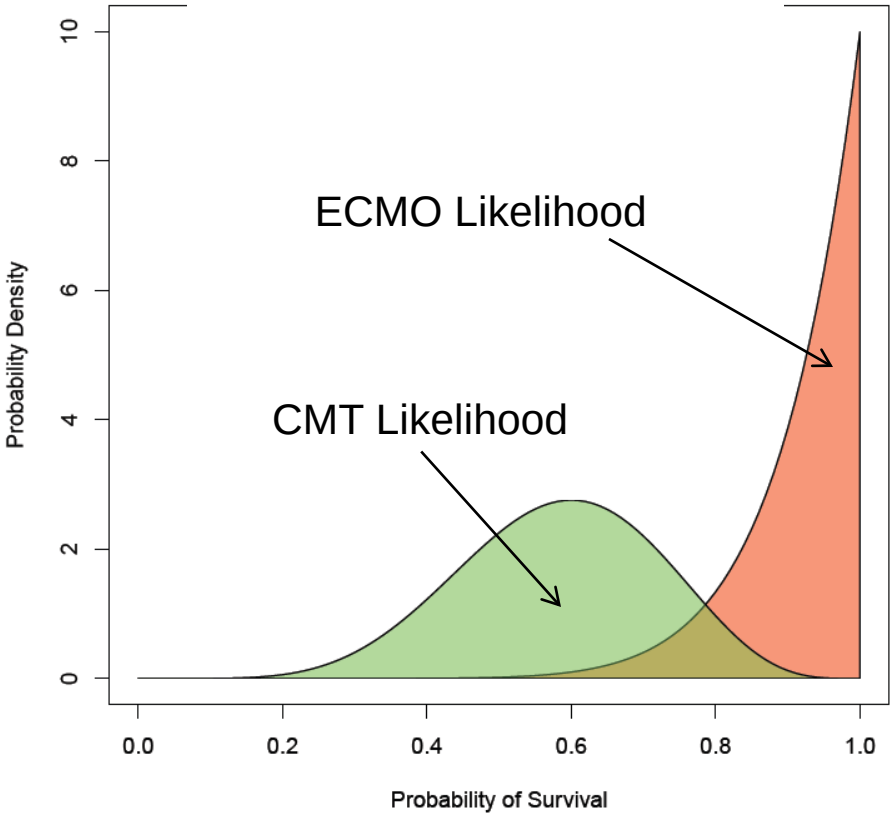
Part 2: "Play the winner"
Randomize to best arm until 4 deaths OR stat. significance



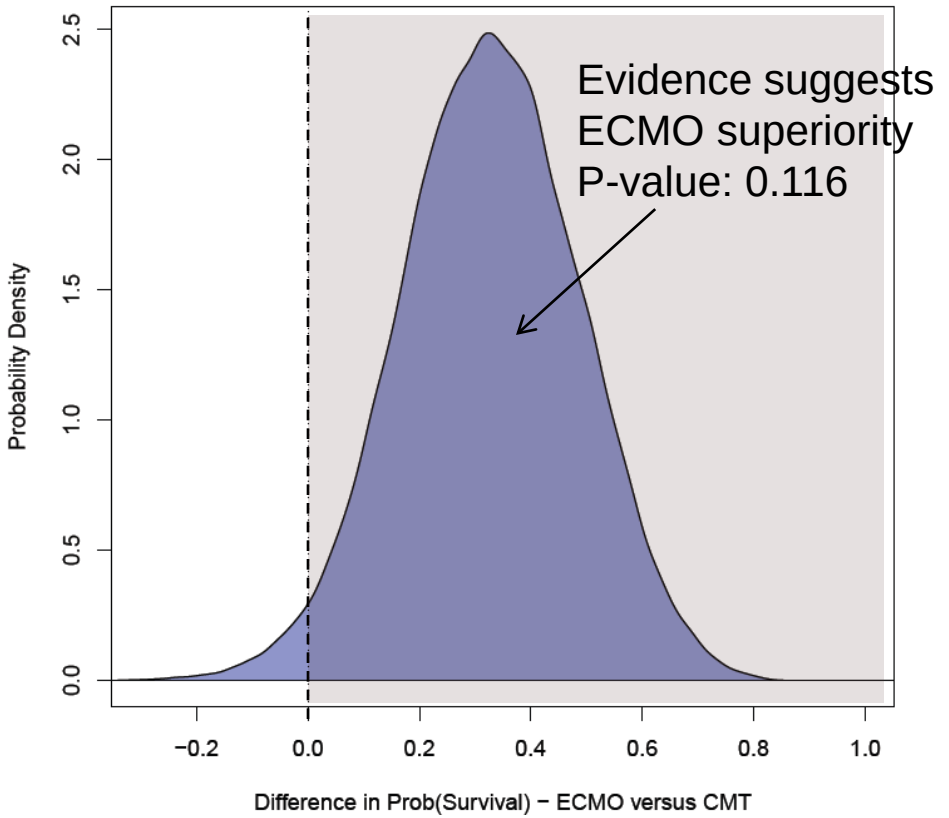
ECMO Trial Part 1 Data and Analysis

- After part 1,
- **ECMO** – **9** survived out of **9**
- **CMT** – **6** survived out of **10**

Part 1: Estimated Survival



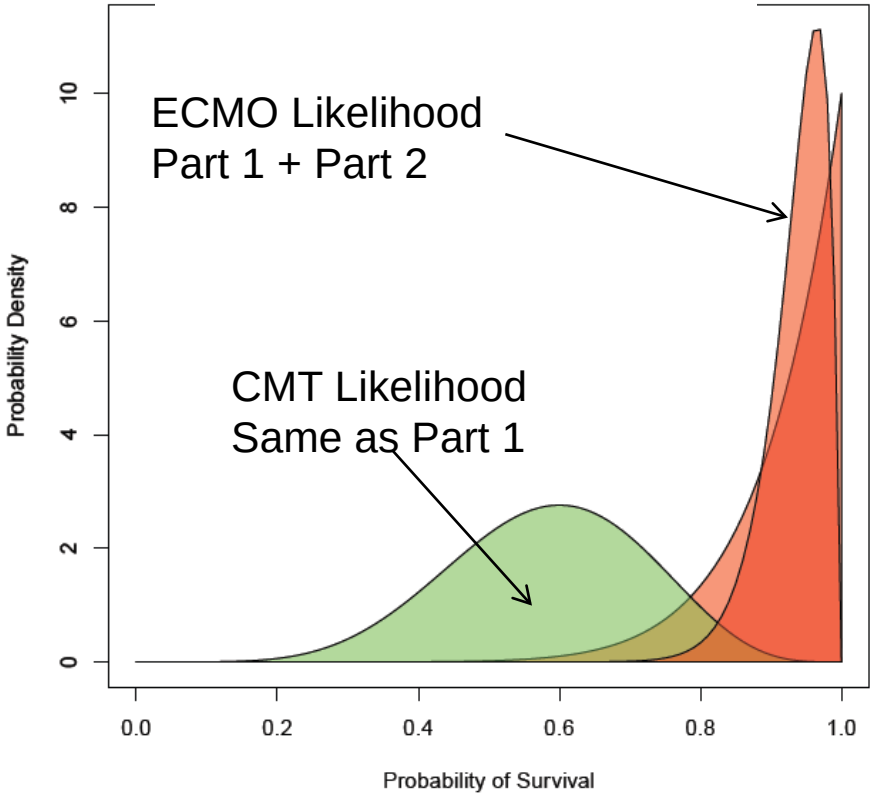
Part 2: Estimated *Difference* in Survival



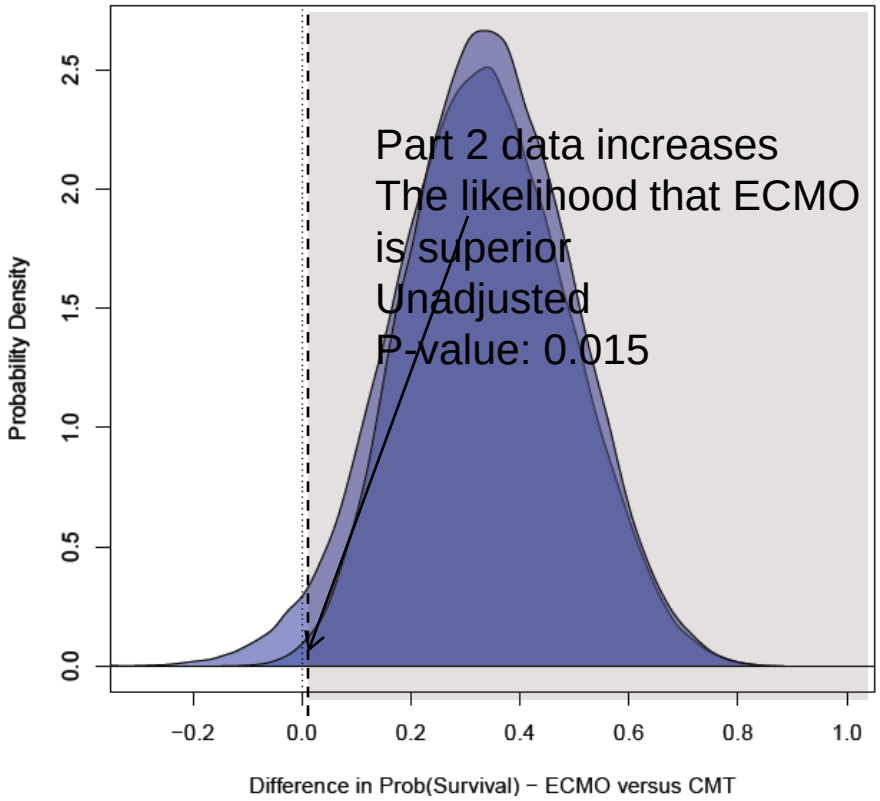
ECMO Part 2: Adaptation & Final Data – What was learned from part 2?

- Given the data & design, the trial allocated future patients to ECMO until 4 deaths or stat. significance
- Result: **ECMO 19** survived out of **20**

Part 2: Estimated Survival

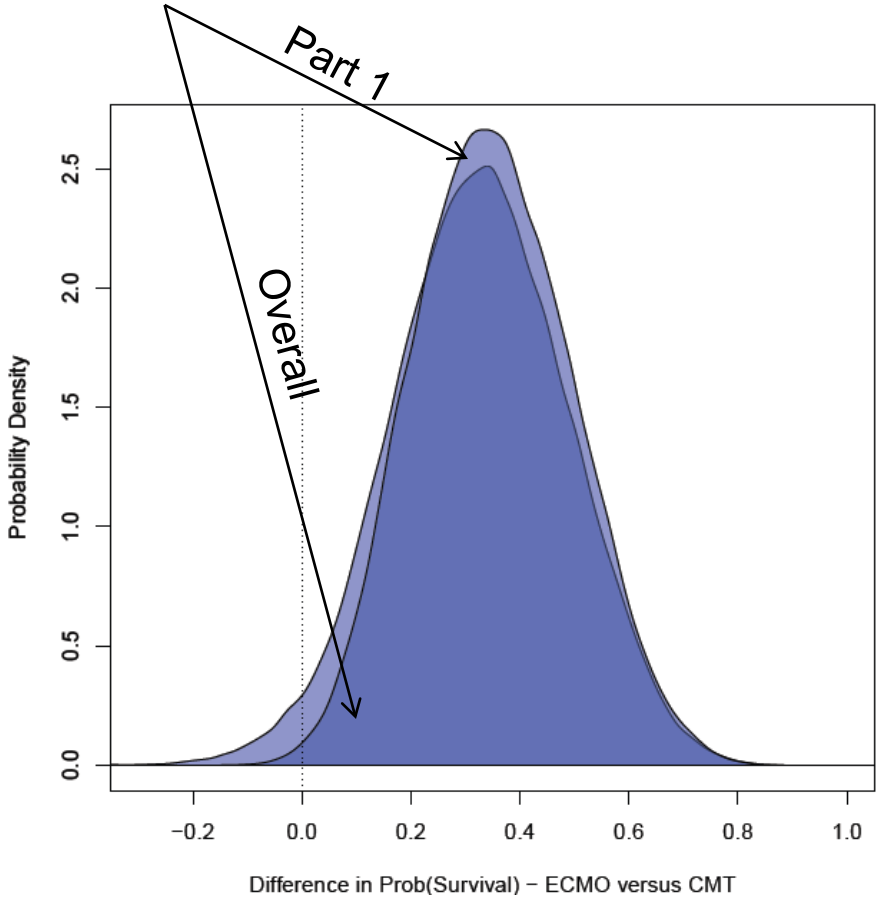


Part 2: Estimated *Difference* in Survival



ECMO: Adaptation, Efficiency & Alternatives

- Part 1 + Part 2 ECMO was superior to CMT (statistically significant)
- Did not provide a dramatically different precision on difference (see histogram)
- Hypothesis test versus estimation
- Uncertainty driven by CMT rate
  - How many patients on CMT?
- Alternative designs?

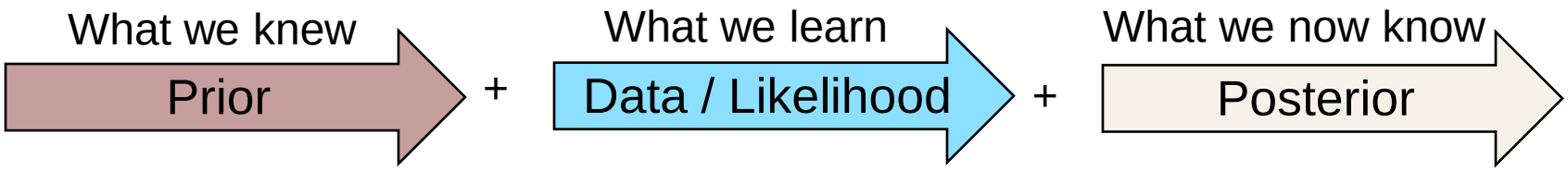


ECMO Revisited – Bayesian analysis & incorporating historical data

- What prior information was available?
  - Clinical experience - CMT mortality ~80%
  - Previous ECMO trial with 12 patients (11/11 ECMO Survived, 0/1 CMT survived) (Bartlett, 1985)

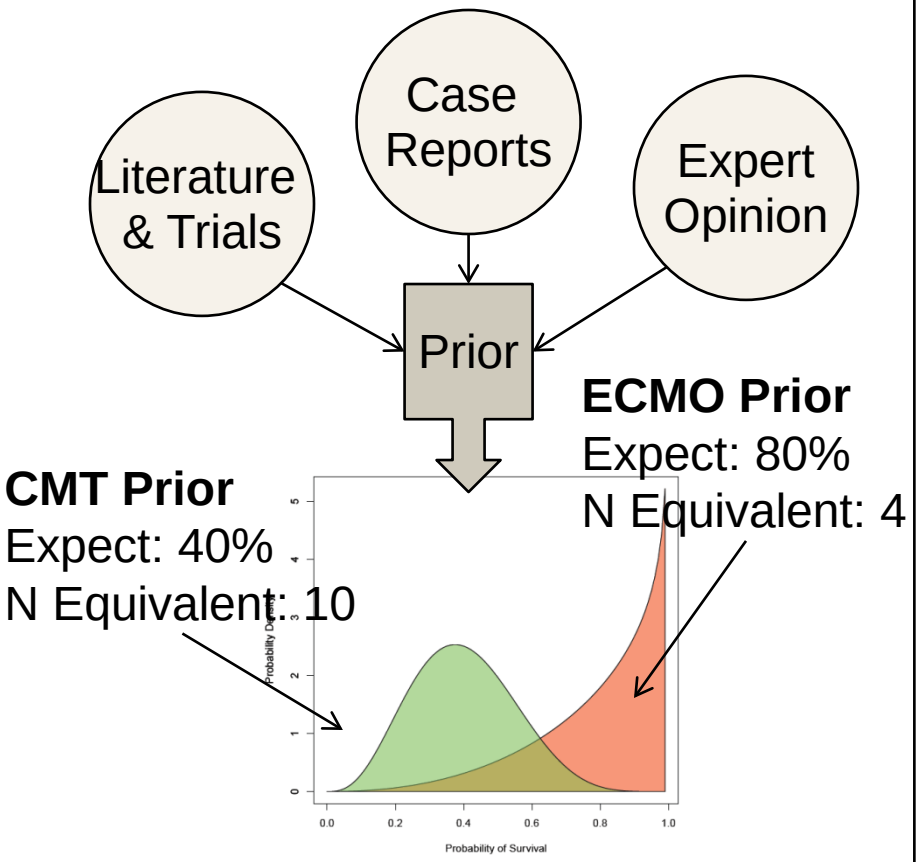
Bayesian analysis & incorporating historical data

- Bayesian methods offer a means to incorporate historical information in a quantitative manner



ECMO Revisited – Bayesian analysis & incorporating historical data

Bayesian Evidence Synthesis (illustration)



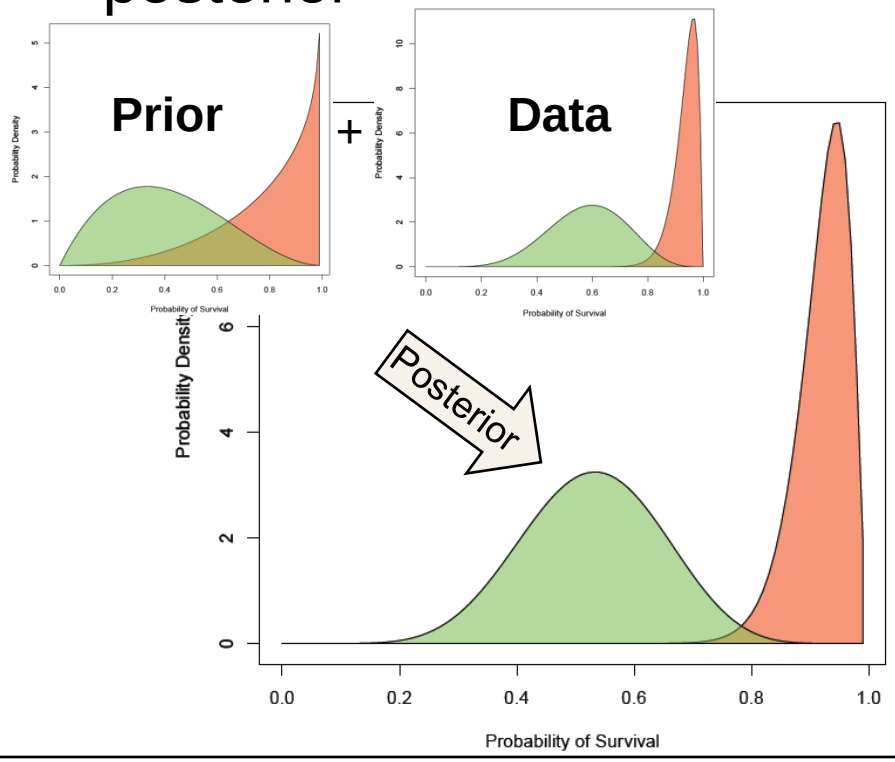
Key points

- Meta-analysis to quantify the prior
- Consider the amount of information to "borrow" from historical data
- Methods available to adaptively borrow from historical data

ECMO Revisited – Bayesian analysis & incorporating historical data

Bayesian Modeling and Analysis

- Prior + Data to generate posterior



Key points

- Leveraging prior data in analysis
- The influence of the prior can be assessed
- Bayesian probability statements about the likelihood that ECMO > CMT (rather than p-values)
  - E.g. Prob(Survival ECMO-CMT > 20%) = 0.97

ECMO Example – Discussion and Key Points

- Ultimately the ECMO trial proved controversial
- UK Collaborative ECMO Trial (1993-1995) – Evaluate survival and morbidity (cost effectiveness)
  - Trial stopped early by DSMB (mortality outweighed potential differences in morbidity
    - ECMO survival 63/93 = 68%
    - CMT survival 38/92 = 41%
    - Relative risk: 0.55 (95% CI 0·39—0·77; p=0.0005)
- What design would have made the UK trial unnecessary?

Example: Pediatric PAH Study: Issues

Uncertainty

- Little information available to design study
  - Different primary endpoints and powering for FDA & EMA
  - Duration differences for endpoints
- Need a clear positive or negative result for labeling
  - Requires estimate of variability to right size the study
  - Rare disease in pediatric population <1000 cases globally

Urgency

- No approved therapy in pediatrics
  - Expected to be difficult to enroll
  - Need study to complete prior to patent expiration

Estimating Variance

- Historical information
  - 1 pediatric study (differences in population)
  - 3 adult studies
    - 2 studies same treatment mechanism as pediatric study
    - 1 study same treatment as pediatric study under design
- Endpoint for FDA (invasive biomarker)
- Bayesian Approach
  - Estimate the variance from the “posterior” of the historic pediatric study
  - Utilize the adult studies as the prior

Power Prior on SD Mean Change

Posterior of SD $\pi(\sigma_1^2, \sigma_2^2 \mid \boldsymbol{y}, \alpha_0)$ $\propto$ **Prior of SD** $\pi(\sigma_1^2, \sigma_2^2)$ $\cdot$ **Weighted Adult Likelihood** $L(\boldsymbol{s}_0 \mid \sigma_1^2, \sigma_2^2)^{\alpha_0}$ $\cdot$ **Pediatric Likelihood** $L(\boldsymbol{s} \mid \sigma_1^2, \sigma_2^2)$

Parameter	Definition
$\boldsymbol{s}_0$	SD from the 3 adult studies (prior for pediatric study)
$\boldsymbol{s}$	SD from the pediatric study
σ_1^2, σ_2^2	Variance for individual response for placebo and treatment respectively

α_0 = 0.25 down-weight adult studies; α_0 = 1 equally-weight adult studies

Since variances are proportional to chi-square, assume:	
$(n_{ik} - 1){s_{ik}}^2 / \sigma_k^2 \sim \chi^2(n_{ik} - 1)$	
s_{ik}	SD from study i and arm k
n_{ik}	Number of patients from study study i and arm k

Power Prior on SD Mean Change

Pediatric study greater variability

Down-weighting resulted in a more conservative estimate

Power Prior on Treatment Mean Differences

Posterior of Effect Size

$$\pi(\mu, \tau, \delta_1^2, \delta_2^2 | \boldsymbol{y}_0, \boldsymbol{y}, \alpha_0) \propto \pi(\mu, \tau, \delta_1^2, \delta_2^2) \cdot L(\boldsymbol{y}_0 | \mu, \tau, \delta_1^2, \delta_2^2)^{\alpha_0} \cdot L(\boldsymbol{y} | \mu, \tau, \delta_1^2, \delta_2^2)$$

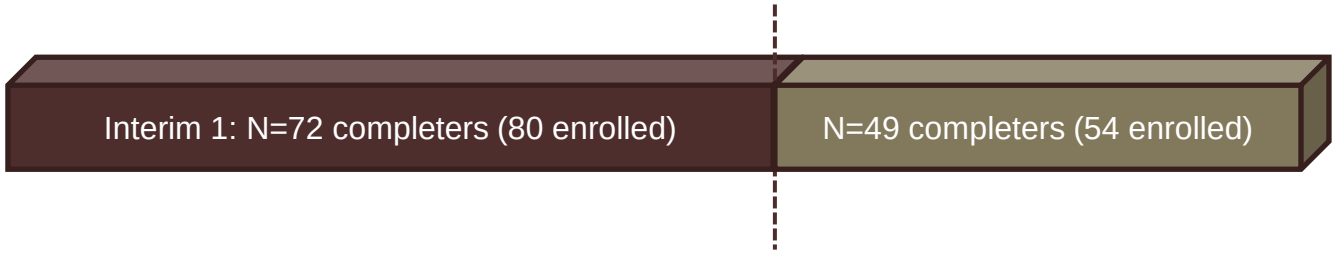
Prior | **Weighted Adult Likelihood** | **Pediatric Likelihood**

Parameter	Definition
$\boldsymbol{y}_0$	LSMeans from the 3 adult studies (prior for pediatric study)
$\boldsymbol{y}$	LSMeans from the pediatric study
μ	Placebo effect
τ	Placebo-adjusted treatment effect (parameter of interest)
δ_1^2, δ_2^2	Variability of LSMeans across studies for placebo and treatment respectively
Non-informative priors used on μ, τ (normal) and δ_1^2, δ_2^2 (inverse-gamma)	

Modeling utilized to estimate expected effect size

Expected to be safer but with similar efficacy to previous pediatric trial

Group Sequential Design



IA for Early Stopping at ~60% Information
Pocock Spending Function
If success is met with invasive biomarker, discontinue measurement, may continue for EMA endpoint

Design Element	Value	
Planned Total N	121 completers, 134 enrolled	
Proposed Type 1 Error	1-sided 0.05	
Alpha Spending Function	Pocock	
Interim Information	**Information Fraction**	**One-sided p-value**
	60%	0.0353
	100%	0.0280

M&S Effort
- Used East
- Scenarios across range of alpha, efficacy and variability

Proposed Design
~85% power, ~65% early success for expected scenarios

Proposed Design

- Type I error 1-sided 0.05
  - Rare disease with few patients
  - Poor prognosis
- Powered on expected effect size
  - If enrolled ALL existing patients, may not be sufficient to power on a minimal effect size
- GSD: Pocock spending function
  - Early stopping for efficacy only
    - Unlikely to meet high hurtle needed to declare futility

Feedback

- **Power on minimal effect size**
  - Agreement on Bayesian methodology to assess variance
  - Proceeding with powering on expected effect size at risk
- **Type 1 error rate 2-sided 0.05**
  - Biomarker endpoint
  - Single study
- **GSD sponsor risk**
  - Interim results must be definitive
  - Minimum interim timing discussed

Pediatric Type 2 Diabetes Efficacy Study

- Indication: Pediatric Type 2 Diabetes
  - Relatively rare but increasing incidence in children and adolescents
  - “More common in certain racial and ethnic groups such as African Americans, American Indians, Hispanic/Latino Americans, and some Asian and Pacific Islander Americans”*
  - Requires recruiting patients with health disparities and reduced access to care
- Key Uncertainties
  - Unknown effect size of the drug on HbA1c
  - Uncertainty variability in HbA1c
  - Uncertain recruitment and retention rate

* https://www.niddk.nih.gov/health-information/health-communication-programs/ndep/living-with-diabetes/youth-teens/diabetes-children-adolescents/Documents/overview-of-diabetes-children-508_2014.pdf

Overview of Designs

- **Efficacy study** – 1 dose arm versus placebo on background of standard of care (Diet/exercise, w/ or w/o metformin or insulin)
  - 26 weeks duration
  - Primary Objective: Reduction in HbA1c
  - Design Goal: 90% power for -0.6% reduction in HbA1c

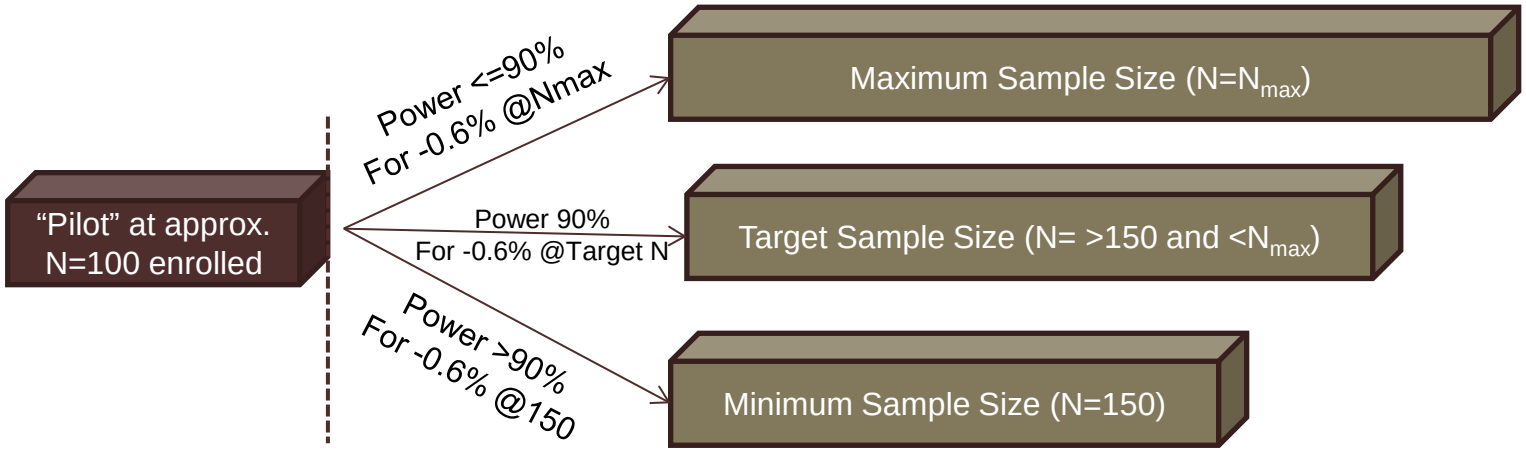
Design Options

- Designs Considered
  - Fixed Design – 150 patients
    - Given key uncertainties – Consider adaptive approaches to ensure appropriate power for labeling
  - Adaptive Designs utilizing sample size re-estimation (SSR)
    - Option 1: Blinded sample-size re-estimation (SSR)
    - Option 2: Information based SSR
    - Option 3: Unblinded Sample-size Re-estimation using Promising Zone Technique

Sample size re-estimation

Sample size per group	$N = 4\frac{\left(z_{1-\alpha} - z_{1-\beta}\right)^2}{(\mu/\sigma)^2}\left(\frac{1}{1-f}\right)$

Parameter	Definition
f	Retention Rate
μ	Mean Difference (Treat – Placebo)
σ	Standard Deviation

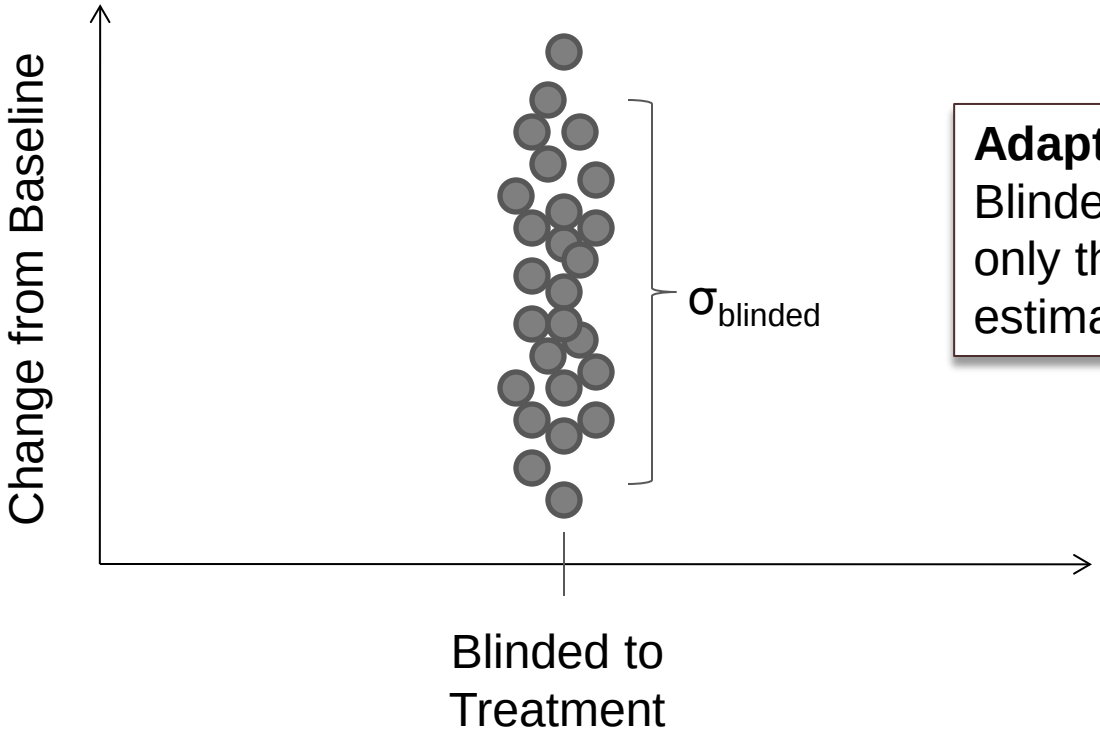


IA for SSR

Model the interim data to re-estimate the sample size needed to maintain power

Understanding Each SSR Option

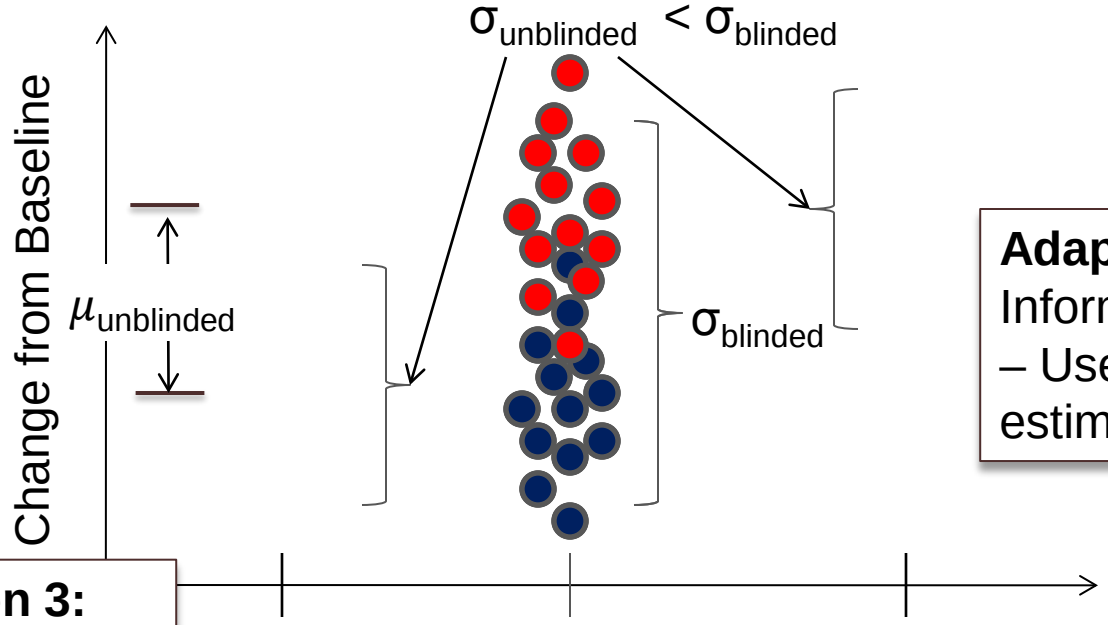
The data we observe at a blinded interim



Adaptive Option 1:
Blinded SSR – uses only these data to re-estimate sample size

Understanding Each SSR Option

The data we **don't** observe during blinded SSR.
Unknown treatment effect explains some of the variability



Adaptive Option 2: Information based SSR – Uses $\sigma_{unblinded}$ to re-estimate sample size

Adaptive Option 3: Unblinded SSR – Uses $\mu_{unblinded}$ and $\sigma_{unblinded}$ to re-estimate sample size

$$N = 4\frac{\left(z_{1-\alpha} - z_{1-\beta}\right)^2}{(\mu/\sigma)^2}\left(\frac{1}{1-f}\right)$$

Assessing design performance

- Each design option was simulated across a range of scenarios of truth
  - Evaluated on ability to maintain 90% power for effect of -0.6% HbA1c Effect
  - Simulated using combination of software: R and East

- Information based SSR performed the best across scenarios:

Scenario			Design Performance			
Name	Mean Effect	Sigma	Fixed Design	Blinded SSR	Information Based SSR	Unblinded SSR
Expected	↔	↔				

Assessing design performance

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Scenario			Design Performance			
Name	Mean Effect	Sigma	Fixed Design	Blinded SSR	Information Based SSR	Unblinded SSR
Expected	↔	↔				
Higher Variability	↔	↑			↓ best across scenarios	
Lower Effect	↓	↔				
All Higher	↑	↑				

Discussion

- Bayesian methods and Adaptive Design have many applications to improve to Pediatric Trial Design
  - Topics covered:
    - Extrapolation to leverage adult data
    - Informative Priors
    - Adaptive Design - Adaptive randomization, group sequential design, sample size re-estimation

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