Dr. Karen Price and Dr. Zach Thomas (Lilly)

Pre-Workshop Course on Bayesian Methods in Clinical Trials

Course duration: 10:00 – 12:00pm

Karen Price received her Ph.D. in Statistics from Baylor University in 2001 and joined Eli Lilly and Company at that time. She is Sr Research Fellow and leads the Statistical Innovation Center, a team focused on innovative design/analysis of clinical trials. In 2011, Karen helped form and led the DIA Bayesian Scientific Working Group and currently serves as past-chair. In 2016, Karen was elected a Fellow of the American Statistical Association.

Zach Thomas is Principal Research Scientist in oncology at Eli Lilly and Company. Zach joined Lilly in 2015 after completing a PhD in Statistics at Ohio State. Zach serves in a general technical consulting role across the oncology portfolio, with a focus on novel trial design and analysis, Bayesian applications in drug development, and trial simulation

Short Course: Bayesian Methods in Drug Development

Karen Price

Zach Thomas

ASA NJ Chapter and Bayer Statistics and Data Insights
Bayesian Methods in Clinical Trials
November 5, 2021

Outline

- Overview of Bayesian Methods and opportunities in clinical trials
- Methods for constructing priors
- Utilization of priors for
  - Design / Decision-making
  - Formal inference
- Innovative designs / adaptations/ other design features
- External / Regulatory Perspective

Overview of Bayesian Methods

Bayesian Statistics Emulates the Way We Think

- We all learn from previous experience
  - Personally
  - Scientific decisions
  - Business decisions
- Pictorially, we can think of this as:

Humans struggle with prediction *and* uncertainty

The instinctual shortcut that we take when we have 'too much information' is to engage with it selectively, picking out the parts we like and ignoring the remainder...

It was hard to tell the signal from the noise. The story the data tells us is often the one we'd like to hear, and we usually make sure that it has a happy ending.

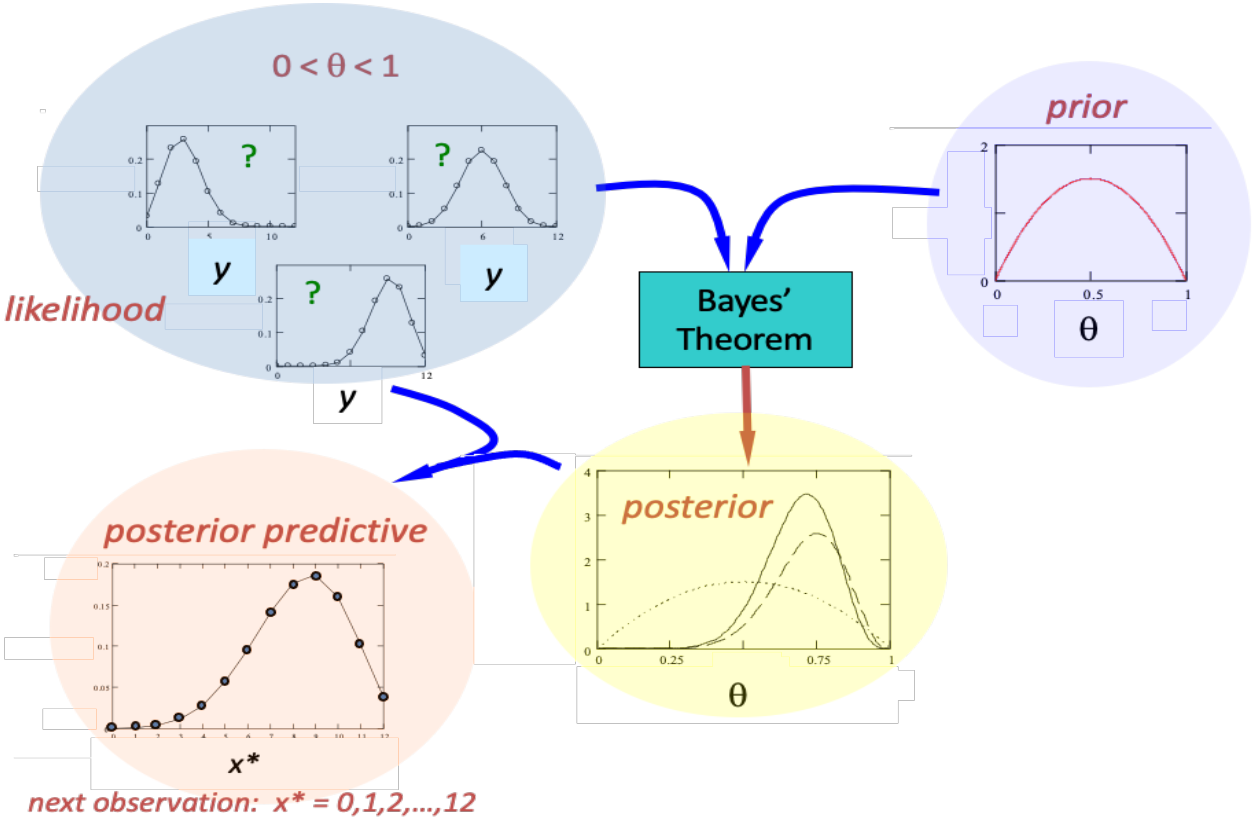
Nate Silver

Why Bayes: A working philosophy

- Bayesian methods lend themselves well to iterative updating of *the science*
  - *'Today's posterior is tomorrow's prior'*
    –Dennis Lindley, 1972
  - *"When the facts change, I change my mind. What do you do, sir?"*
    –attributed to economist John Maynard Keynes
- Bayes facilitate rigorous integration of what we **know already** (i.e. via informative priors) within analyses of new data designed to shed light on what we **don't know**
  - Strives for **transparent** integration of data from diverse sources to inform decision-making
- Allows straightforward statements of probability and uncertainty
- Bayesian design can reduce sample size/study duration
- Flexible hierarchical modeling with computational conveniences

Rev. Thomas Bayes?

Bayesian Approach



Numerous Opportunities in Clinical Trials

- Design / Decision Making
  - Critical success factors (CSFs) at design and program level
  - Probability of study success (PrSS)
  - Enable trade-offs amongst design/program options
- Formally leverage relevant historical data to improve inference and decision making without increasing enrollment/study duration
  - Bayesian augmented control (BAC) designs
  - Informative prior based on effect-size from Ph2
  - Extrapolation of adult data for pediatric
- Other innovative designs
  - Master protocols of related diseases and/or treatments
  - Bayesian informed adaptive trials
- Improve operational elements of clinical trials
- …

Prior Distributions

Prior Elicitation

Formal Synthesis of Data

Overview of Potential Data Sources

- Expert / patient / caregiver opinion
- Natural history studies
- Summary level data (RCTs, observational)
- Individual-level patient data
  - Internal to Sponsor or at FDA (or other regulators)
  - Patient registries
  - Observational studies
- PK/PD modeling
- Pre-clinical data

Need to assess relevance of historical data to new data: similar indications, patient population, time since data collection, relevance of endpoints, timepoints, etc. (exchangeability)

Prior Elicitation

Why Formal Prior Elicitation?

Expert elicitation is suitable when…

- Information/data is absent or available data might not be suitable as a statistical input;
- Empirical data are not reasonably obtainable, analysis are not practical to perform;
- Uncertainties are 'large' and/or related to high stakes;
- Complexity in multiple sources prohibits a coherent summary.

Because it …

- Helps take stock of the uncertainty about quantities of interest without the cost of additional data collection;
- Provides transparency with regards to how we came up with the prior.

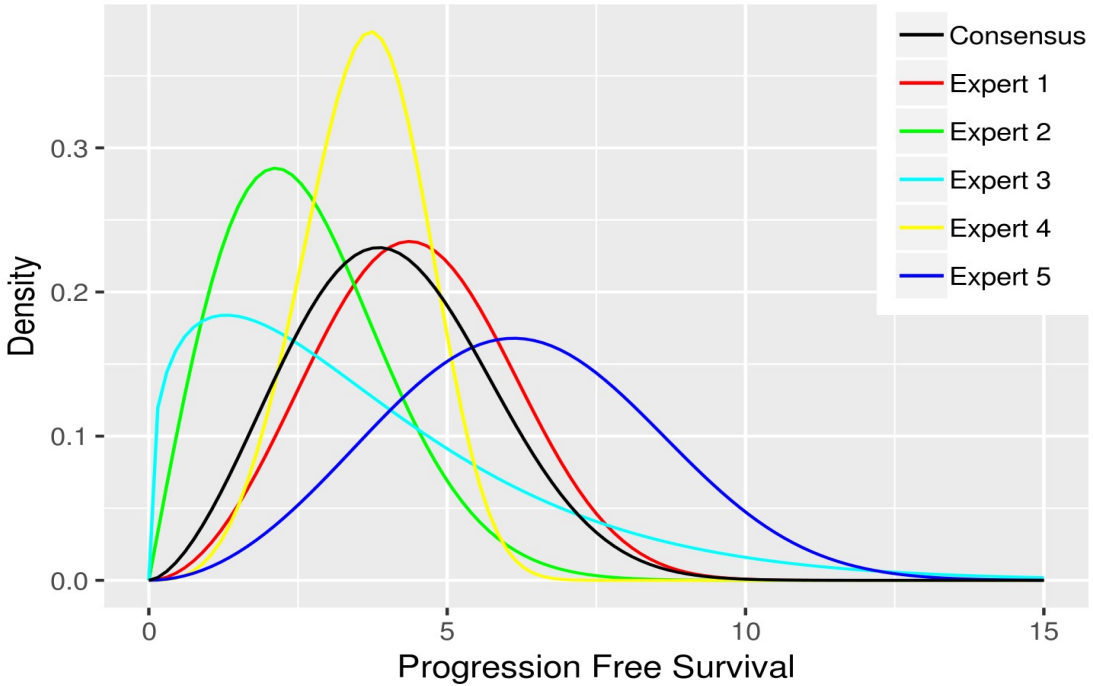
Role of Expert Opinion

- Elicit distributions of belief about key efficacy / safety endpoints
  - There are formal, well-tested protocols
  - Not required to fully borrow elicited distribution
  - May be used as portion of prior or down-weighted
- Elicit distributions about belief in relationships between endpoints, doses, populations, etc.
- Can use to inform about relevance of historical information

Some Best Practices

- Develop a prior elicitation **protocol** ahead of the elicitation exercise
  - **Endpoints** to elicit, **populations** to elicit, **questions** that will be asked, **who** are the experts (+ Individual vs group?)
  - How will answers to questions be mapped to parameters/distributions?
- Review protocol with experts ahead of time and conduct careful **training** on elicitation
  - Agreement on the objectives
  - Clear endpoints with common, agreed-upon definitions/timepoints
  - Clarity on compounds that will be elicited (e.g., will placebo also be elicited)
- Allow expert to **interactively adjust** prior inputs during elicitation
  - Only while working on the elicited distribution(s)
  - NOT after calculating how the belief translates into probability of success
- If individual, have group follow-up on aggregate findings so that the value of the exercise may be better understood
- Note there's actually a robust literature on the topic of prior elicitation

Example Elicitation Results



Many unexpected benefits!

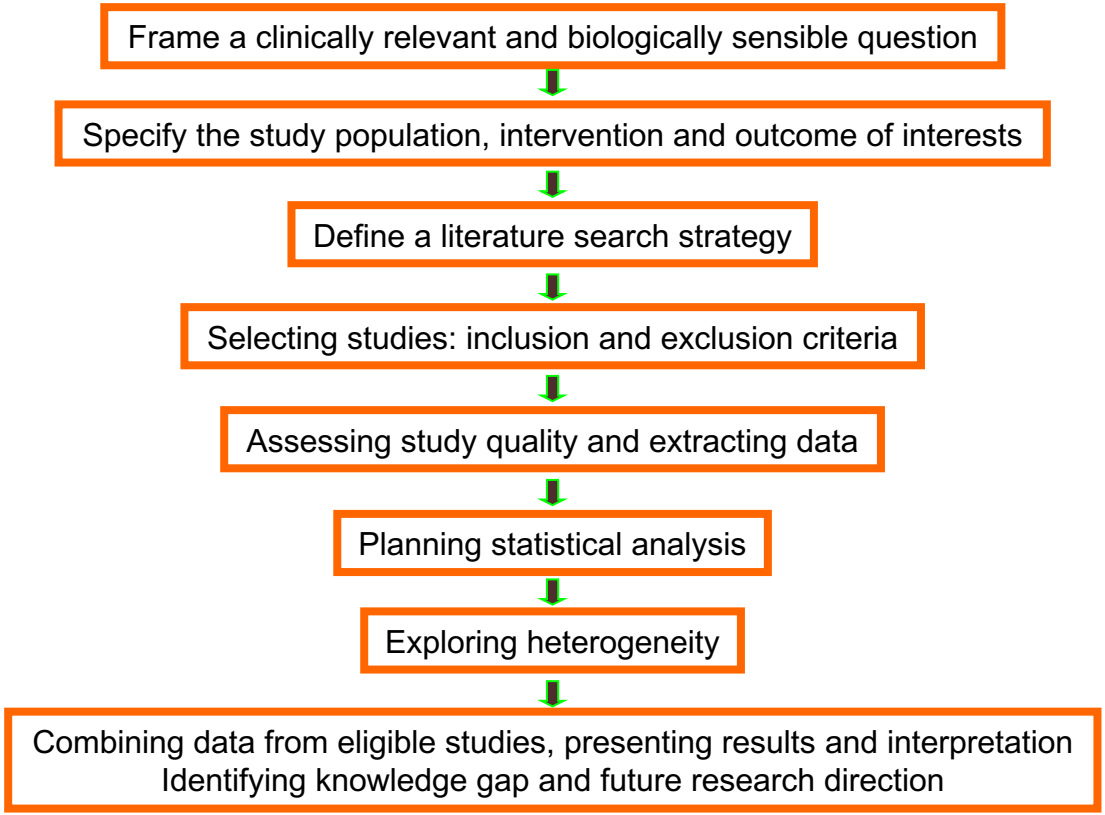
Provides transparency and open discussion of beliefs / use of available data

Synthesis of Data

Why use Bayesian statistics for meta-analysis?

- Natural approach for accumulating data / meta-analysis
- Unified modeling and the ability to explore a wide range of modeling structure
  - Synthesis of evidence from multiple sources / multiple treatments
- Formal incorporation of other sources of evidence by utilizing prior distributions for modeling unknowns. e.g.
  - Ability to incorporate prior information regarding background event rates
  - Ability to model between-study variability properly in random effects models
- Probability statements about true effects of treatment answer questions of interest

Planning of systematic review and meta-analysis

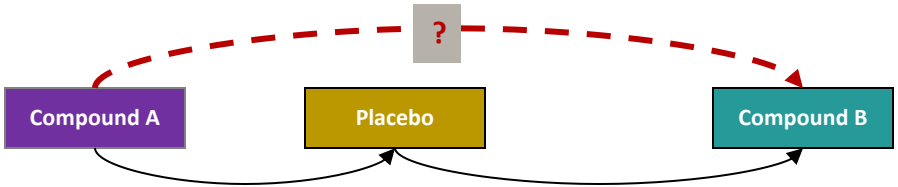


Network Meta-Analysis (NMA)

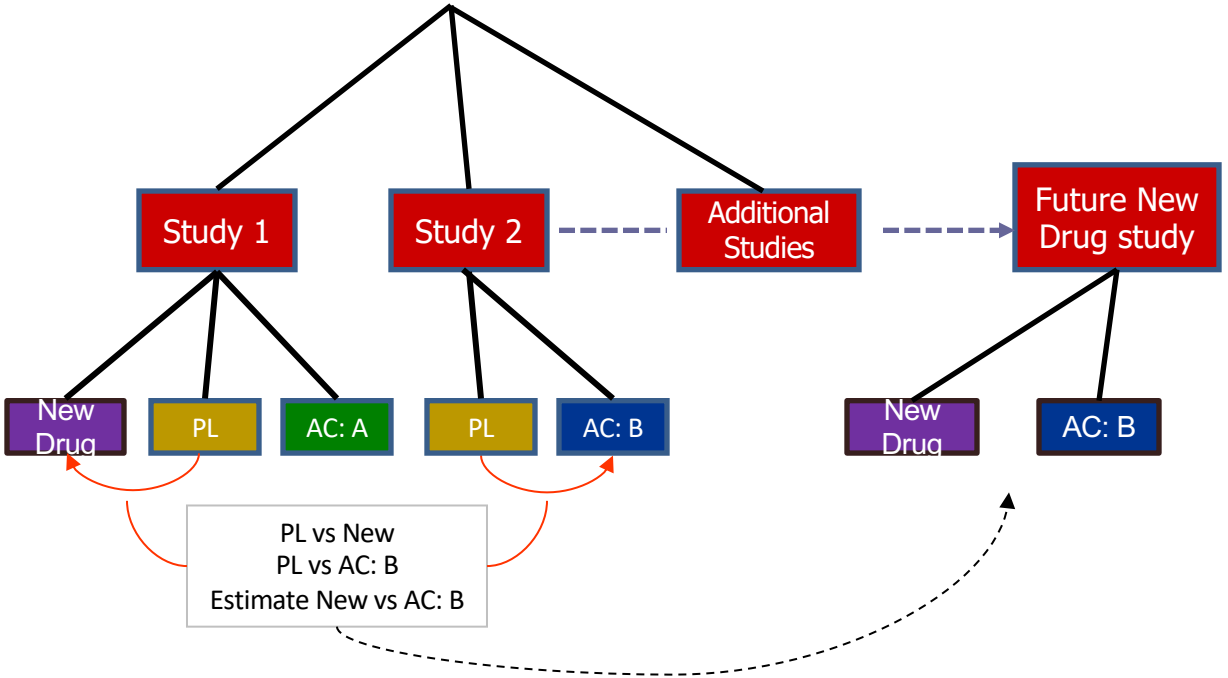
- Combines direct and indirect information from multiple studies on multiple treatments
- Maintains study-level randomization
- Important for variety of decision makers, including patients, physicians, industry and payers
- Estimate relative treatment effects between multiple treatments
- Bayesian approach provides probabilities relative treatment effect achieves clinically meaningful margins
- Allows ranking and probability each treatment is “best”
- Used to predict probability of success in future studies

Need for NMA

- Active Comparator (AC) trials typically require larger sample sizes
  - In Phase 2, large sample sizes may be prohibitive
  - For Phase 3 and 4, information on ACs is needed to guide the plan
- Only indirect evidence of AC performance may be available



Pictorial Representation of NMA



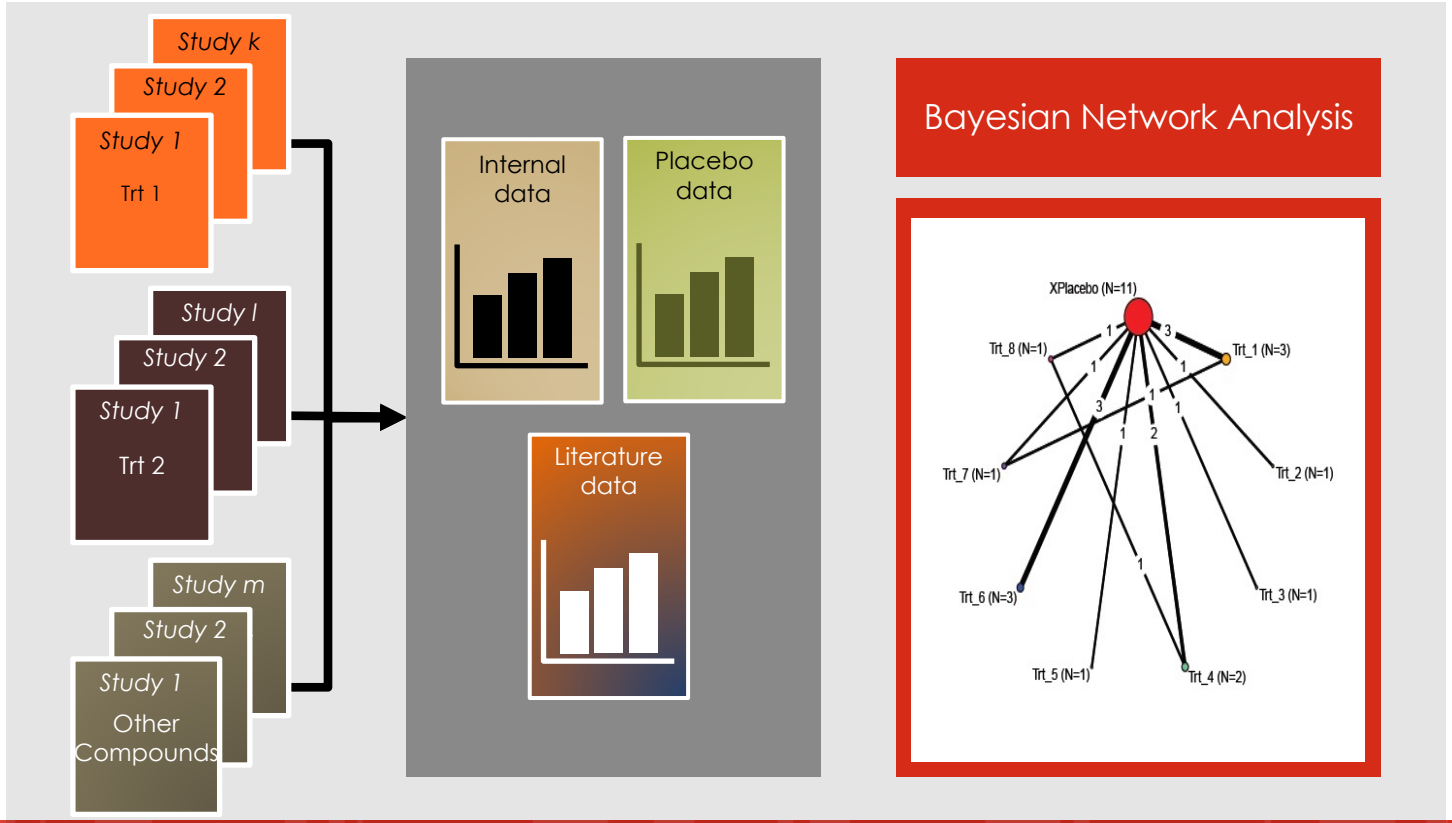
Many utilities of NMA

- Simulation of future studies
- Define clinical relevance
- Evaluate comparators
- Health technology assessments
- Influence drug development
- etc…

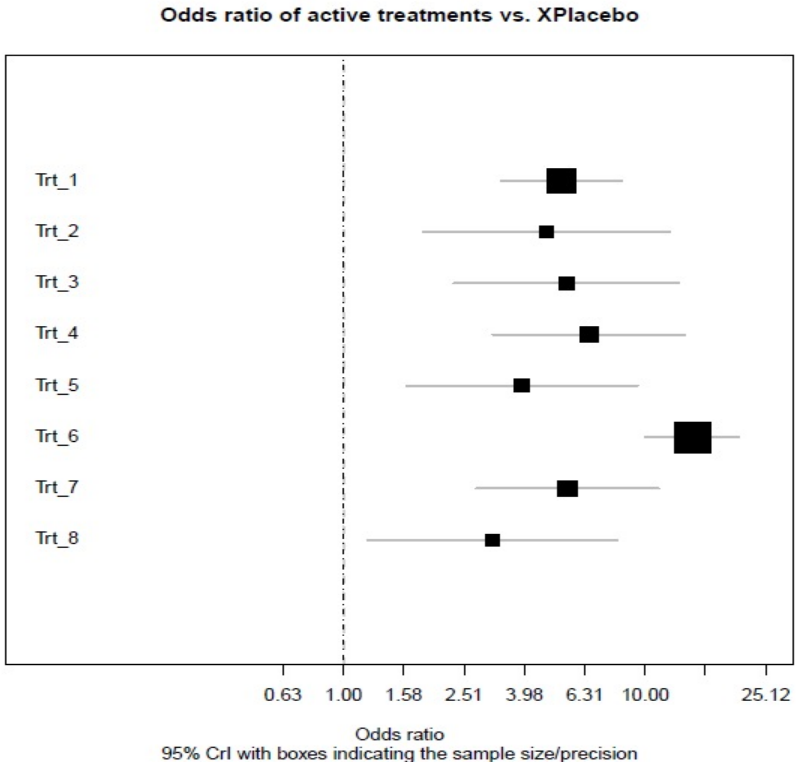
Key assumptions

- Homogeneity: similarity between trials
- Consistency: the similarity between direct and indirect evidence
- Assessment of the assumptions is vital to ensure results are valid and interpreted appropriately
- Methods to assess key assumptions exist

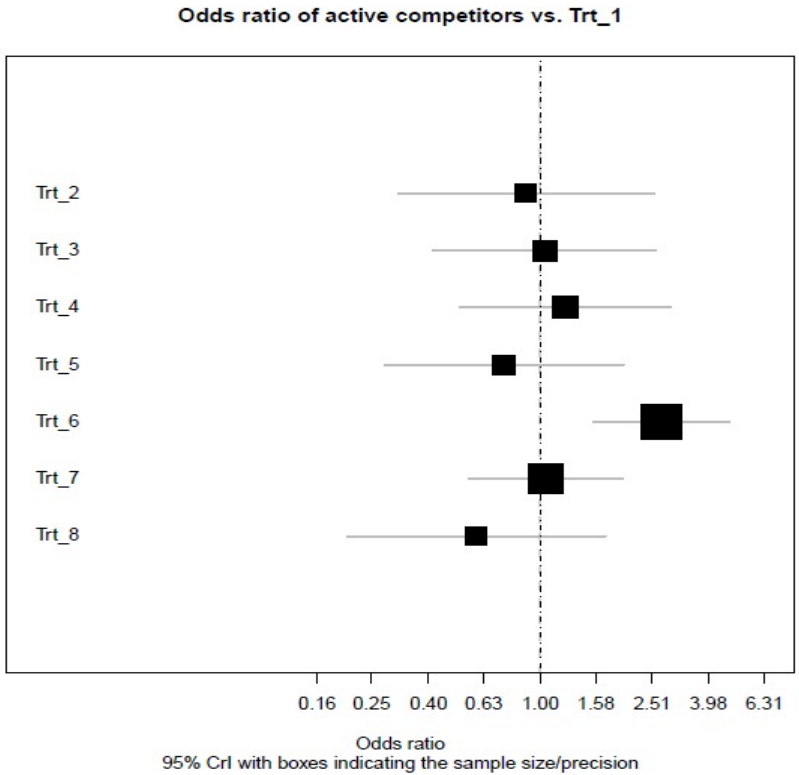
Example: Rheumatoid Arthritis (RA)



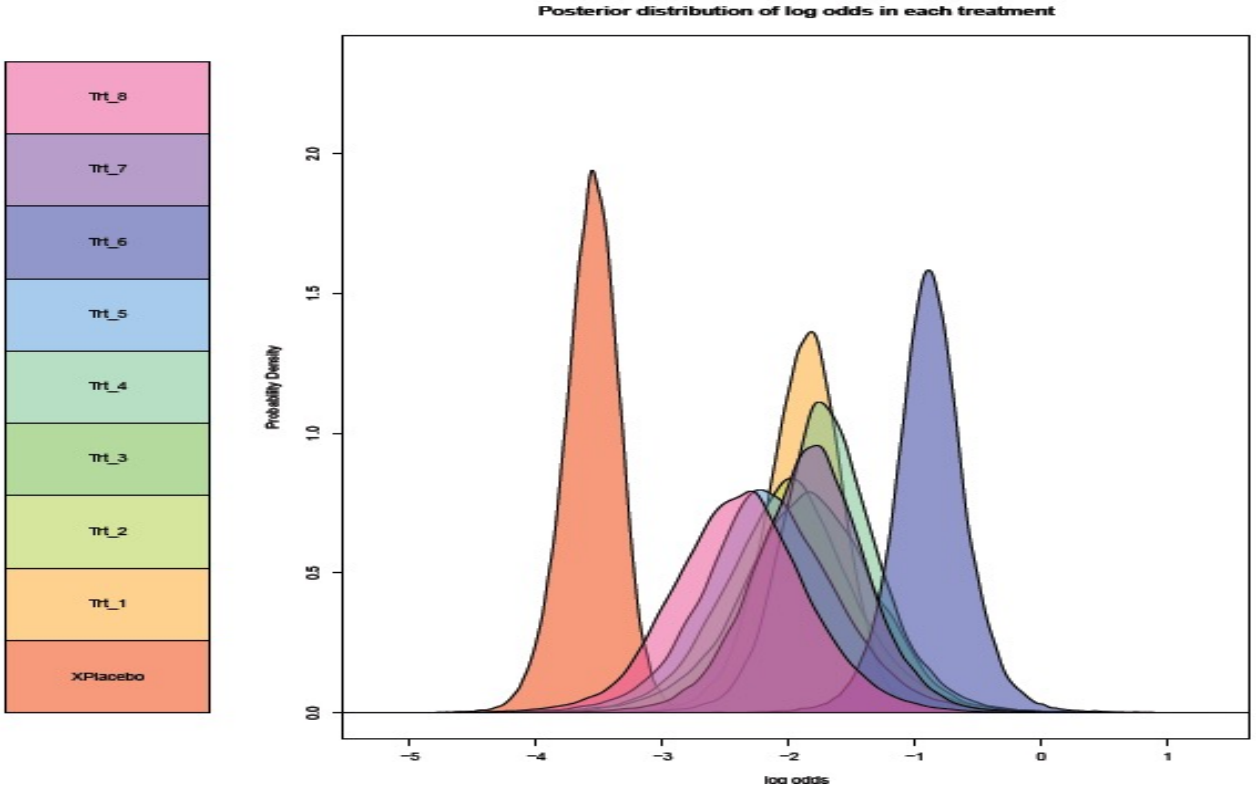
RA case example:
Forest plot (relative to placebo)



RA case example:
Forest plot (relative to treatment 1)



RA case example:
Posterior distributions of effect



RA case example: Examples of Key Summaries

Parameter	Posterior Mean	Posterior SD
Odds ratio (Pbo,1)	5.43	1.30
Odds ratio (Pbo,2)	5.33	3.20
Odds ratio (Pbo,3)	6.02	2.74
Odds ratio (Pbo,4)	7.02	3.38
Odds ratio (Pbo,5)	4.34	2.14
Odds ratio (Pbo,6)	14.58	2.72
Odds ratio (Pbo,7)	5.89	2.14
Odds ratio (Pbo,8)	3.54	2.18
Odds ratio (4,5)	0.70	0.40

Pbo = placebo

Treatment	Prob(best)
Placebo	0.000
1	0.000
2	0.018
3	0.016
4	0.027
5	0.004
6	0.929
7	0.005
8	0.001

Utilization of Priors for Design/Decision Making

CSF Probability Statements

- CSFs use a posterior distribution to calculate the probability that a treatment effect exceeds some minimal effect of interest **(EOI)** conditional on the data/prior.
- The CSF is "met" if we achieve high confidence (specified by **PrTH**, between 0 and 1) that the treatment effect is greater than the **EOI**
- **Usual (frequentist)**: focus on statistical significance:
  - *'Drug X was associated with statistically significantly higher response rate compared to Drug Y (2-sided p-value < .10)'*
- **Bayesian CSF**: a direct statement of confidence:
  - *'Given the observed data, we are 75% sure that the true response rate for Drug X is at least 10% higher than that for Drug Y'*

$$\Pr(\Delta_{X \to Y} > EOI \mid Data_{X \to Y}) > PrTH$$

True treatment effect

Effect of interest

Probability threshold

CSF Specification

- EOI: often a highly cross-functional discussion
  - What's the minimally clinically meaningful effect-size?
  - What's the precedence historically?
    - Bayesian meta-analysis or NMA could inform an uncertainty distribution for EOI (not just a fixed value)
  - What kind of effect for the POC endpoint could translate to Ph3 success based on a different endpoint?
- PrTH: carefully calibrated via simulation
  - Control of error rates of interest
  - Linked directly to PrSS (CSF 'met' → high chance of Ph3 study success)

$$\Pr(\Delta_{X \to Y} > EOI \mid Data_{X \to Y}) > PrTH$$

Some Considerations

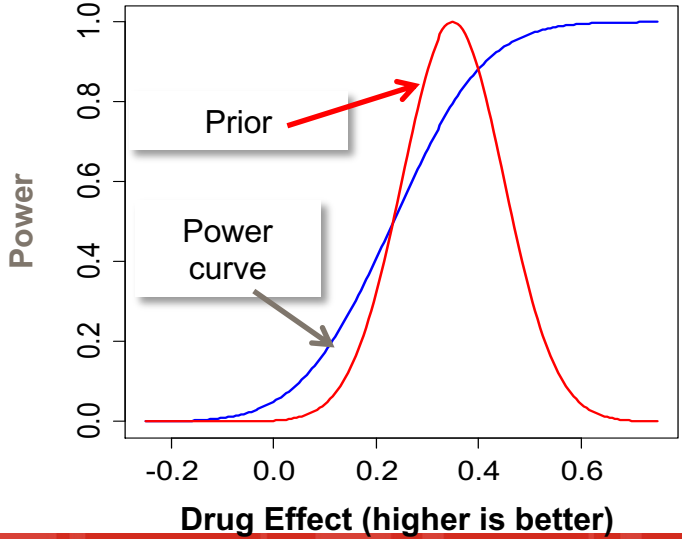
- Prior distributions used to calculate success/failure probabilities require careful consideration
- Key elements of prior data and study(ies) of interest need to best reflect study being designed
- A priori documentation of prior construction is important
- Relationship between endpoints needs to be modeled
- Consider discounting and/or inflating variability to accommodate shifts across phases (see, e.g., Kirby et al 2012)

Probability of Study Success (PrSS)

- Hypothesis test $\phi_\alpha(X) = \begin{cases} 1 \; if \; X \in R_\alpha \\ 0 \; if \; X \notin R_\alpha \end{cases}$ with rejection region R_α indexed by α (prespecified Type I Error probability)
- Power is $\beta_\alpha(\theta) = E_\theta[\phi_\alpha(X)]$ where $X \sim f(\theta)$ (some presumed density/mass function)
- In designing a clinical trial, we select sample size/events such that $\beta_\alpha(\theta_A) = \beta^*$ (=85%, say)
- β_α and θ_A are simply calibration tools which help to qualify the precision to be delivered by a given design/sample size
- θ_A may have no basis in reality and $\beta_\alpha(\theta_A)$ cannot be interpreted as Pr(Study Success)
- Pr(Study Success) = Pr($\phi_\alpha(X) = 1$) is a critical input for portfolio management (and even trial design)…how do we get this?

Probability of Study Success (PrSS)

- Strive to characterize 'all' direct/indirect evidence regarding θ
  - Uncertainty distribution $\pi(\theta)$
  - $\pi(\theta)$ may be a posterior distribution from Ph2, say: $\pi(\theta \mid X_{Ph2})$
    - Perhaps mapped from a surrogate endpoint (or distinct but related population)
  - $\pi(\theta)$ may be an expert elicited 'prior'
- PrSS = $\int \phi_\alpha(x)\, f(x|\theta)\, \pi(\theta) dx\, d\theta = \int \beta_\alpha(\theta)\, \pi(\theta)\, d\theta$
- Easy to evaluate via simulation:
  1. Draw a sample of the underlying parameter $\theta^* \sim \pi(\theta)$
  2. Draw a sample of the data $X^* \sim f(x|\theta^*)$
  3. Store $\phi_\alpha(X^*)$
  4. Repeat and count how many $\phi = 1$

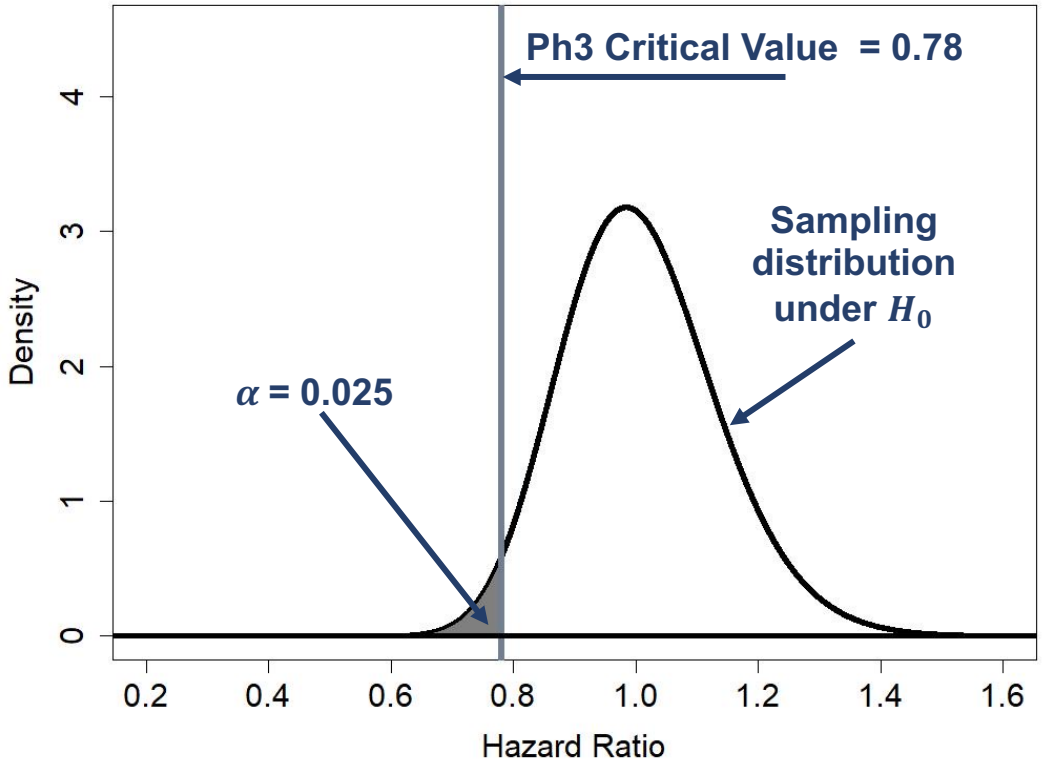


PrSS Easy Example

- Effect-size of interest: hazard ratio (HR) comparing some treatment vs. control
- Available data from Phase 2 trial:
  - Observed Phase 2 HR = 0.70 based on 100 events
- We now need to plan for Phase 3 which will be designed to target 250 events, say. Further assume:
  - ✓ Same endpoint as Ph. 2
  - ✓ Same population as Ph. 2
  - ✓ Same treatments as Ph. 2
- We want to test for the following hypothesis: H_0: HR = 1 vs. H_a: HR ≠ 1
  - Pre-specified one-sided significance level of α = 0.025

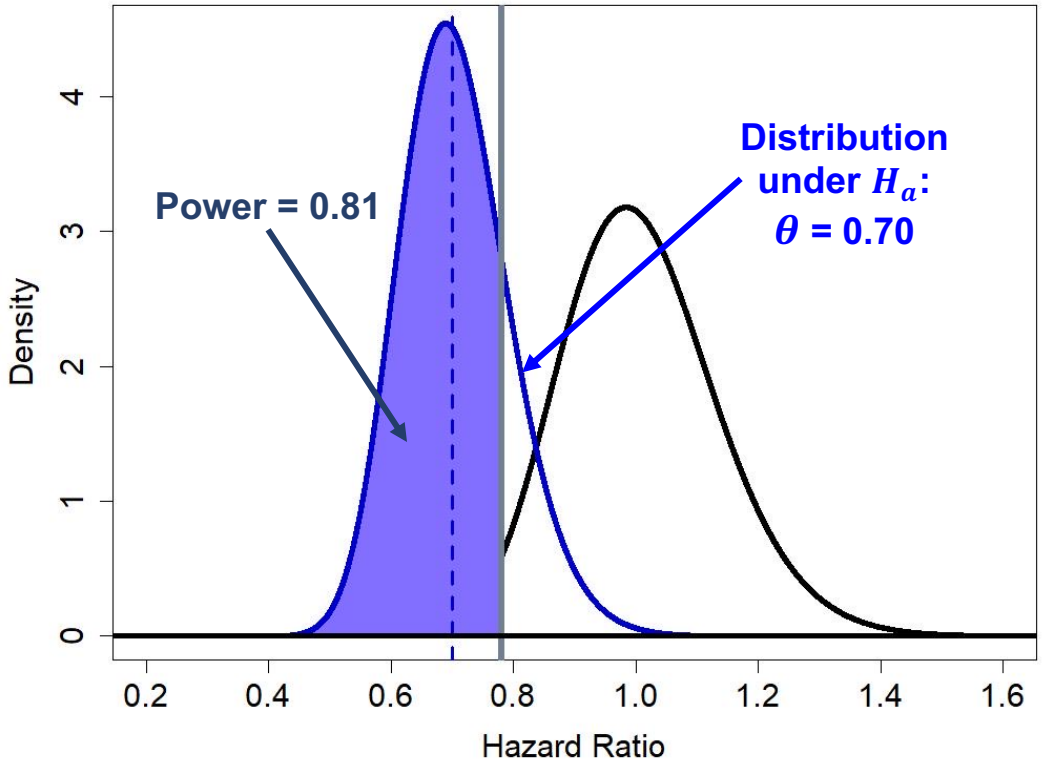
PrSS Easy Example

- The rejection region for the hypothesis test is determined by the pre-specified significance level $\alpha = 0.025$
- H_0 is rejected for any value of HR that lies below the critical value of 0.78



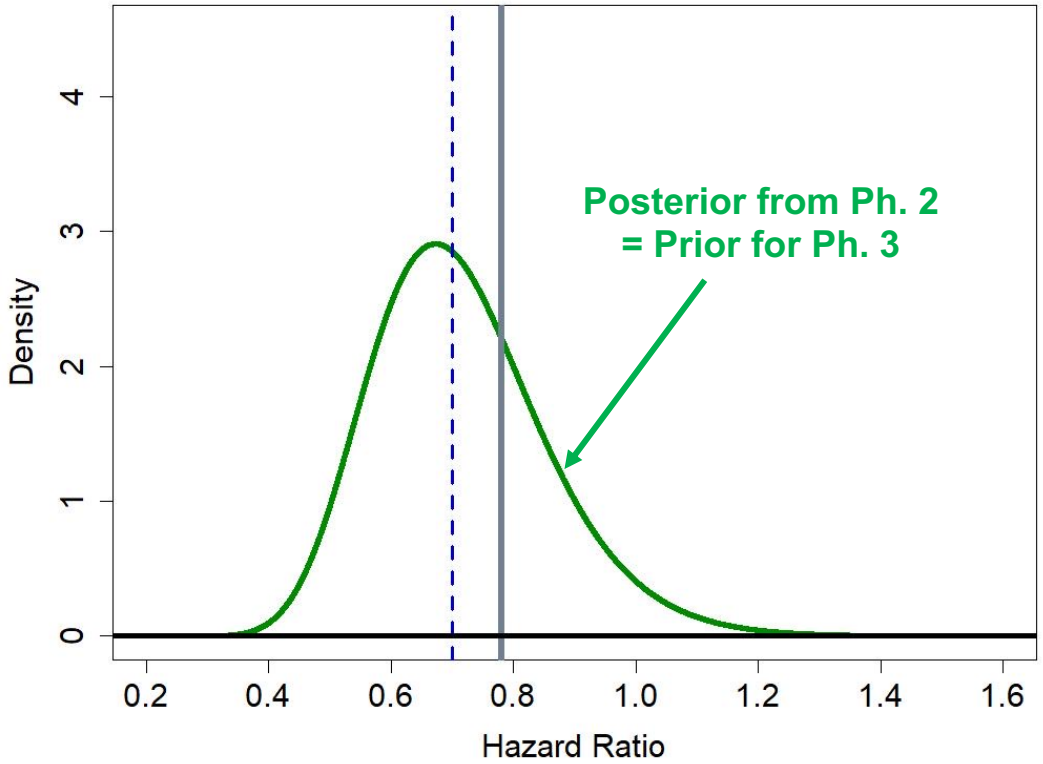
PrSS Easy Example

- Recall definition of **power**: $\beta_\alpha(\theta) = E_\theta[\phi_\alpha(X)]$, where $X \sim f(\theta)$
- Compute power at the observed Ph2 HR = 0.70
- $\beta_{\alpha=0.025}(\theta = 0.70) = 0.81$



PrSS Easy Example

- Recall definition of **PrSS**:
  $\text{PrSS} = \int \beta_\alpha(\theta)\, \pi(\theta)\, d\theta$
- This can be expressed as:
  $\text{PrSS} = \int \text{P}(\text{study success}|\theta)\, \pi(\theta) d\theta$,
  where
  - θ is the treatment effect or HR
  - $\text{P}(\text{study success}|\theta)$ is the power function at a fixed θ
  - $\pi(\theta)$ is the posterior distribution using data from Ph. 2 = $\pi(\theta \mid X_{Ph.2})$, which serves as a prior in this setup



PrSS Easy Example

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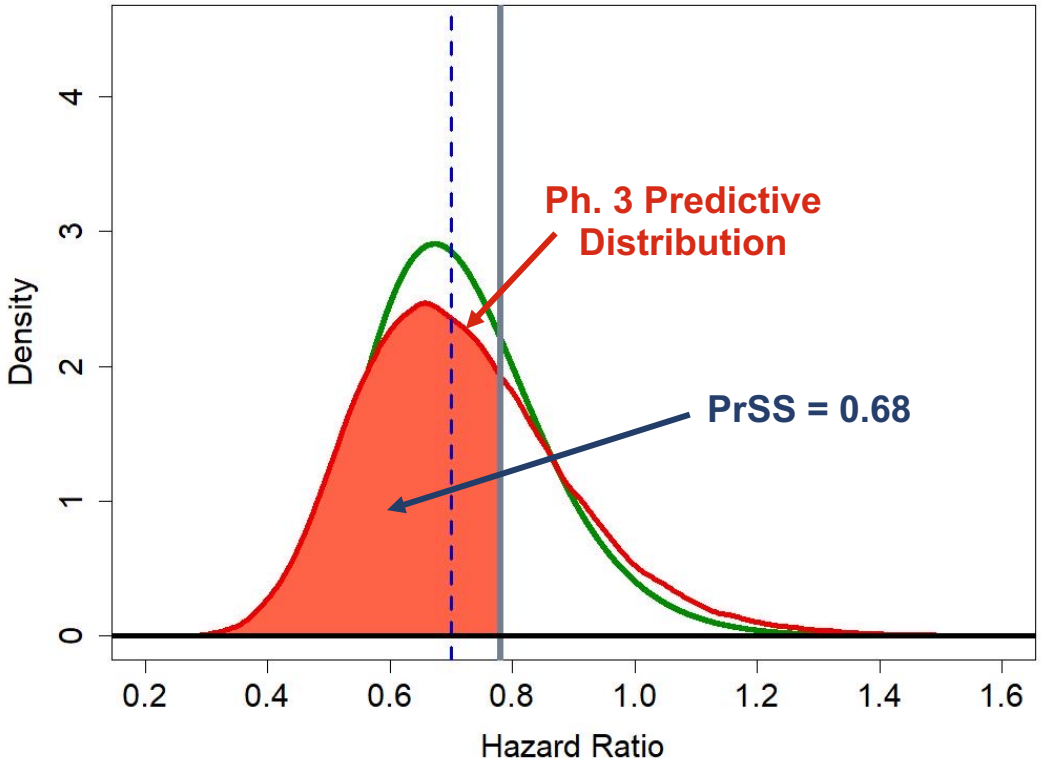
- $PrSS = 0.68$



PrSS Easy Example

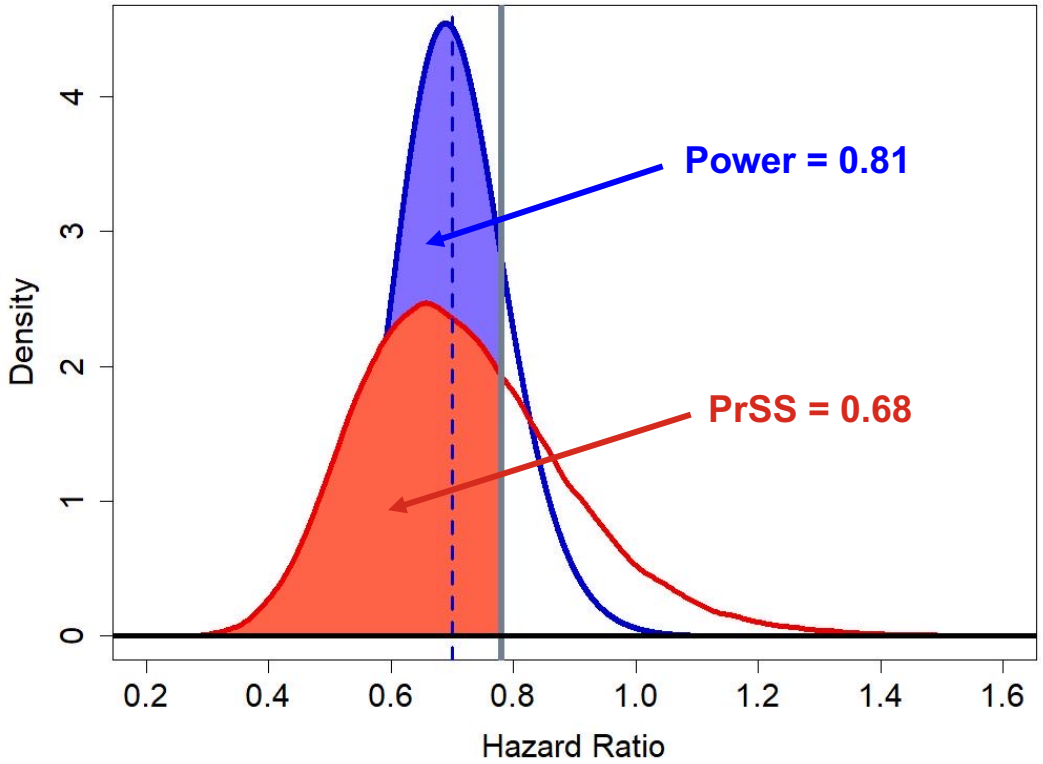
- Note the difference:

Power is the probability of study success, i.e., achieving statistical significance, at an assumed fixed effect size ($\theta = 0.70$).

$$\beta_{\alpha=0.025}(\theta) = 0.81$$

PrSS uses available data (observed Ph. 2 data) to derive the distribution of the unknown true treatment effect, and then average the power function of the new study over the distribution.

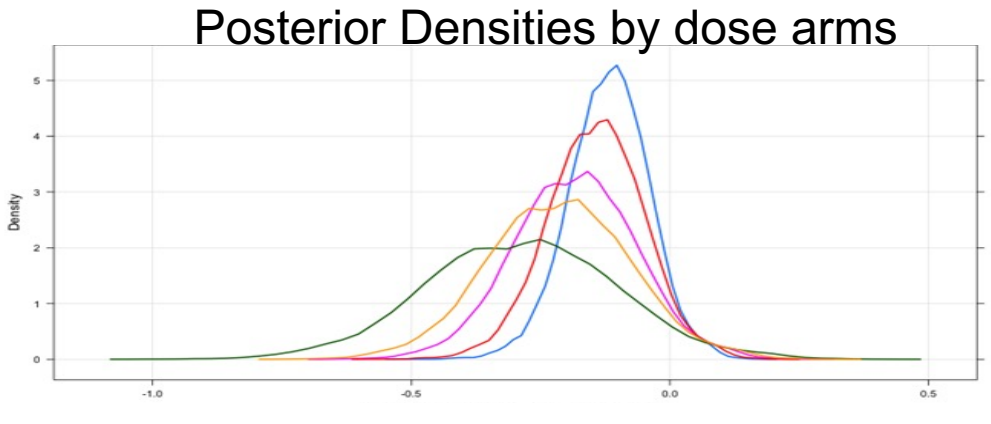
$$PrSS = 0.68$$



PrSS Challenges and Additional Considerations

- Even in ‘easy’ example, consider: what other information should be captured in prior (besides Ph2)?
  - Data from other molecules in same/similar class
  - Other Ph2 endpoints (joint model)
  - Some basis for ‘adjustment’ (Ph2 → Ph3)
- Other (more) common situations:
  - Single arm study (especially in oncology…think Ph1b expansion cohort)
    - Couple with prior based on historical control outcomes (perhaps via meta-analysis)
  - Ph2 endpoint ≠ Ph3 endpoint
    - Correlative analysis to produce mapping
    - Joint modeling (e.g. PFS + immature OS + historical correlation)
- No direct POC data? → Prior elicitation

Evaluate Results from Phase 2 Surrogate Endpoint



Summary of critical success factors for high dose using non-informative prior

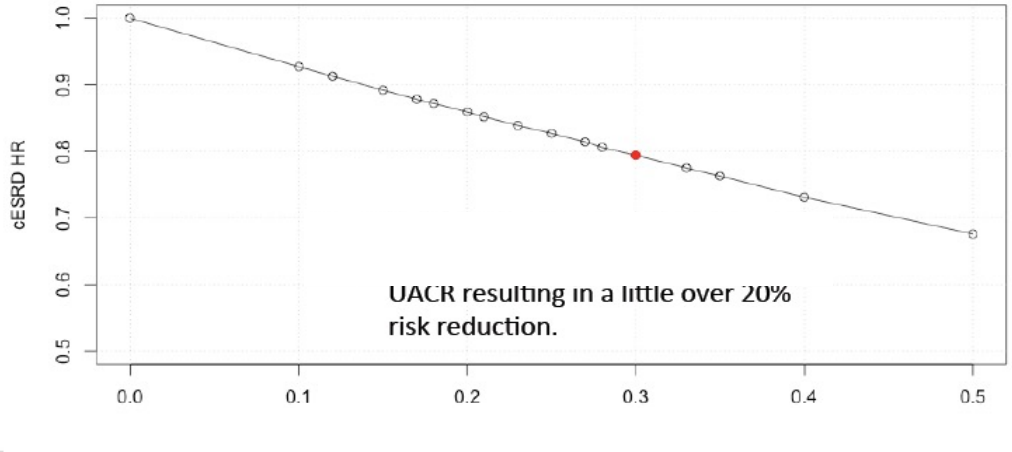
Timing of surrogate EP	Posterior Mean Treatment Effect	Pr(PBO –LY > 0)	Pr(PBO –LY > 0.2)	Pr(PBO –LY > 0.3)
24-week	-0.14	0.82	0.35	**0.15**
12-week	-0.22	0.95	0.54	**0.27**

- Surrogate, highly variable endpoint
- Lower is better
- Showing 12-week endpoint results
- Significant variability

Likely to be better than 0 but not likely to be competitive

Phase 3 Probability of Success

- The posterior of phase 2 and the relationship to phase 3 endpoint is used to obtain phase 3 prior



- **Estimated phase 3 endpoint and calculated probability of success, accounting for multiple sources of uncertainty with phase 2 data**
- **Demonstrated probability of success low**
- **Convinced decision makers not to proceed to phase 3**

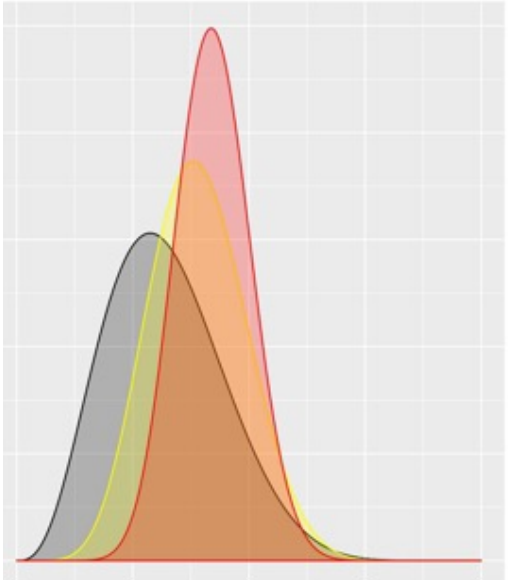
EXAMPLE:
Synthesis of Information Following Phase 2 Trial in SLE

Synthesis of Information Following Phase 2 Trial in SLE

- Systemic Lupus Erythematosus (SLE)
  - Inflammatory disease damaging various body systems (including joints, skin, kidneys)
  - Characterized by sudden worsening of symptoms or flares
- Primary endpoint: SRI-4 response
  - SRI – composite index that assesses disease activity in SLE
  - SRI-4 response defined as ≥ 4 improvement from baseline disease activity score and no worsening in physician's global assessment

- Example: real modeling and simulation to support Ph3 decisions using Ph2 data
  1. Creation of prior distribution
  2. Phase 3 simulation
- Two types of priors used in example:
  - **Analysis priors:** used in data analysis models
  - **Design priors:** represent expectation and uncertainty of treatment response, used for trial simulation

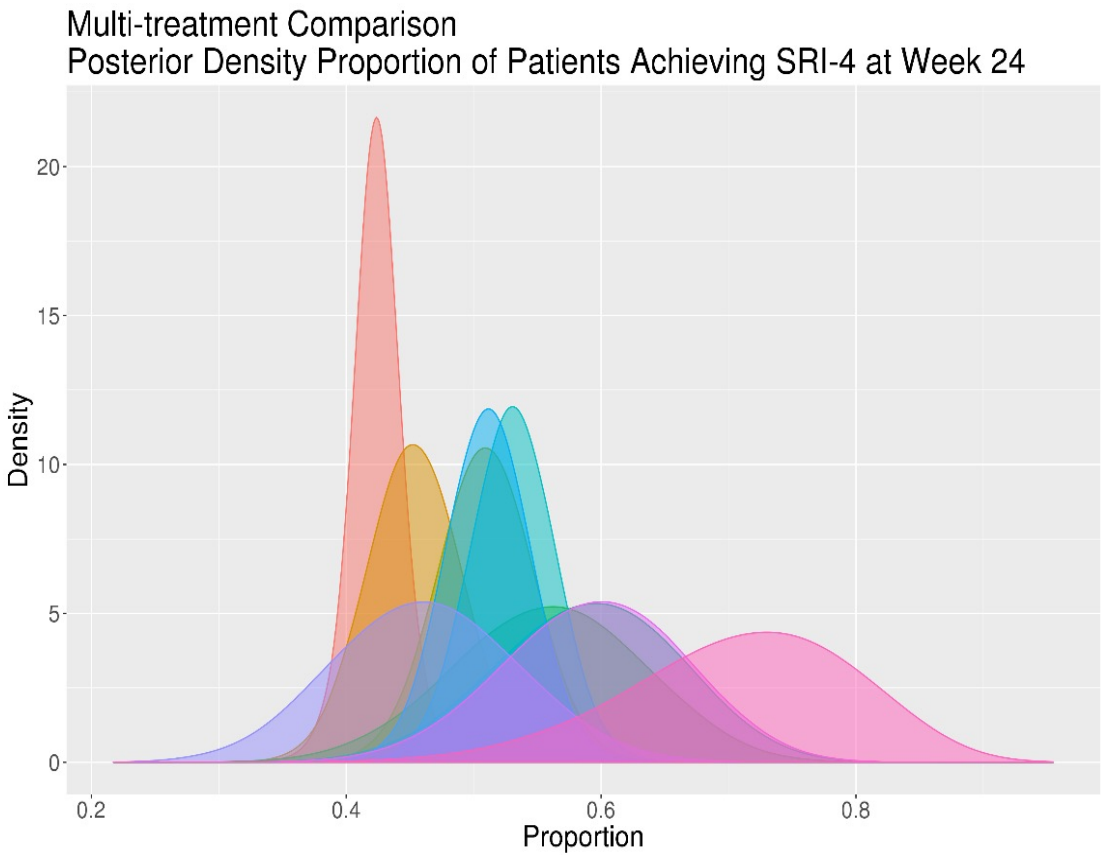
SRI-4 Elicited Priors

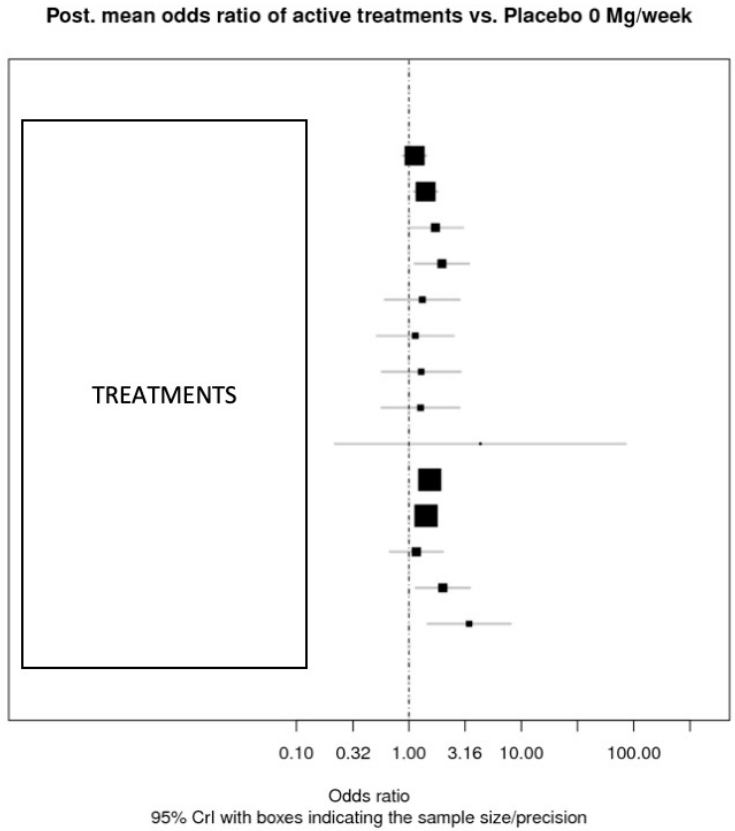


Combined Expert Prior Distributions:
SRI-4 Response Rate

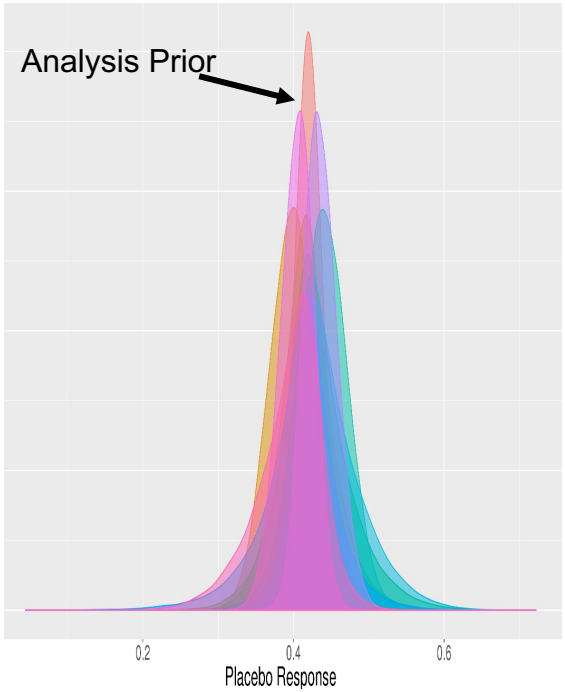
- Priors for study treatments and PBO elicited from experts familiar with treatment MOA and SLE
- Represents expert knowledge prior to running Ph2 study
- Initially used for decision-making and design of Ph2
- Employed in this example as informative analysis prior in Ph2 model

SLE Bayesian Network Meta Analysis (BNMA)





Creating Ph3 Design Priors Using Available Evidence

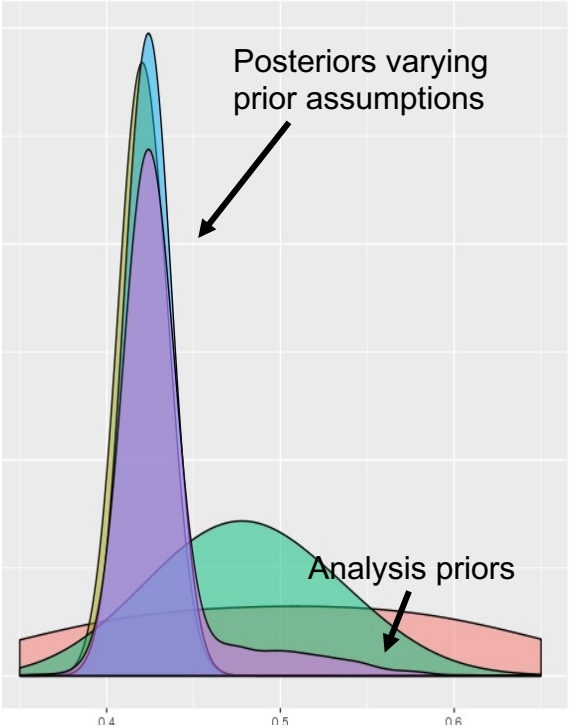


Historical PBO Distributions: SRI-4

Left: Historical PBO distribution, peaked distribution is from BNMA

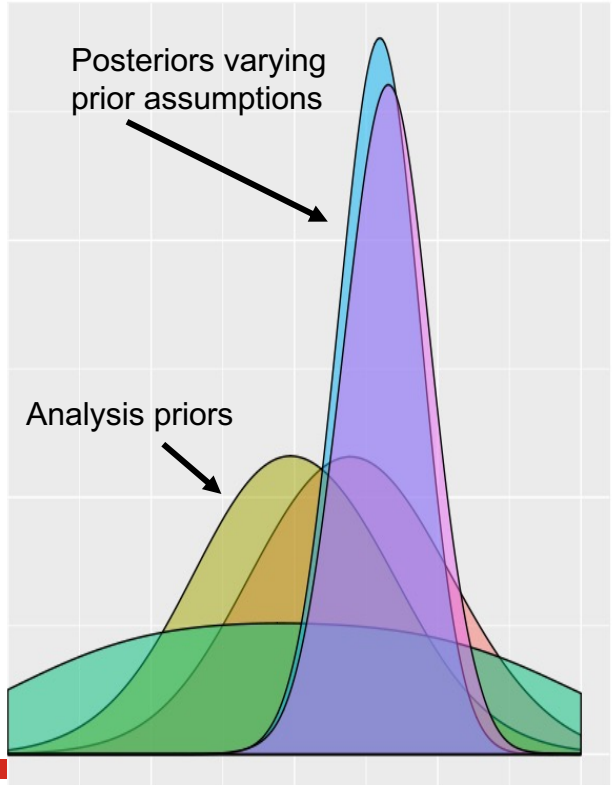
Right: Posterior distributions created using various analysis priors

Design prior (purple) from mixture prior using BNMA and diffuse distributions



PBO: Priors and Ph2 Posteriors

Creating Ph3 Design Priors Using Available Evidence



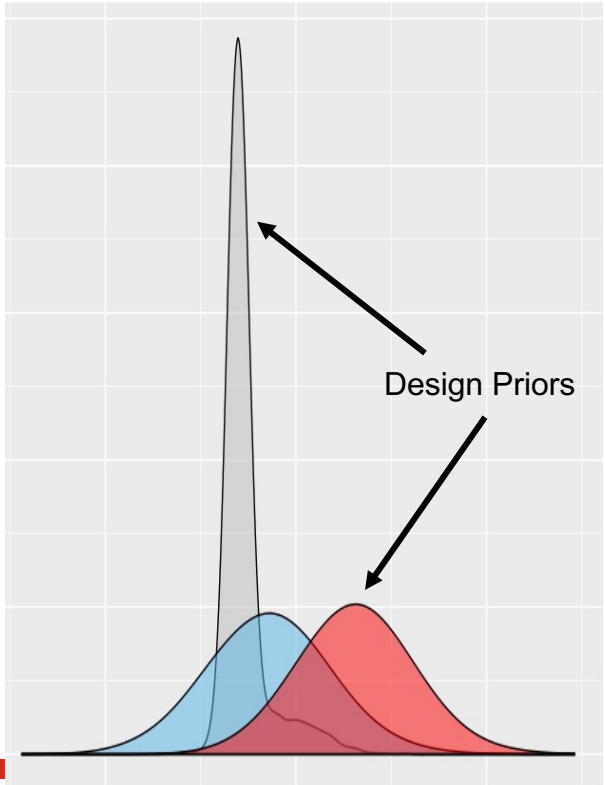
TRT: Priors & Ph2 Posteriors

Left: Posterior distributions created using various analysis priors

Design prior (blue) from mixture prior using elicited, pessimistic and diffuse priors.

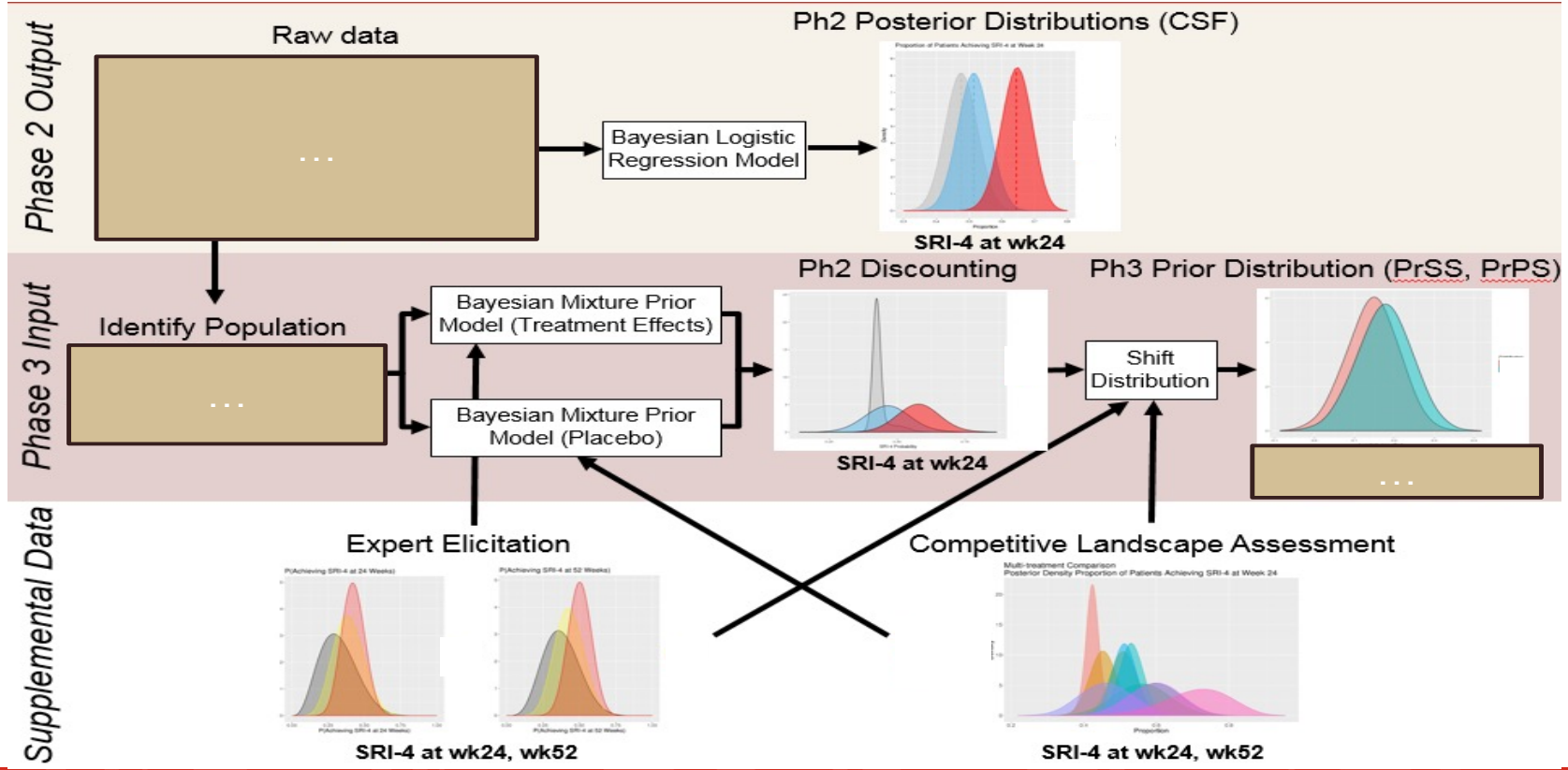
Additional adjustments included for endpoint time and study population included

Right: Final design priors for PBO and TRT



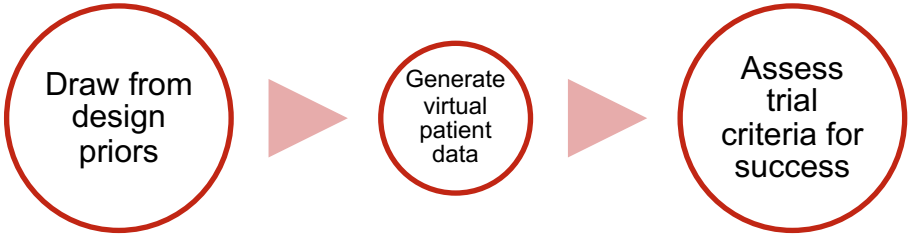
Design Prior Distributions: SRI-4

SLE Analytics Flowchart: Incorporation of Available Data/Information & Quantification of Key Uncertainties



Phase 3 Simulation

- Candidate phase 3 trial designs simulated using design priors to generate patient response data
- Simulation process (repeat many times):



- Example simulation results:

Design	prSS – Primary	prSS – Secondary 1	prSS – Secondary 2
1	75%	60%	50%
2	65%	50%	45%

Design tradeoffs on cost, time, etc. can be assessed using prSS results

Formal Borrowing of Prior Data

Borrowing Approaches

- Borrowing can be on control arm and/or treatment arm(s)
  - Arm-level information only or effect-size
- Static vs Dynamic
  - **Static**
    - Pooling
    - Single arm trials
    - Power priors
  - **Dynamic**
    - 'Hierarchical' prior[1]: $\theta_1, \theta_2, \ldots, \theta_k \sim N(\mu, \tau^2)$
      - Really just an random-effects meta-analytic construction
      - Hyperprior on τ affects 'propensity' to borrow
    - Mixture priors[2,3]: $\theta \sim w \cdot \pi_1(\theta) + (1 - \mathrm{w}) \cdot \pi_2(\theta)$
      - Often π_1 is informative and π_2 is vague (e.g. 'robust' meta-analytic prior approach)
      - Many other mixture based approaches
- Static vs dynamic can differ for control/treatment

Appeal of dynamic borrowing:
- Borrows more when current data are similar to historical data
- Protects against over-borrowing in circumstances of prior/data conflict

[1]Viele, et al. (2014); [2]Schmidli et al. (2014); [3]Neuenschwander et al. (2016)

General Comments about Borrowing

- How much to borrow?
  - ✓ What data is eligible to be included in the prior
  - ✓ Currently need to simulate operating characteristics
  - ✓ Consider “prior effective sample size” and “prior probability of success”
  - ✓ Should assess prior to posterior sensitivity
- May borrow different amounts for different treatments, based on medical need, etc.
- Note, borrowing may ‘dampen’ the effect in current trial (so borrowing does not always favor Sponsor)

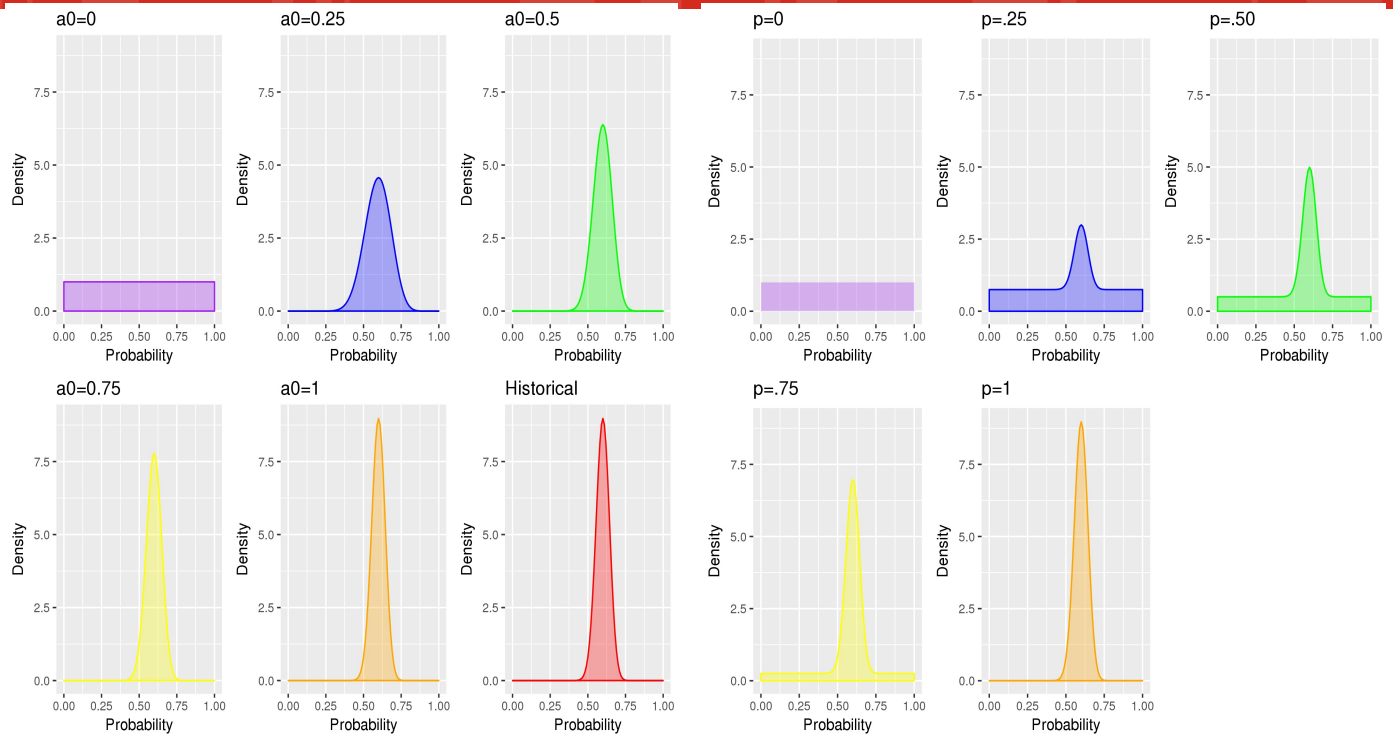
Suggestions available in CDRH/CBER Bayesian Guidance document

Examples of Borrowing Approaches

Example 1: Borrowing historical control

- Previous data is available on the control group.
  - Specifically, a trial with 120 subjects and 72 responses.
  - Thus the historical rate is 60%.
- This historical information is kept constant throughout the simulation.
- The sample sizes for the current study are 70 for the controls and 140 for the new treatment.

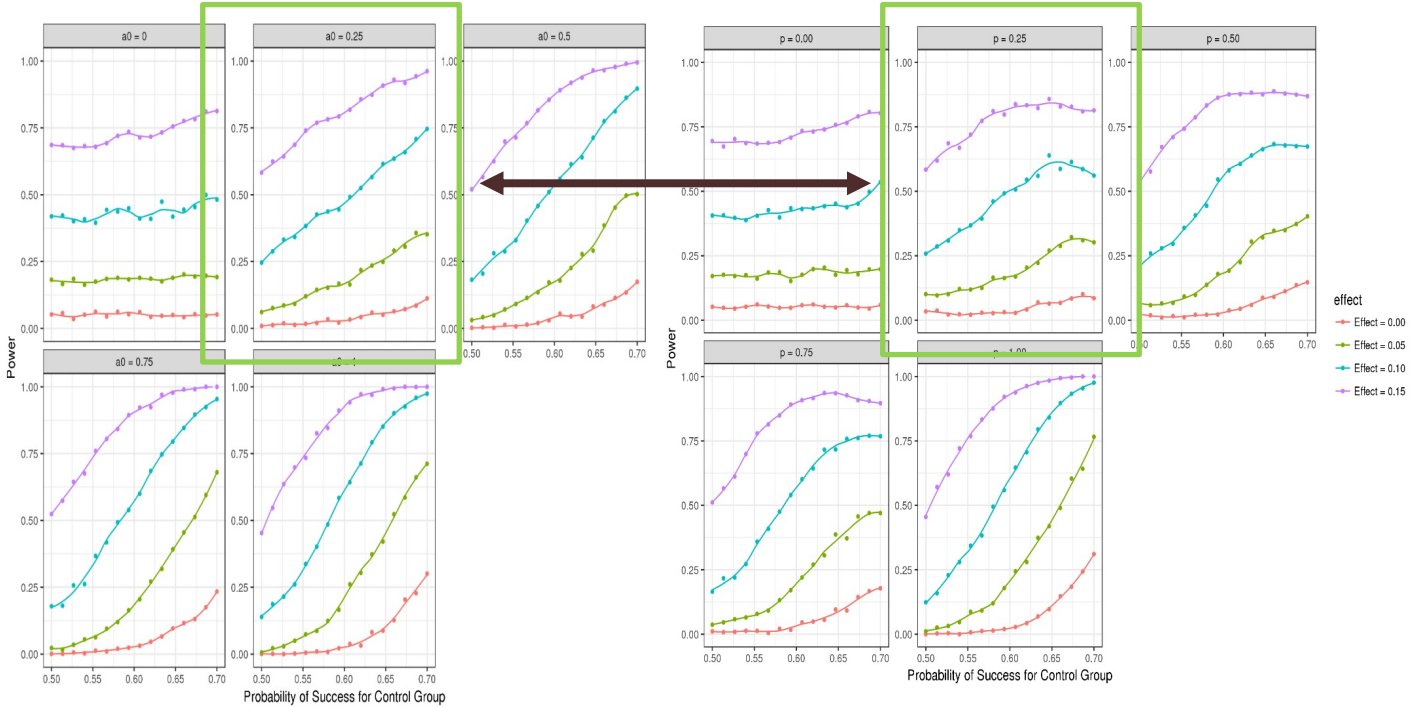
Example 1:
Power Prior vs Mixture Priors



Power prior with various α_0 values

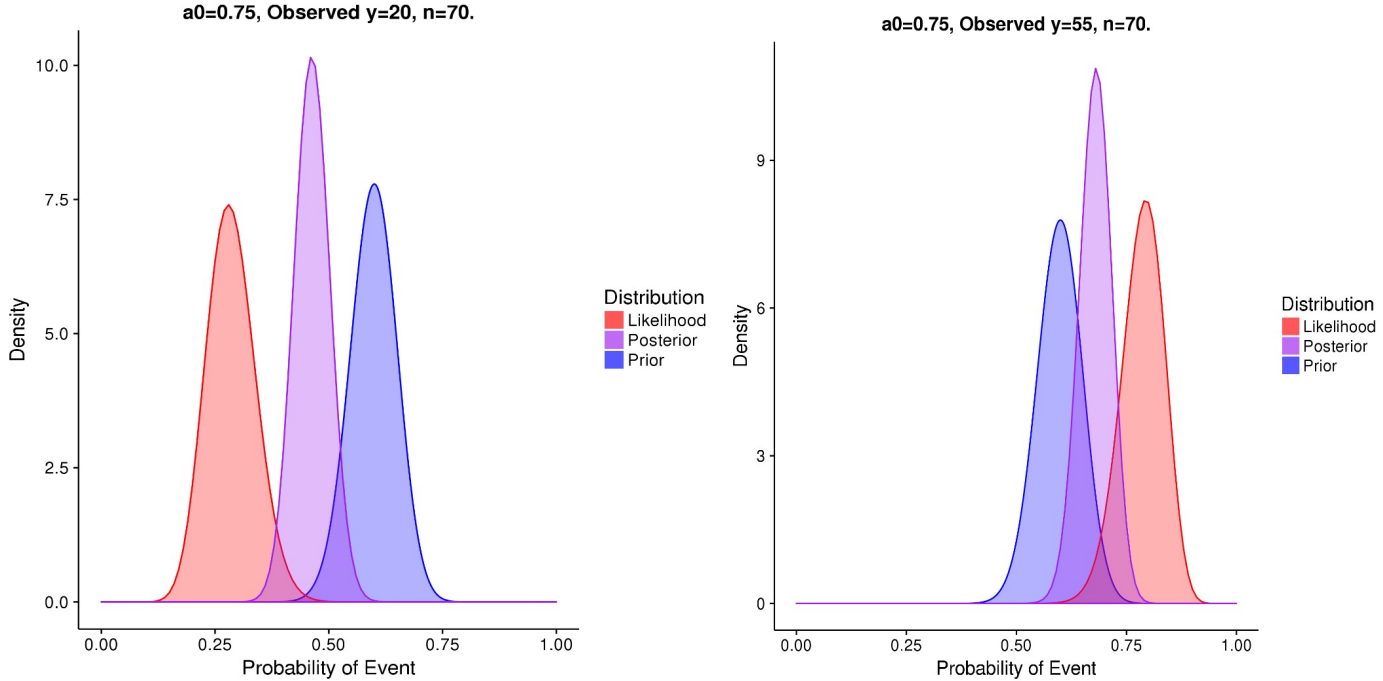
Mixture priors with beta(72, 48) and beta(1,1) at various mixing proportions

Example 1: “Power” Plots



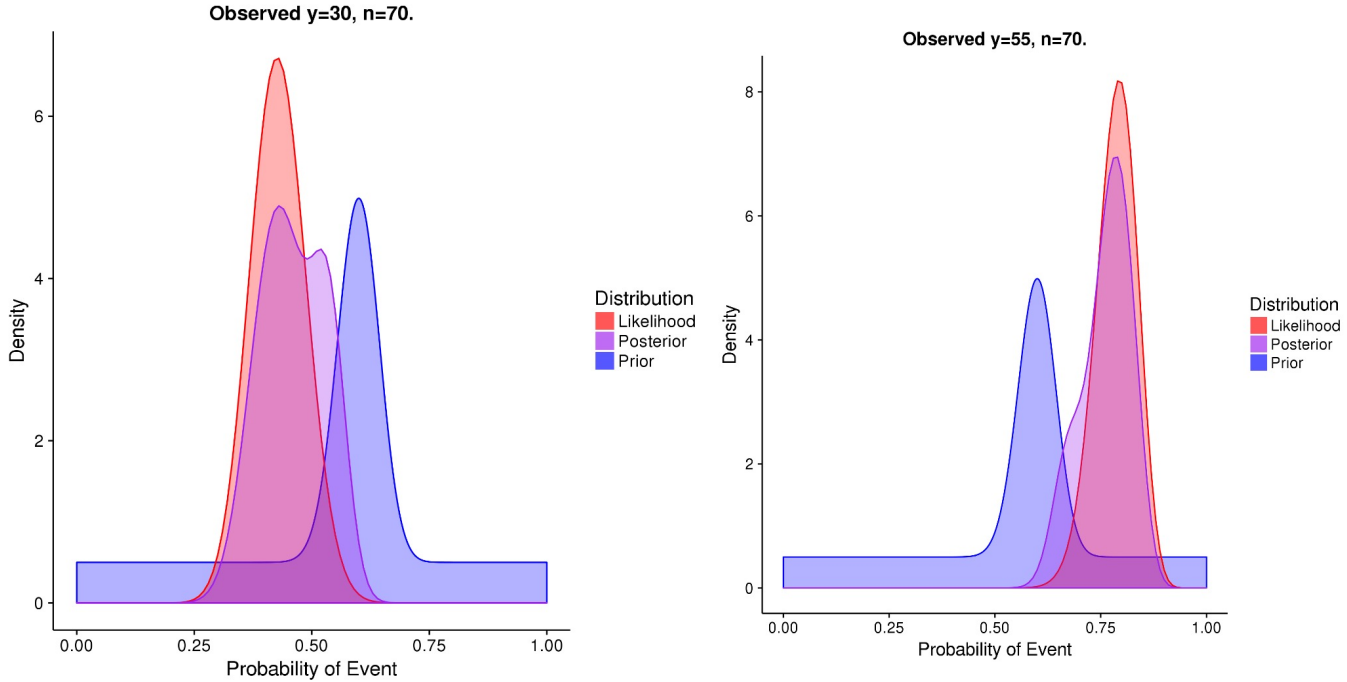
Plots of **power** for power priors (left) with various α_0 values and mixture priors (right) with various mixing proportions.

Example 1: Impact of Borrowing on Results



Plots of example posterior distributions for control arm, based on different trial outcomes, using power prior (α_0 = .75)

Example 1: Impact of Borrowing on Results



Plots of example posterior distributions for control arm, based on different trial outcomes, using mixture prior (p = .5)

Example 2: Dynamic Borrowing of Adult Data to Pediatrics

- We are considering a pediatric rare disease trial in 50 patients: 40 active, 10 placebo (pbo)
- Primary Endpoint is binary response variable
- We want to use all relevant information to focus on bringing valuable scientific information to patients, prescribers and regulators
  - ✓ Network Meta-Analysis of studies was performed
  - ✓ Drug of Interest was featured in one study in adults
- We consider the new trial successful if

$$P(\text{diff} > 0.4) > 80\%$$

Could be based on medical impact of disease, patient/prescriber input

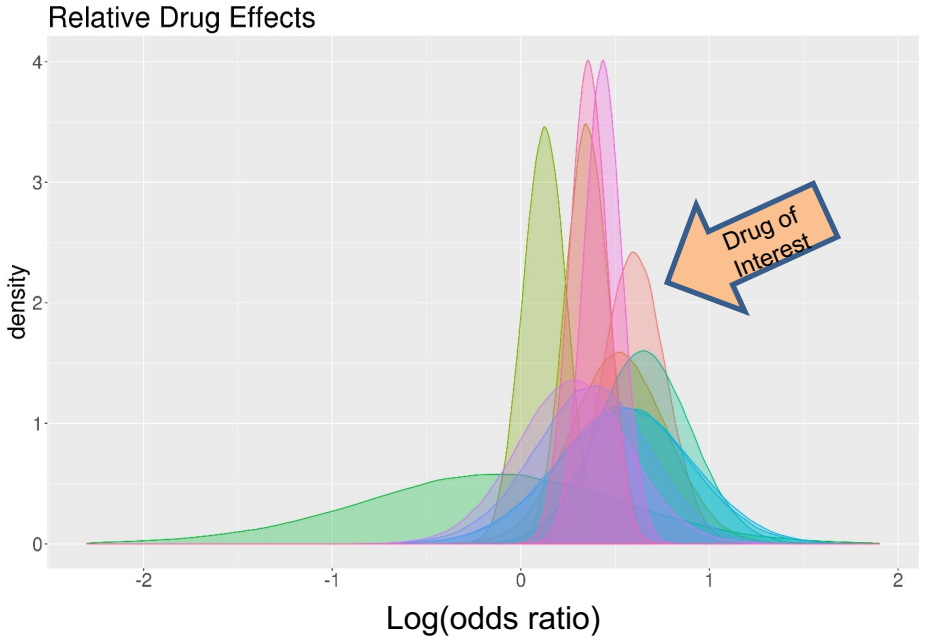
where diff is the difference in log odds for drug and pbo

Example 2: Historical Adult Placebo Data

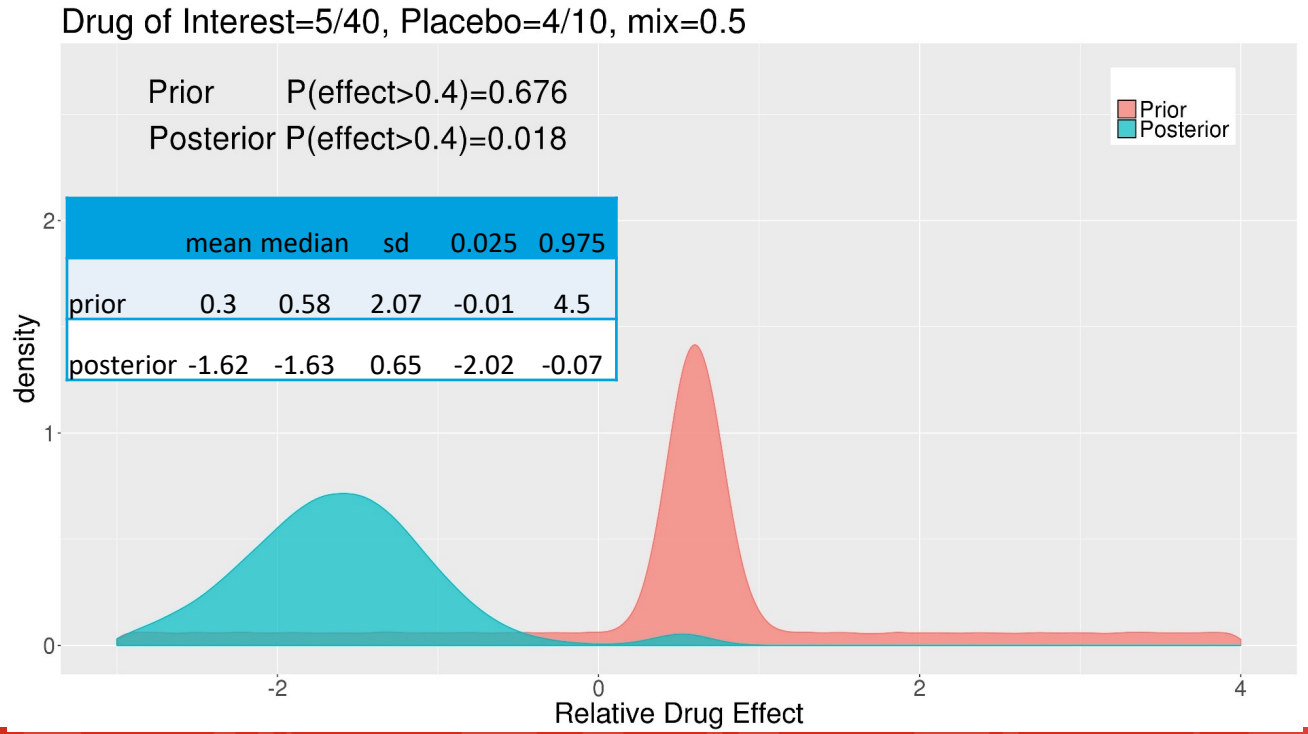
- 10 relevant studies (all controlled).
- 13 different dose / treatments.
- Average Control Rate = 0.4 (*n*=1853)

Example 2: Historical Adult Active Drug Data

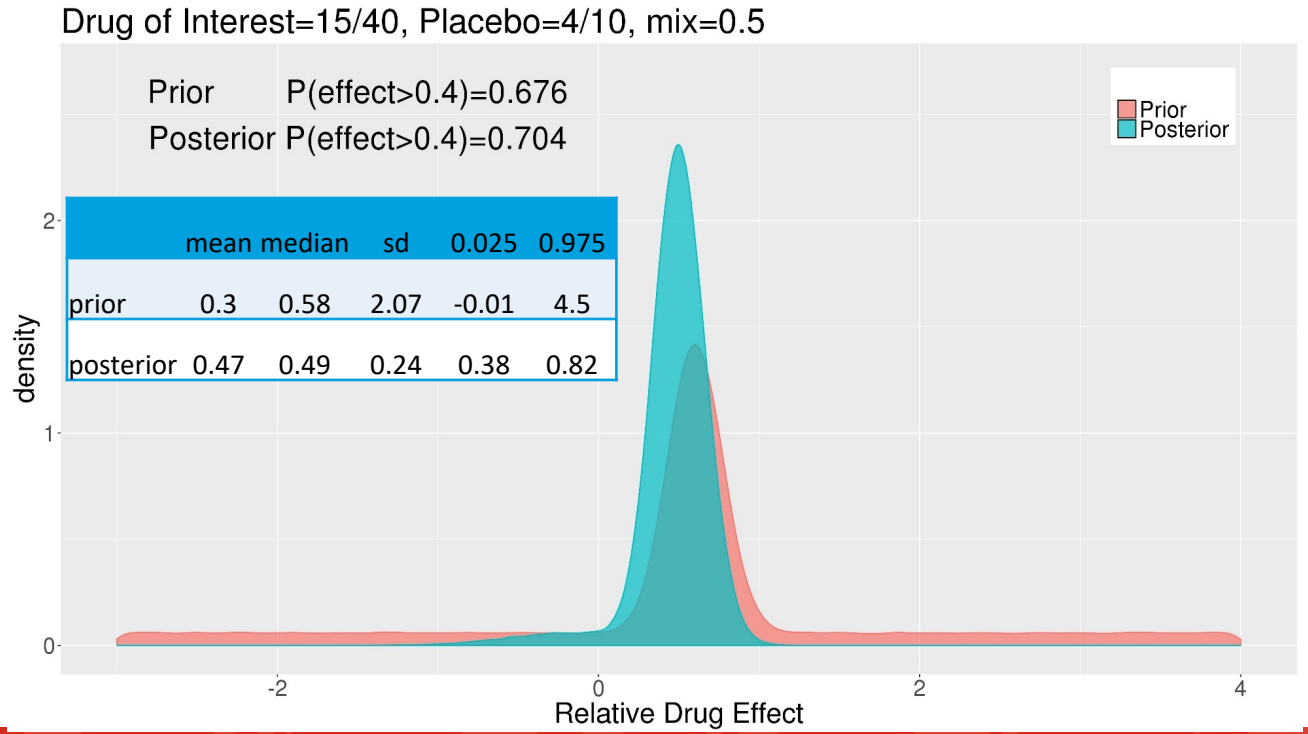
- 10 relevant studies (all controlled)
- 13 different dose / treatments
- Drug of interest rate = 0.5 (*n*=300)



Example 2: An example outcome

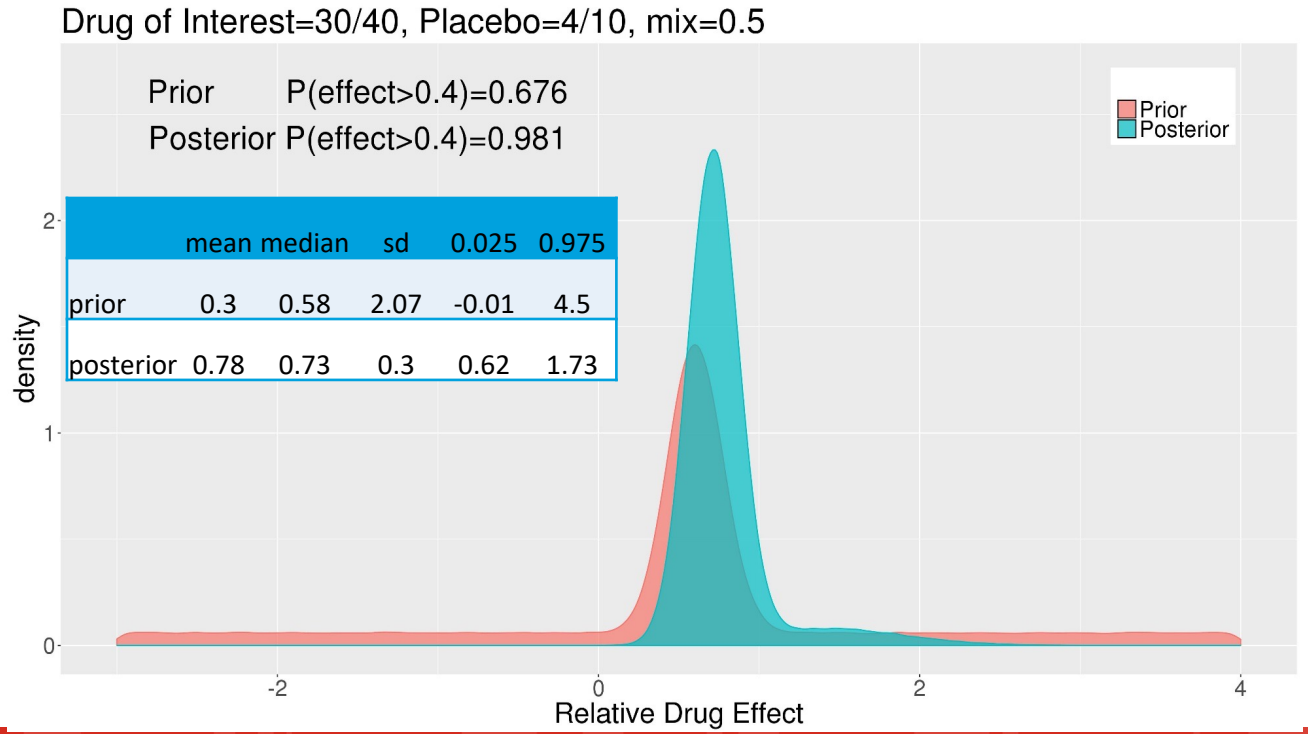


Example 2: An example outcome



	mean	median	sd	0.025	0.975
prior	0.3	0.58	2.07	-0.01	4.5
posterior	0.47	0.49	0.24	0.38	0.82

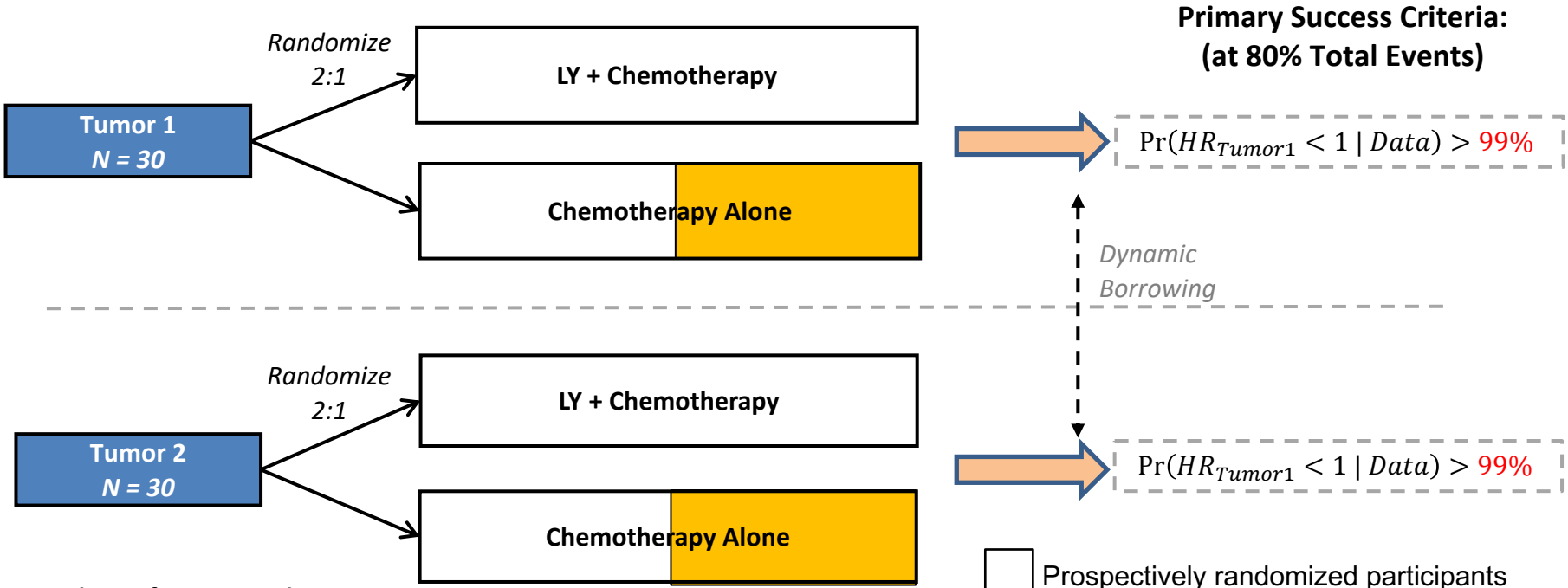
Example 2: An example outcome



	mean	median	sd	0.025	0.975
prior	0.3	0.58	2.07	-0.01	4.5
posterior	0.78	0.73	0.3	0.62	1.73

Innovative Designs

A Bayesian Design for Rare Pediatric Cancers



Bayesian Analysis of PFS Hazard Ratios:

- 'Dynamic' meta-analytic borrowing on HR between tumors
- Augment control arms with historical data via informative priors

A Bayesian Design for Rare Pediatric Cancer

Two elements of Bayesian hierarchical model for PFS:

(1) Between-tumor 'borrowing' on PFS log HR

$$\log(HR_{Tumor1}), \log(HR_{Tumor2}) \sim N(\mu, \sigma)$$

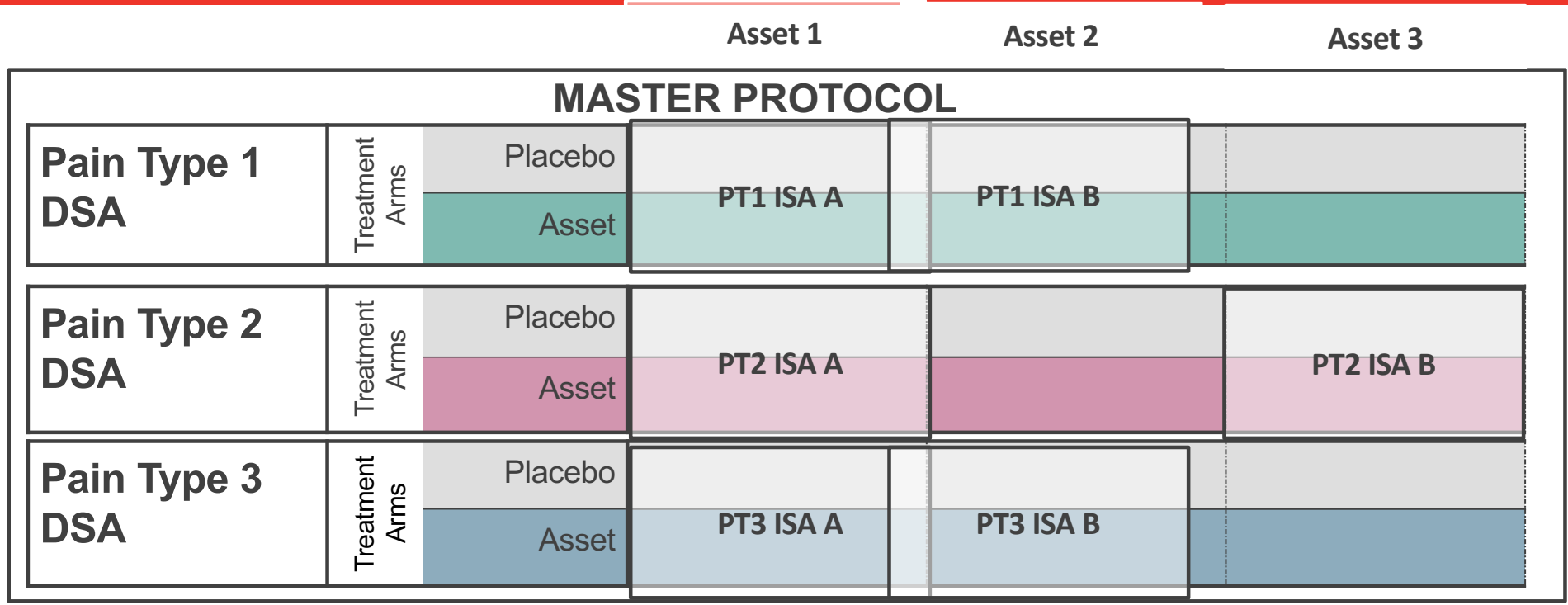
μ: *Common mean*; σ: *Between-tumor SD*

(2) Informative priors for control PFS based on matched RWE

- Propensity score matching (1:1 LY patient → historical control patient)
- Integration into power prior (Weibull likelihood with power parameter $a = 0.50$)
  - Prior effective number events approximately equal to that from prospective trial

Pain Master Protocol

Pain Master Protocol



DSA = Disease State Addendum
ISA = Intervention-Specific Appendix

Trial Selected for FDA Complex Innovative Design Pilot Program

Lilly

Who We Are | Caring | Discovery | Products | Careers | Investors | Partners

Lilly's Pain Clinical Trial Protocol Selected for FDA Complex Innovative Trial Designs Pilot Meeting Program

09/05/2019

INDIANAPOLIS, Sept. 5, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced the U.S. Food and Drug Administration (FDA) has accepted its application to enter the Complex Innovative Trial Designs (CID) Pilot Meeting Program, an initiative which aims to further modernize drug development, improve efficiency, and promote innovation. Lilly's proposed program involves a master protocol for the development of novel approaches to the treatment of multiple types of chronic pain, one of the largest unmet medical needs in the United States.

Download PDF

Both face to face meetings have occurred with FDA

Positive interactions between Lilly and FDA have led to an improved master protocol

Key Features of the Master Protocol

Common scales/endpoints:

- Pain: Numerical Rating Scale (primary)
- Physical functioning
- Emotional functioning
- Patient global assessment

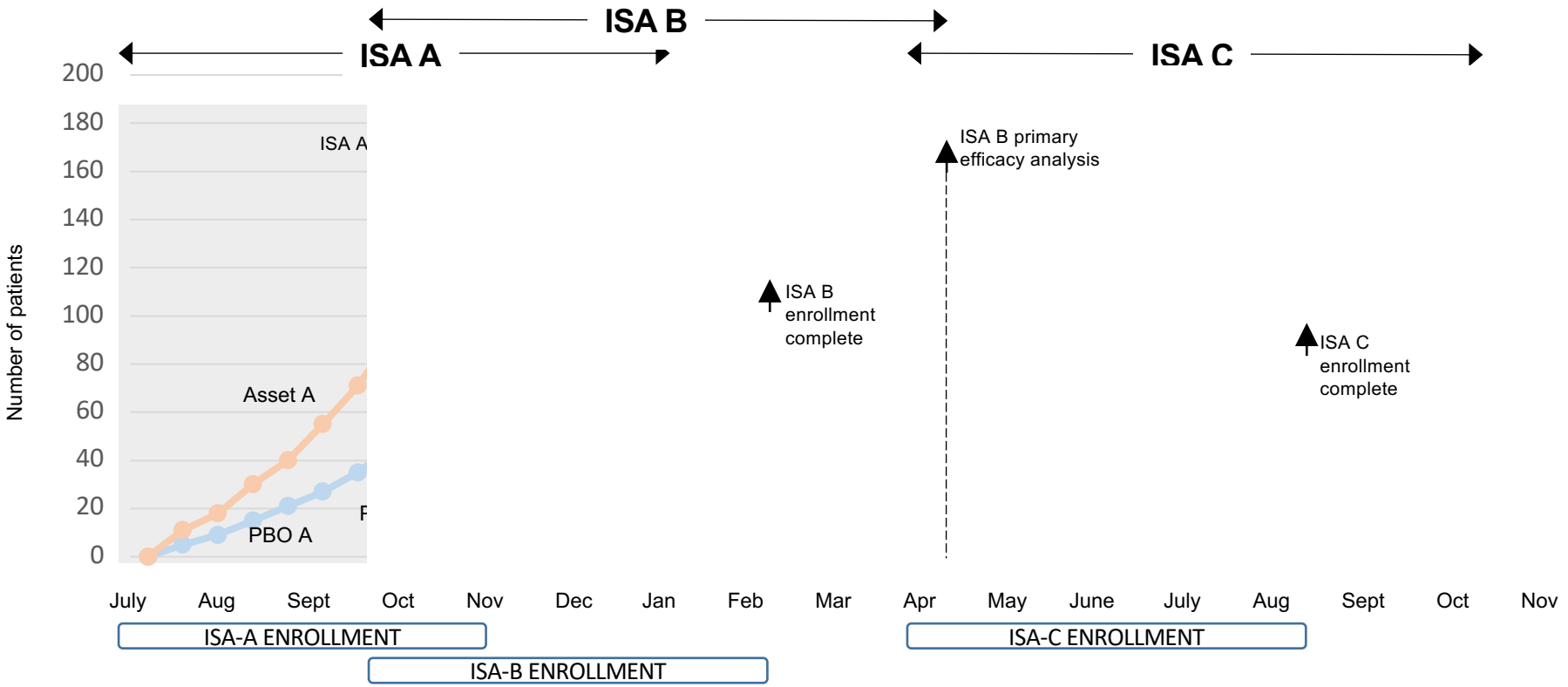
Commonalities:

- Standardized data collection across the ISAs, including similar visit schedules, induces higher confidence in portfolio level decisions
- A master protocol level team will be established to analyze efficacy analysis data and to establish key decision rules for more accurate, consistent, and efficient portfolio-level decisions

Desired Flexibility:

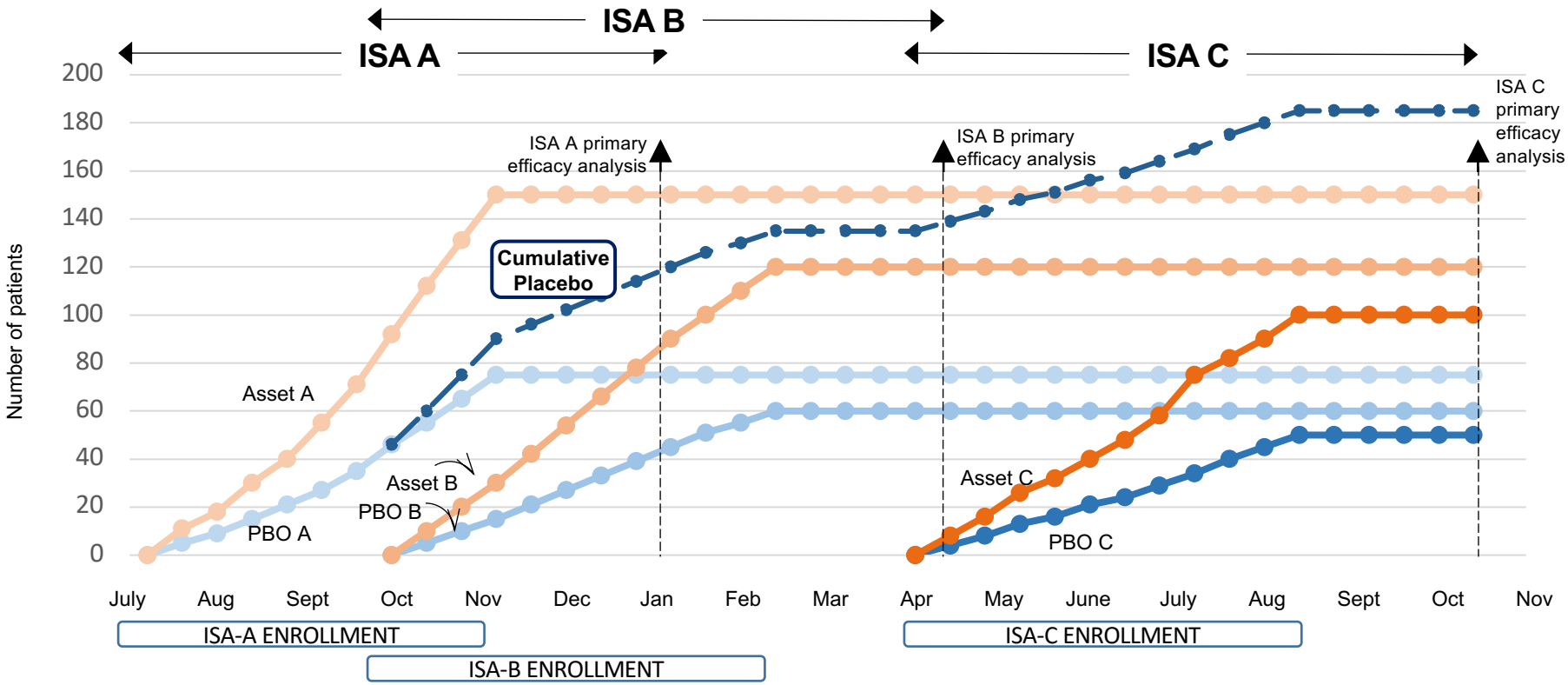
- Allow for potentially differing sample sizes/treatment durations (and associated analysis approaches) across the ISAs
- ISA –specific eligibility (requires careful consideration!)

Schematic of Master Protocol Over Time
Example: Pain Type 1



Upward black arrow indicates point of primary analysis in each ISA

Schematic of Master Protocol Over Time
Example: Pain Type 1



Upward black arrow indicates point of primary analysis in each ISA

Statistical Benefits of Master Protocol

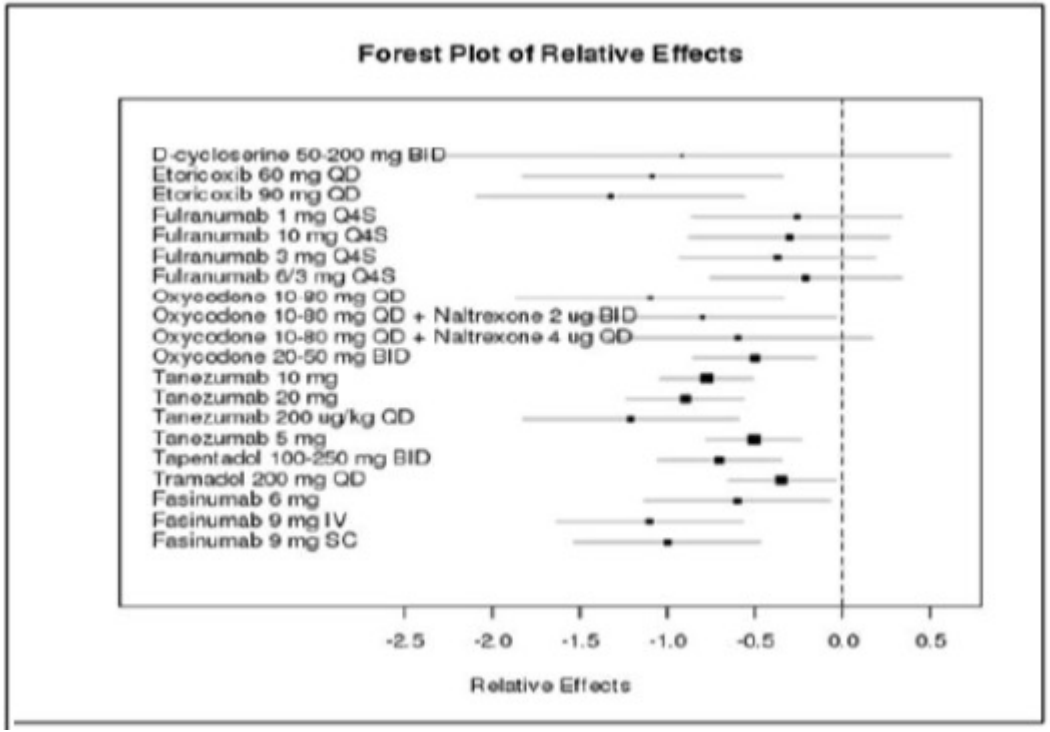
- Allows for direct comparisons of assets within and between pain types
  - Advisory Board comment from a participant (paraphrasing): “How often do we wish a drug was in the same protocol and we didn’t have to rely on a meta-analysis.”
  - FDA expressed enthusiasm in the opportunity to assess the relevance of one type of chronic pain state to another
- Standardized data collection
  - In pain research, the question of ‘how much pain do you have’ is often asked in many different ways (e.g. NRS, VAS, different recall periods, etc.)
  - Consistent collection of safety and/or biomarker data across the master protocol
- Reductions in sample size of both active and placebo arms
  - Accomplished by borrowing of placebo information within a pain type, and treatment effect information between pain types

Sources of Borrowing in the Master Protocol

1. Historical Controls
   - Not unique to the master protocol
2. Borrowing of placebo information from other ISAs within a pain type
3. Borrowing of treatment effect information for a given asset between pain types

Information can be borrowed from ongoing or completed ISAs from patients who have had the opportunity to complete the placebo-controlled portion of the trial

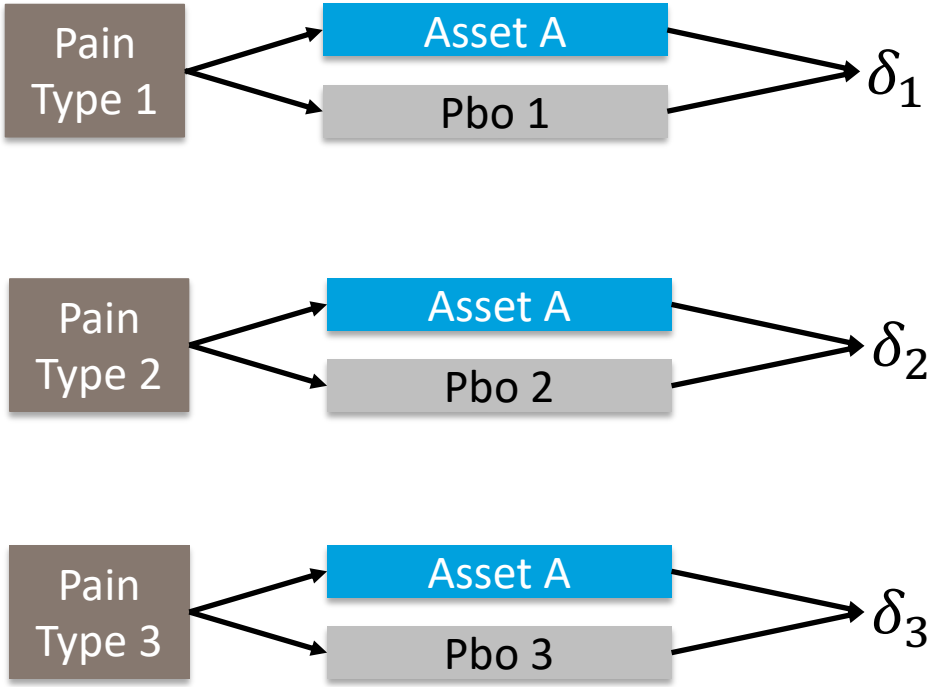
Borrowing Source: Historical Controls Bayesian Network Meta-Analysis



Uses of Bayesian Network Meta-Analysis:

- Identify historical controls that can be used in the analysis
- Understand the relationship of the treatment effect between pain types
- Can be used to define the prior distributions on key modeling parameters
- Understand the variability of the treatment effect for simulations, and the between-study variability
- Critical success factors: Probability(Treatment difference < effect of interest) > probability threshold
  - Used to identify what is considered a meaningful effect of interest

Borrowing Source: Treatment Effect Information Between Pain Types

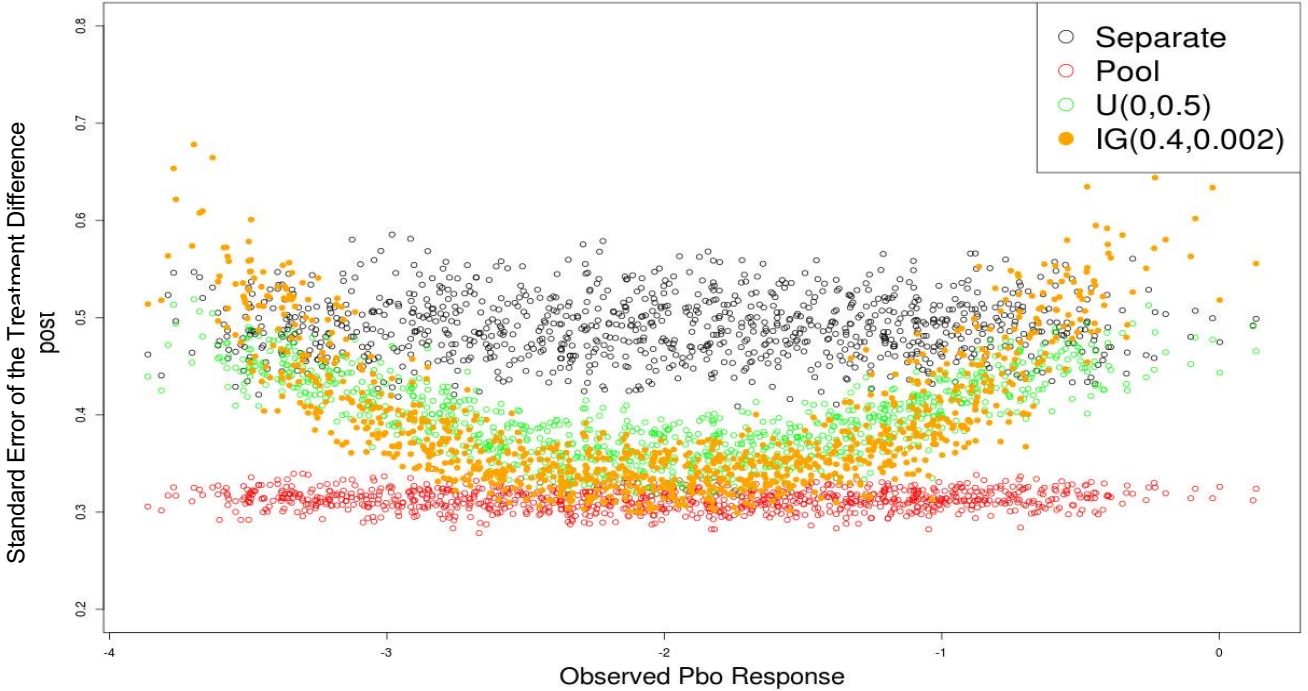


- Dynamically share treatment effect information across pain types within one asset
- Allows pain-specific conclusions
- Boosts power in light of small sample size
- Basic "Hierarchical Borrowing":

$$\delta_1, \delta_2, \delta_3 \sim N(\mu_b, \tau_b^2)$$

- Key question and assumption: Are the treatment effects between pain types exchangeable?

Dynamic Borrowing of Placebo Information



Simulation Details:

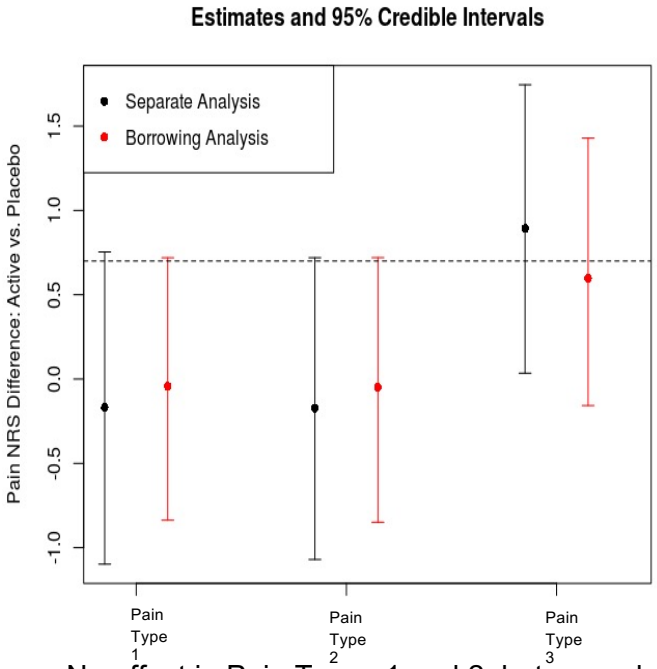
- Multiple ISAs simulated with a true mean of -2 placebo response
- The placebo estimates from the final ISA are represented in the graphic

Key points:

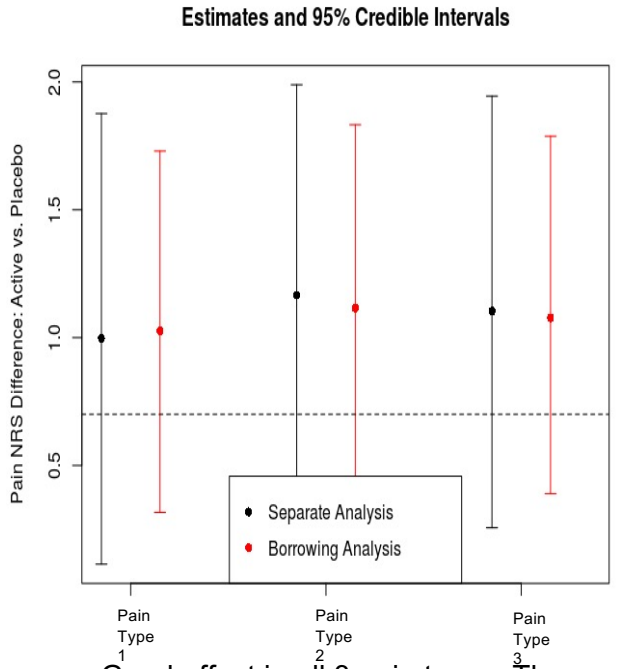
- Lower points in the graphic represent a reduction in the standard error of the treatment difference (good)
- The closer the observed mean to -2, the dynamic borrowing emulates pooling
- As the observed mean gets further from -2, less borrowing occurs and emulates a separate analysis

Dynamic Borrowing of Treatment Effect Information

Examples of Simulated Trial Outcomes



No effect in Pain Types 1 and 2, but a good effect in Pain Type 3. The Pain Type 3 estimate is pulled down based on the Pain Type 1 and 2 estimates.



Good effect in all 3 pain types. The estimates are very similar between modeling approaches, but the credible intervals are shorter in all cases.

Two models considered for each data set:

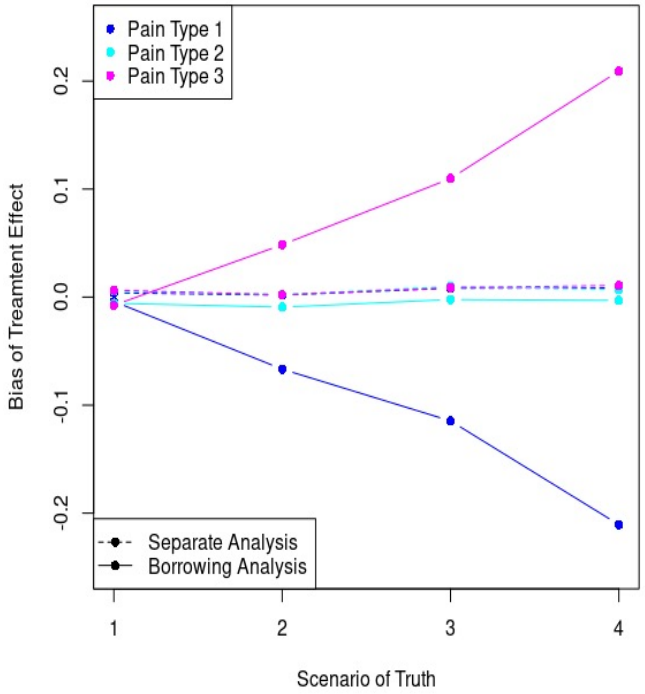
- Separate analysis (ISA only)
- Borrowing analysis (borrow treatment effect information between pain types)

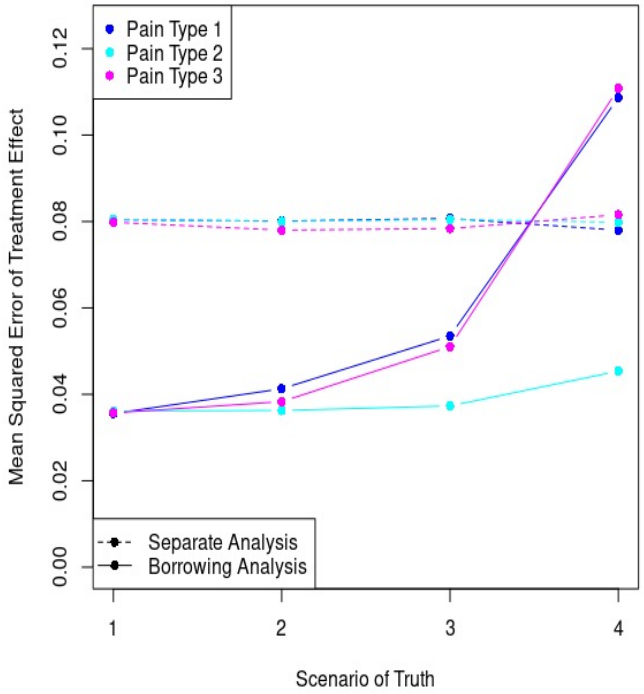
Each simulated trial includes 80 LY and 40 placebo patients

Treatment effect borrowing reduces the length of the credible interval in all cases

The estimated means are adjusted based on the performance in other pain types

Dynamic Borrowing of Treatment Effect Information
Assumption: All 3 treatment effects have a different mean





Scenario of truth of treatment effects for Pain Type 1, 2, and 3:

- Scenario 1: 0.5, 0.5, 0.5
- Scenario 2: 0.4, 0.5, 0.6
- Scenario 3: 0.3, 0.5, 0.7
- Scenario 4: 0.0, 0.5, 1.0

Sample size of 150:75 (active: placebo) per pain type

Two models fit for each simulated data set:

- Separate analysis (ISA only)
- Borrowing analysis (borrow treatment effect information between pain types)

Key Conclusions of treatment effect borrowing:

- The bias of pain type 1 and 3 increases as the underlying treatment effects become more disparate
- The MSE of the treatment effect is lower using dynamic borrowing, other than scenario 4

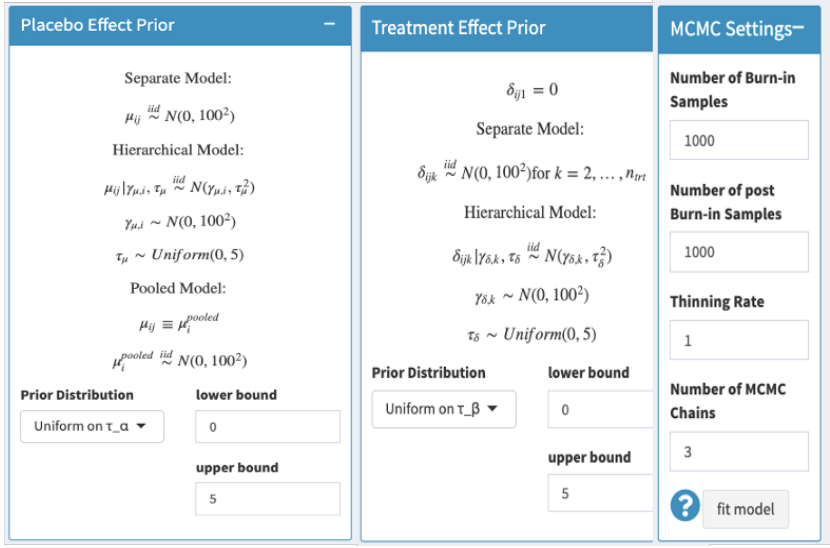
External/Regulatory Perspective

Key regulatory initiatives

- 21st Century Cures Act
- PDUFA VI includes pilot program
  - FDA announcement of the CID Pilot Meeting Program “As displayed in the *Federal Register* notice on August 29, 2018, FDA is conducting a Complex Innovative Trial Design (CID) Pilot Meeting Program to support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs.”
- PDUFA VII includes continued pilot program, public workshop and commitment for Draft Bayesian guidance by end of FY 2025

Some Challenges

- More knowledge needed
- Lack of comfort discussing Bayes approaches, especially medical
- Need for interactive simulations
- Need consistency in reporting simulation results
- Need to align on data for prior and borrowing approach, including "type 1 error control"



If interested in getting more involved, connect with DIA BSWG and/or DIA IDSWG

Conclusion / Wrap-up

- Bayesian methods are broadly used to improve the drug development process
- Bayesian methods provide a natural framework for synthesizing data and formal use of various data sources
- Bayesian methods enable natural interpretation and increased transparency to design and decision making

Additional Q&A

Some References

- Hobbs, Brian P.; Sargent, Daniel J.; Carlin, Bradley P. Commensurate Priors for Incorporating Historical Information in Clinical Trials Using General and Generalized Linear Models. Bayesian Anal. 7 (2012), no. 3, 639--674. doi:10.1214/12-BA722. https://projecteuclid.org/euclid.ba/134615877
- Ibrahim, Joseph G.; Chen, Ming-Hui. Power prior distributions for regression models. Statist. Sci. 15 (2000), no. 1, 46-60.
- Schmidli, H. , Gsteiger, S. , Roychoudhury, S. , O'Hagan, A. , Spiegelhalter, D. and Neuenschwander, B. (2014), Robust meta-analytic-predictive priors in clinical trials with historical control information. Biom, 70: 1023-1032.
- Hampson, Whitehead, Eleftheriou, Tudur-Smith, Jones, Jayne, Hickey, Beresford, Bracaglia, Caldas, Cimaz, Dehoorne, Dolezalova, Friswell, Jelusic, Marks, Martin, McMahon, Peitz, van Royen-Kerkhof, Soylemezoglu, Brogan. (2015). Elicitation of Expert Prior Opinion: Application to the MYPAN Trial in Childhood Polyarteritis Nodosa. *PLoS One*, 10(3): e0120981.
- Viele, Berry, Neuenschwander, Amzal, Chen, Enas, Hobbs, Ibrahim, Kinnersley, Lindborg, Micallef, Roychoudhury,Thompson. (2014). Use of historical control data for assessing treatment effects in clinical trials. *Pharmaceutical Statistics*, 13(1): 41-53.
- Spiegelhalter, Abrams, Myles. *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. Wiley 2003.
- Sutton and Abrams. Bayesian methods in meta-analysis and evidence synthesis. *Statistical Methods in Medical Research*. 2001; 10: 277-303.

Some References, cont.

- Sutton and Higgins. Recent development in meta-analysis. *Statistics in Medicine*. 2008; 27: 625-650.
- Cochrane Handbook: http://www.cochrane-handbook.org/
- Hoeting et al (1999). Bayesian model averaging tutorial. Statistical Science, 14(4)
- Berry et al (2009) BMA in meta-analysis: vitamin E supplementation and mortality. Clinical Trials 2009; 6:28-41
- Warn, Thompson, and Spiegelhalter. Statist. Med. 2002; 21:1601–1623. "Bayesian random effects meta-analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales"
- Janssen et al. "Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report." *Value in Health* 2014, 17: 157-173.
- Ohlssen et al. "Guidance on the implementation and reporting of a drug safety Bayesian network meta-analysis" Pharmaceutical Statistics 2014,13: 55-70.
- Spiegelhalter, Abrams, Myles. *Bayesian Approaches to Clinical Trials and Health-Care Evaluation*. Wiley 2003.
- NICE DSU Technical Support Documents
- Canadian Agency for Drugs and Technologies in Health Report

Some References, cont.

- Complex Innovative Trial Design Pilot Meeting Program. Retrieved on September 7, 2021, from https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-pilot-meeting-program.
- PDUFA VII: Fiscal Years 2023-2027. Retrieved on September 7, 2021, from https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027.
- J. Woodcock , L. M. LaVange. Master protocols to study multiple therapies, multiple diseases, or both, N. Engl. J. Med. 377 (2017) 62-70.
- Complex Innovative Trial Design Brochure. Retrieved on September 7, 2021, from https://www.fda.gov/media/129256/download.
- Interacting with the FDA on Complex Innovative Trial Designs for Drugs and Biologic Products, Guidance for Industry, December 2020. Retrieved on September 7, 2021, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/interacting-fda-complex-innovative-trial-designs-drugs-and-biological-products.
- Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics, Draft Guidance for Industry, October 2018. Retrieved on September 7, 2021, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and.
- Adaptive Designs for Clinical Trials of Drugs and Biologics, Guidance for Industry, December 2019. Retrieved on September 7, 2021, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry.
- Adaptive Design Clinical Trials for Drugs and Biologics, Guidance for Industry, December 2019. Retrieved on September 7, 2021, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry.
- Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design, October 2007. Retrieved on September 7, 2021, from https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-methodological-issues-confirmatory-clinical-trials-planned-adaptive-design_en.pdf.