Learnings from Chronic Pain Master Protocol: FDA Complex Innovative Designs Pilot Program

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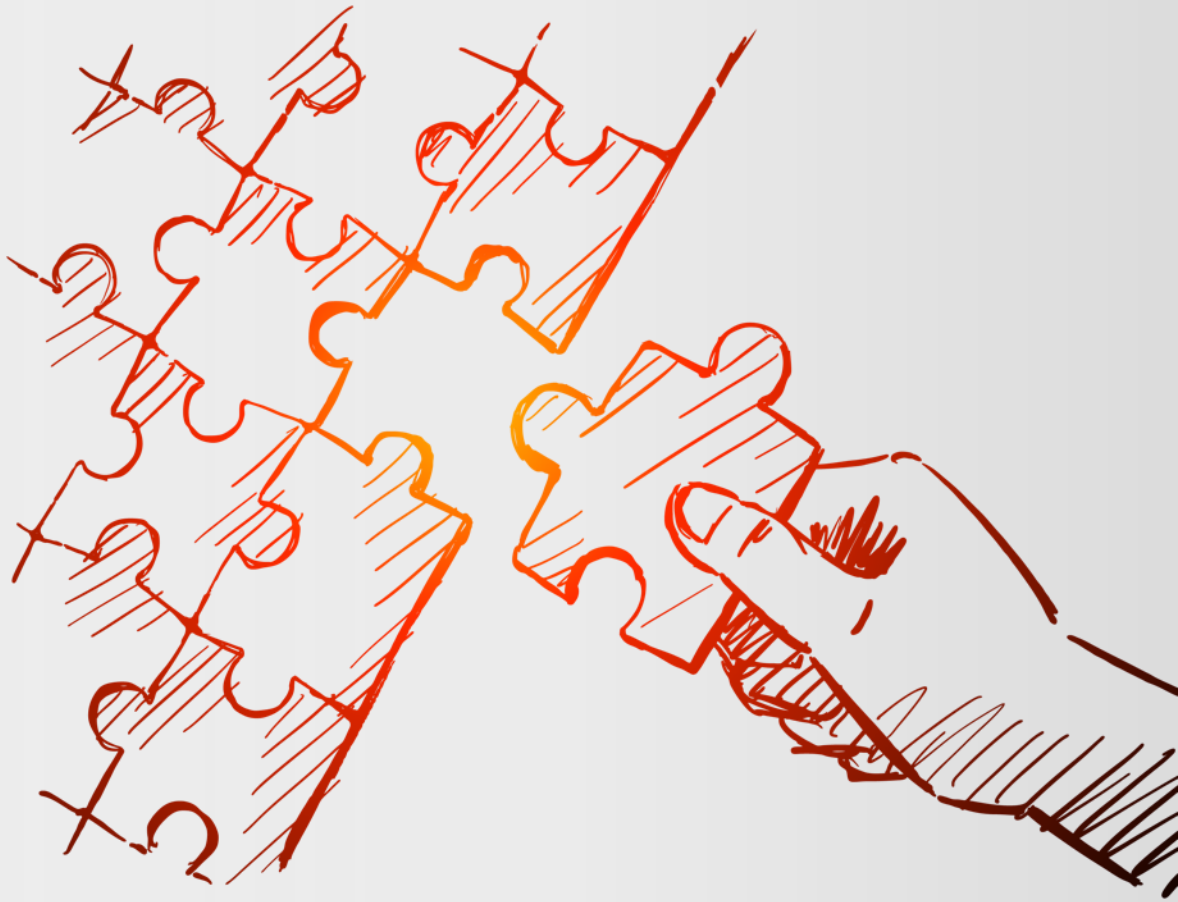
Outline

- Motivation: Signal Seeking, Rapid Lean Proof of Concept Development for Chronic Pain
- CPMP Design and Participation in CID
- Statistical Borrowing Consideration
  - Placebo borrowing
  - Longitudinal hierarchical model for placebo borrowing
  - Treatment effect borrowing
  - Challenges in Borrowing
- Key learnings & challenges:
  - Operational
  - Using data from ongoing blinded studies for borrowing requires blinding considerations
  - Placebo borrowing, especially with differences in route of administration.

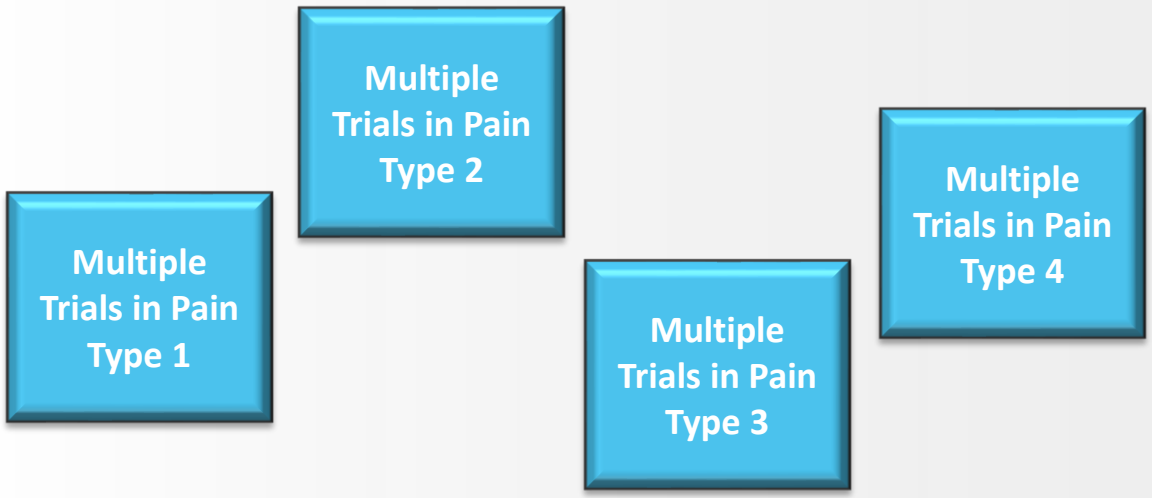
The Challenge

How can we develop a clinical approach to quickly evaluate multiple assets in multiple pain indications without *a priori* differentiation information?

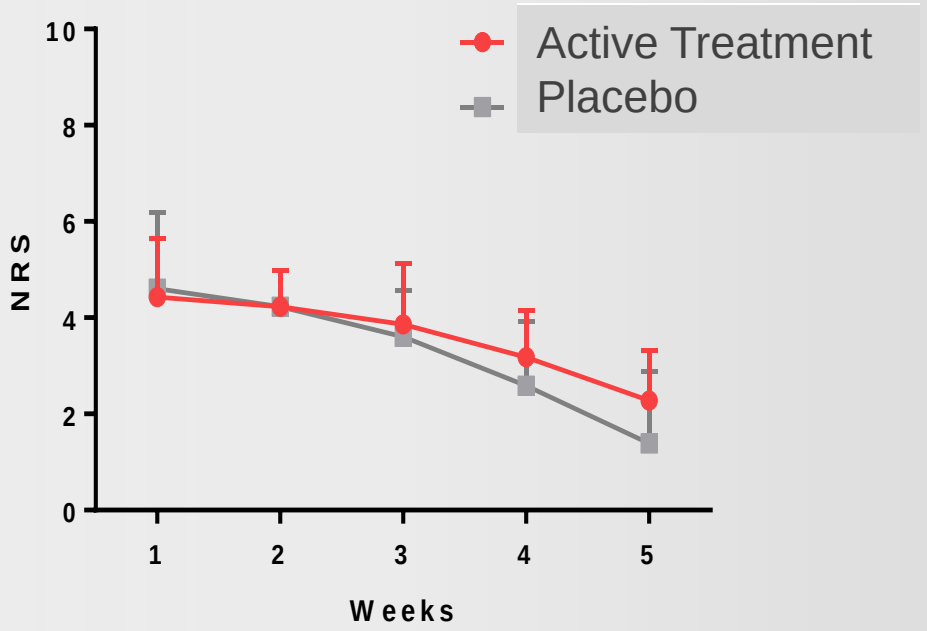


How Can We Efficiently Address the Early Phase Clinical Questions?

Molecule evaluated in multiple chronic pain conditions

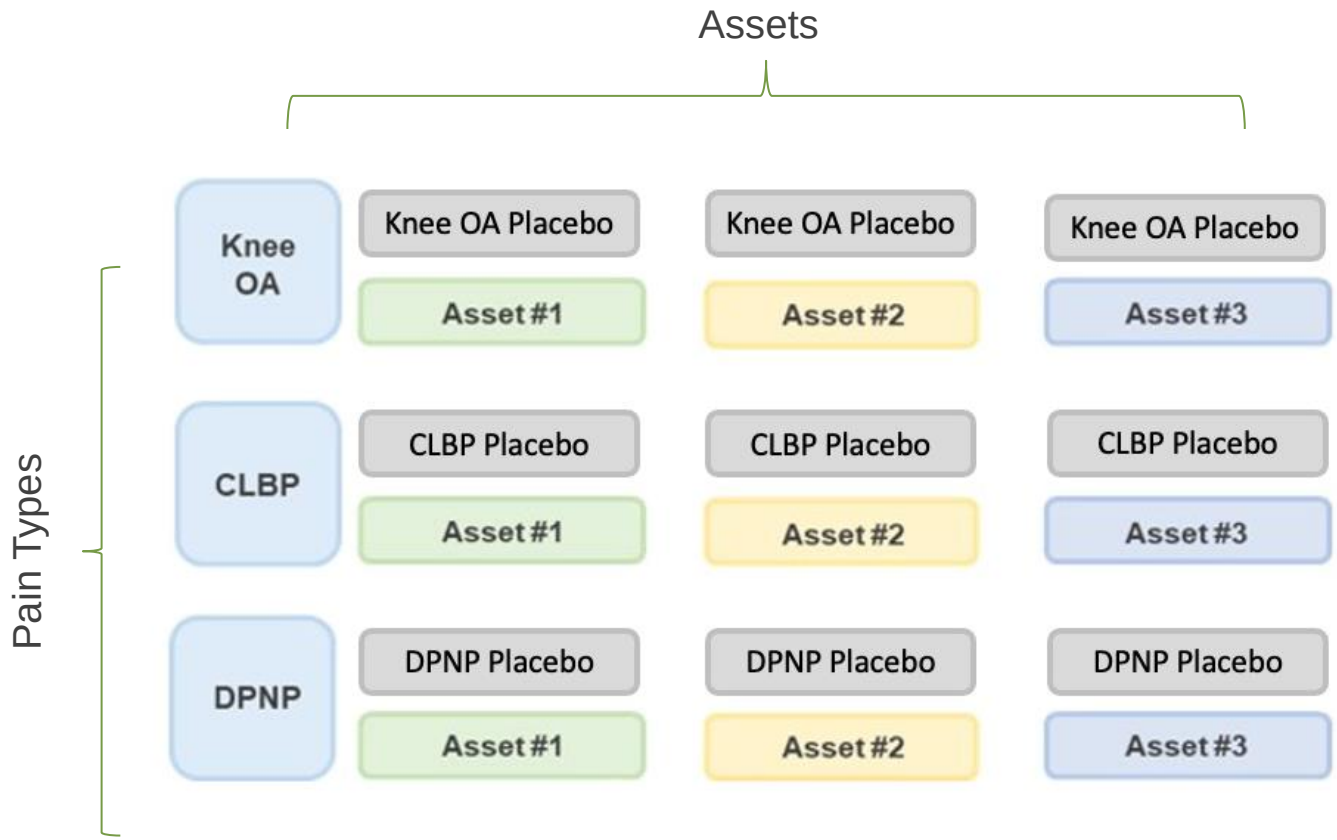


Molecule Terminated After Single POC in One Pain Type



CPMP Framework

Challenge in Chronic Pain Development: Preclinical models and clinical outcomes in one pain condition are not predictive across chronic pain states, leading to lengthy and costly development plans with multiple negative studies



Goal:
Lean, Efficient Signal Identification for Multiple Assets in Multiple Pain Types

Each pain type is a DSA (Disease State Addendum) to the Master Protocol.
Each sub-study is an ISA (Intervention-Specific Appendix)

Master Protocol: Structure

Tier 1: Master Protocol (MP)

- Established entry criteria for MP
- Outlines randomization schema
- Tests the common, shared hypothesis across multiple indications and interventions
- Facilitates advanced statistical modeling and operational efficiencies
- Allows flexible treatment durations when supported by an ERB supplement

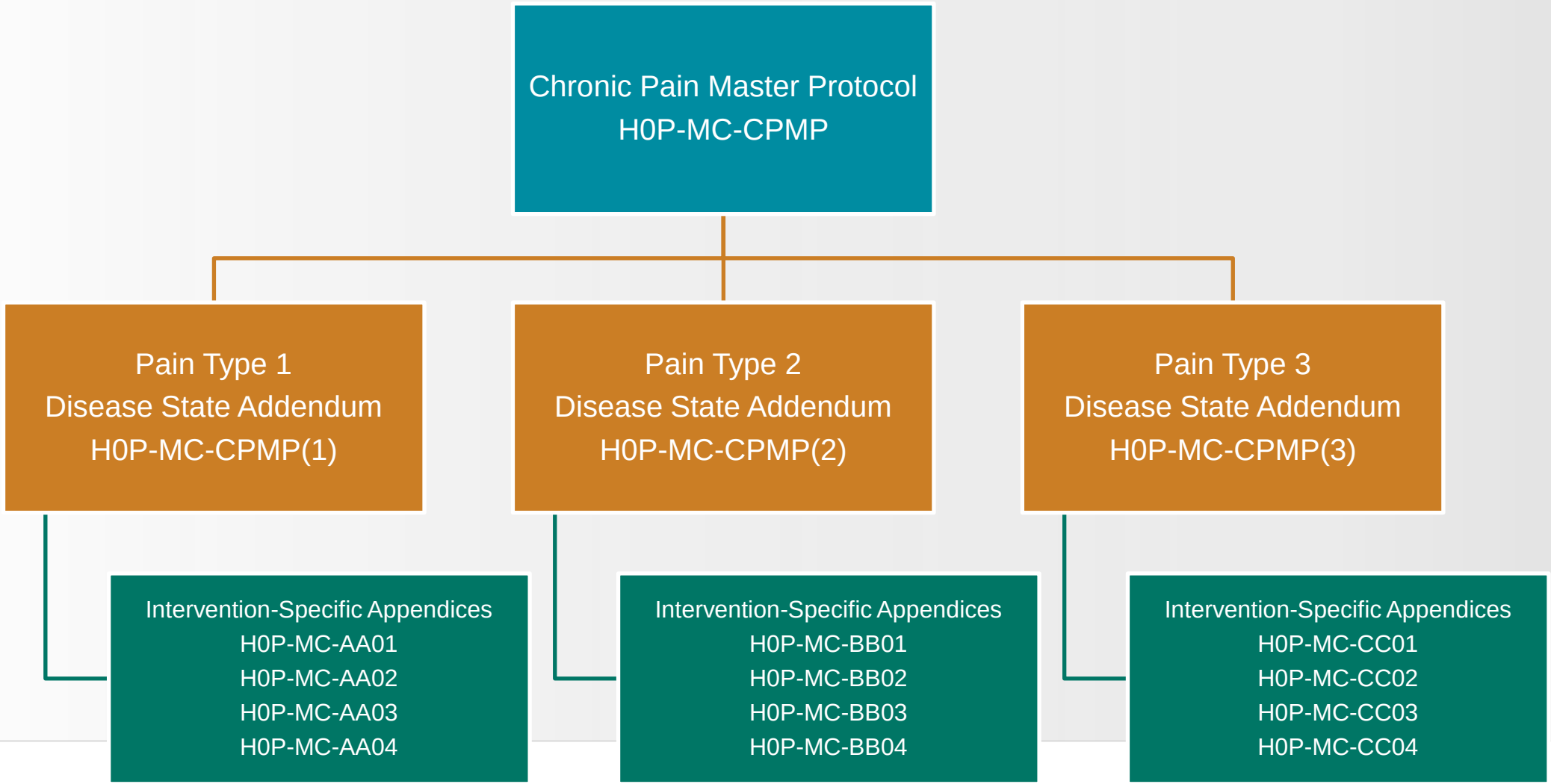
Tier 2: Disease-state Addenda (DSA)

- Contain study elements specific to target population and unique scales for assessments
- Ability to add additional DSAs

Tier 3: Intervention-specific appendices (ISA)

- Contain study elements specific to the LY under study, such as dosing regimen, unique eligibility criteria and assessments, or other requirements
- May start independently of one another as assets become available for clinical testing
- May end independently, either when an intervention has concluded, or as interim analyses show that an intervention's criteria for futility or success have been met

Master Protocol, DSA, ISA Flow



Building a Pain Platform
Strategic considerations and assumptions

"The common denominator is a need to answer more questions more efficiently and in less time."[1]

Strategic considerations:

- Maximize flexibility to meet portfolio needs
- Scope is phase 2 proof-of-concept (POC) only
  - A phase 1 data package was done prior and separately
- Design decisions do not need to be constrained by registration requirements
- Maximize transferability to phase 3
- Limit sites to North America to keep it simple
- Establish master protocol structure independent of ISAs

1. Woodcock J, et al. N Engl J Med. 2017; 377:62-70.

Key Features of the Master Protocol

Common scales:

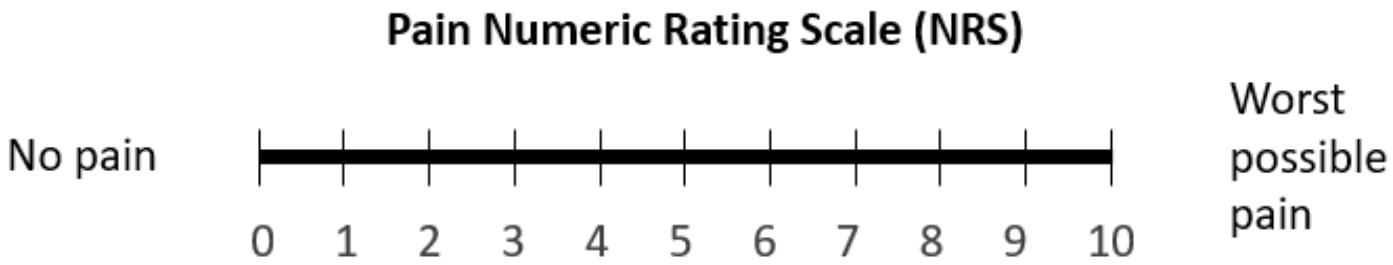
- Pain: Numerical Rating Scale (primary)
- Physical functioning
- Emotional functioning
- Patient global assessment

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

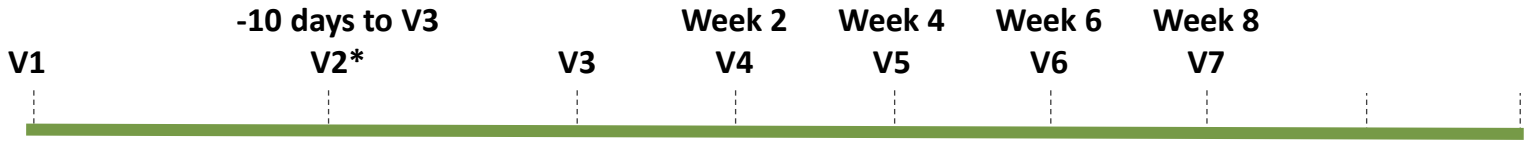
Primary Objective and Endpoint

- Primary objective: evaluate the efficacy of the investigational agent in pain relief in each ISA compared with placebo across various pain states
- Pain intensity measure: Numeric Rating Scale (NRS), collected daily using a tablet
- Patient question: “Select a number [0-10] that best describes your average pain in your [target area] in the past 24 hours”



Primary Efficacy Analysis

- A Bayesian mixed model repeated measures (MMRM) model will be the primary efficacy analysis
  - The average of the NRS will be calculated by time intervals, and the average value will be used in analysis



- Each ISA will specify the Bayesian primary critical success factor (CSF) based on the NRS:
  - Probability(Treatment difference < effect of interest) > probability threshold
  - Each ISA will specify the effect of interest and the probability threshold

- Each ISA may specify additional CSFs to accommodate interim analyses and additional treatment arms

Randomization

- 2:1 randomization within an ISA (2 active arm:1 placebo arm)
  - Balance between minimizing expectation of placebo response and maximizing the efficient use of patients in the trial
- Simultaneous ISAs may be enrolling patients at the same time
- Key: every patient has a 33% chance of receiving placebo regardless of the number of active ISAs

Scenario: two ISAs are enrolling patients within a DSA

How to Balance?

Standardization

- Same primary endpoint across the master protocol (pain numerical rating scale collected daily)
- 33% of patients randomized to placebo
- Double blind period duration is 8 weeks (either active arm or placebo)
- Common visit schedule and data collection methods
- Identical inclusion/exclusion criteria

VERSUS

Flexibility

- ISA teams can specify the sample size, critical success factor, primary efficacy analysis model, amount and type of borrowing
- Multiple active treatment arms can be included for each ISA
- Active treatment duration can vary
- Additional scales and visits may be added
- Additional inclusion/exclusion can be added at ISA level

Trial Selected for FDA Complex Innovative Design Pilot Program

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.

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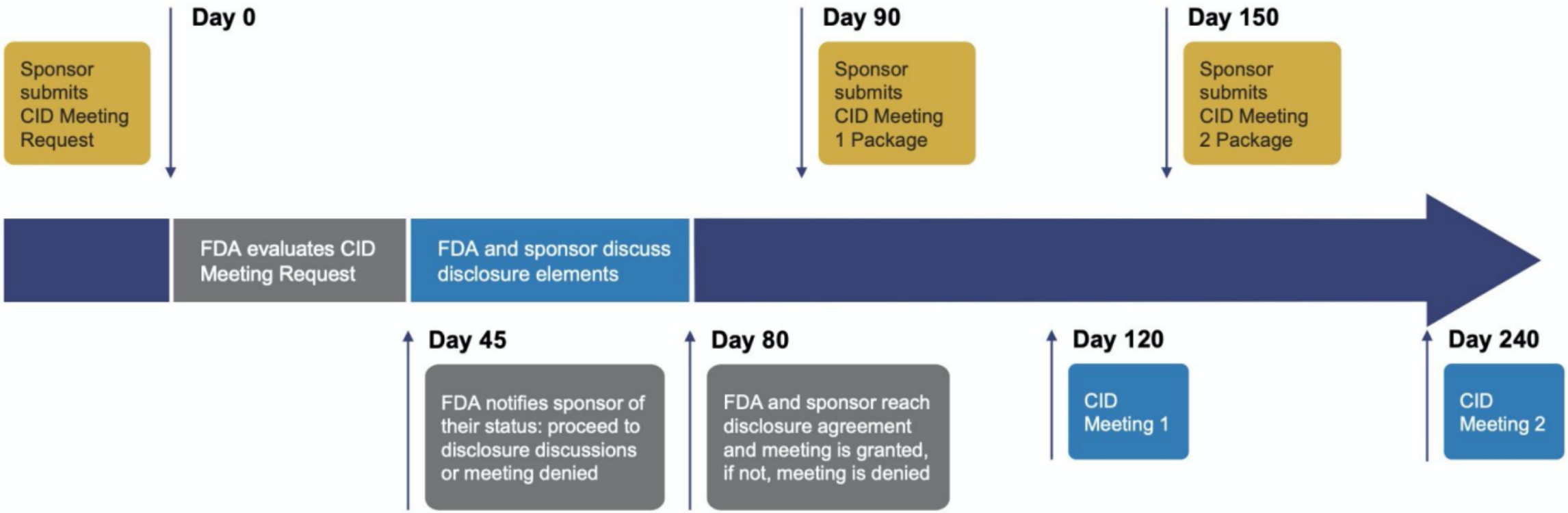
CID timeline



Overall Feedback from CID Program Experience

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

Benefits

- Collaborative setting to obtain technical statistical input from FDA. FDA Statistical representatives were present and engaged.
- Joint FDA statistics/division contributions to the study design early in the design process was beneficial.
- CID program progressed how Lilly (Sponsors) & FDA should communicate on Bayesian methods, simulation plans and results.
- Identified the need to develop a mechanism for long-term statistical discussion between sponsors and FDA (i.e. outside the CID pilot program).
- R shiny collaboration: CID program enabled nimble and informal dialogue regarding the novel simulation technology with FDA.

Opportunities for Improvement

- Timeline of overall process (~10mo) and time between second briefing document due and the second CID Meeting (90d for FDA review) may be shortened
- FDA comments may be provided 5-10d before the meeting (received ~36 hrs before second meeting), and expectation of Sponsor providing feedback to the comments 2-3d in advance of the meeting to enable most informed dialogue (see FDA Formal Meeting guidance for more appropriate example time frames)
- Recommend follow-up after second meeting, between Sponsor/FDA to continue discussion as the study progresses to inform FDA of key learnings.
- Consistency in FDA meeting attendees between the first and second CID meeting is appreciated

Statistical Considerations

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 Considerations for each ISA

- How much placebo or treatment effect information should we borrow?
- What is the method we should use to borrow (e.g. pool data, hierarchical model, commensurate prior, mixture prior, etc.)?
- Do we think placebo ‘drift’ has occurred that may impact placebo borrowing?
- For the asset, do we think the treatment effects are related between pain types?
  - Does success (or failure) in two pain types change our expectation of success in a third pain type?

Placebo borrowing

- Leverage placebo data from historical ISAs to analyze the current ISA.
- Potential to improve operating characteristics such as power.
- Operational conditions that allow placebo borrowing in CPMP:
  - Multiple candidate drugs studied within each pain type.
  - Statistical exchangeability.
    - Standardized data collection, pain scales, randomization, visit structure.
    - Same investigative sites across ISAs*.

*ISA = intervention-specific appendix, a clinical trial within the master protocol.

Caveat

- What happens when historical placebo data is not commensurate with current data?
- Which better reflects the truth about the drug, the current data or the historical data?
  - Can depend on operational issues (e.g. different modes of administration), or the responses in the current vs historical datasets could systematically differ for unknown reasons.
  - To minimize human subjectivity, it is critical to plan for these scenarios before accessing the data.
- Dynamic borrowing methods automatically decide how strongly to borrow.
  - Often done by comparing historical outcomes to current outcomes.
  - Also possible to use baseline covariates.

Borrowing Approaches

- Borrowing can happen on control arm and/or treatment arm(s)
- Static vs Dynamic
  - Static
    - Pooling
    - Single arm trials
    - Power priors
  - Dynamic
    - Hierarchical modeling
    - Mixture priors
    - Commensurate priors
- Static vs dynamic can differ for control/treatment

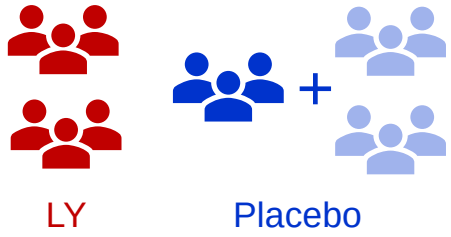
Appeal of dynamic borrowing:
- Borrows more when current data are similar to historical data
- Protects against over-borrowing

See, e.g., Viele, et al., Pharm Stats 2014.

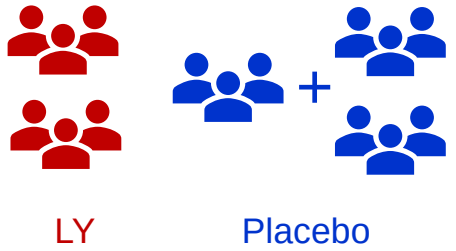
Placebo Borrowing in the CPMP

No borrowing:
Use current study data only for primary analysis

Dynamic borrowing:
Borrow placebo data based on similarity to current study

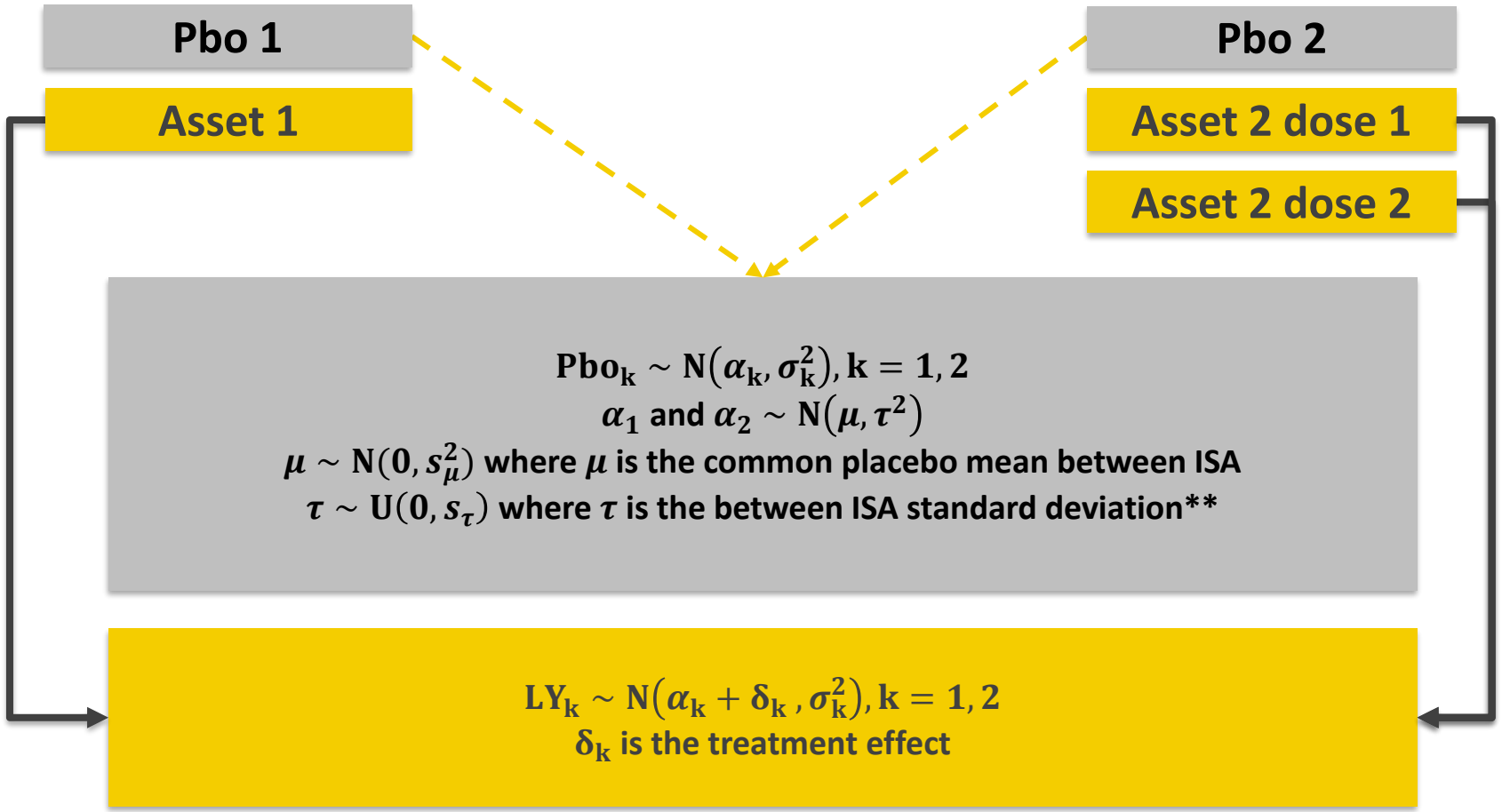


Full borrowing:
Pool placebo data from other CPMP studies for primary analysis.



- Dynamic approach adapts the level of borrowing based on the similarity of the placebo response, and protects against "over-borrowing". In CID discussions, FDA was supportive of this approach.
  - We expect the dynamic borrowing estimate to fall between the extremes of no borrowing and full borrowing.
- Simulations demonstrated that dynamic borrowing can control type I error and **increase study power**, under certain conditions.

Borrowing Placebo Information within a Pain Type Bayesian Hierarchical Model



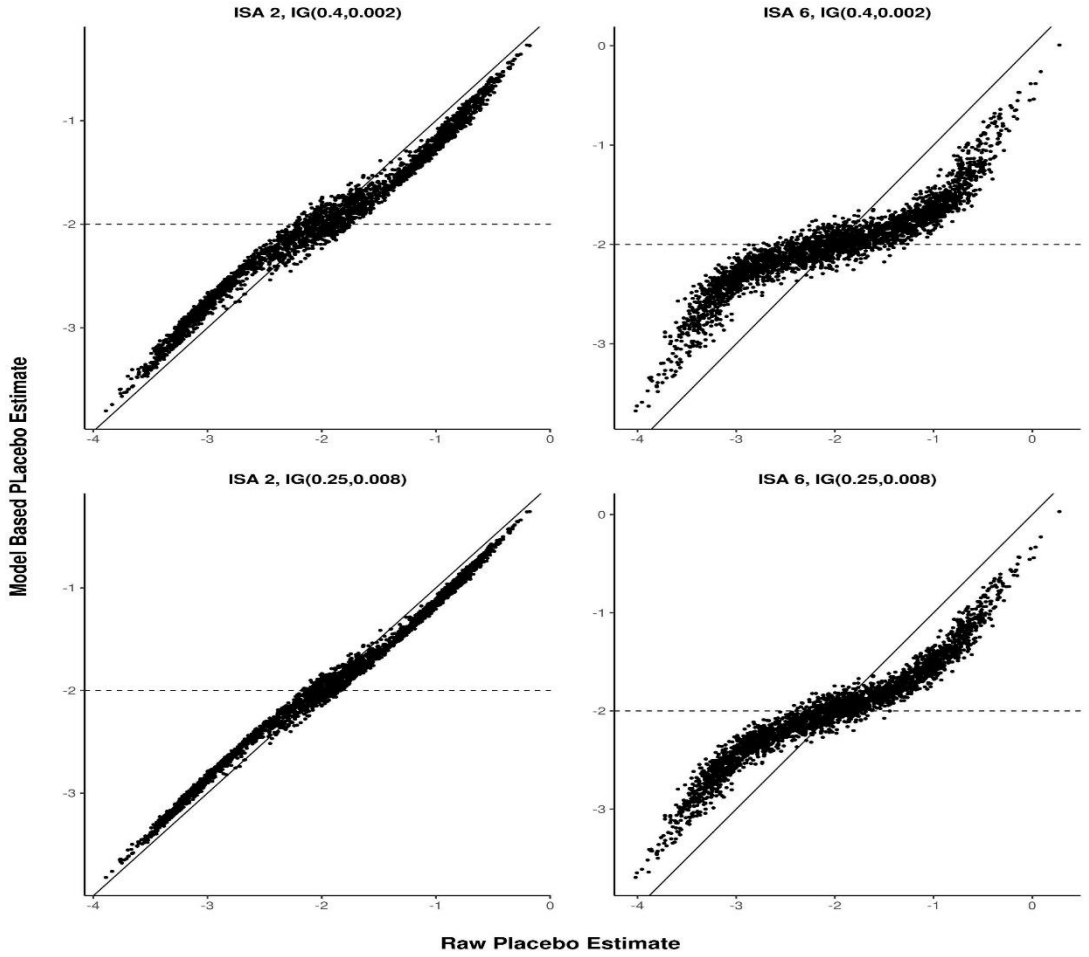
- The placebo patients are assumed to have a common population characterized by common placebo mean and between-study standard deviation
- The hierarchical structure facilitates sharing of placebo across different ISAs.
- The amount of borrowing is defined by the τ parameter

**An inverse gamma prior can also be used.

Impact of Initial Choice of τ

- The borrowing of control data depends on the value τ along with the observed data
- The extreme values of τ would reduce the dependency on the observed data
- In dynamic borrowing, a discrepancy between the ISAs places more weight toward larger τ values in the posterior distribution than an agreement between the ISAs
- A sensitivity analysis will be performed to estimate τ

Choice of Hierarchical Model



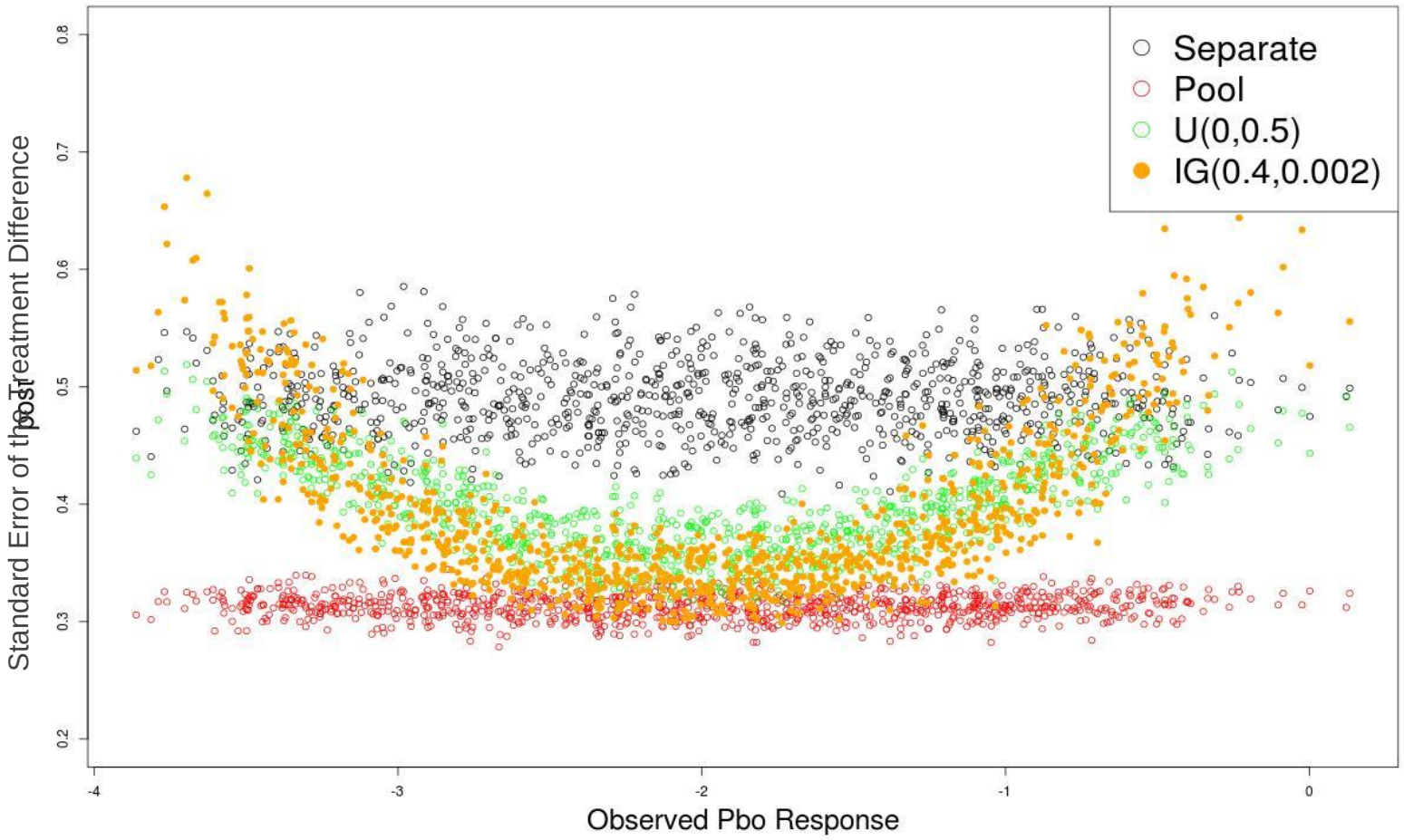
Simulation Details:

- 2-6 ISAs simulated with a true mean of -2 placebo response
- The model based placebo estimates from the final ISA are illustrated against the raw placebo observations

Key points:

- Illustrates the dynamic nature of hierarchical borrowing.
- The model based estimates are gravitated towards -2 when the raw placebo estimates are around -2
- With observed placebo means far from -2, model based estimates gradually shift towards the diagonal

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 Placebo Borrowing: Longitudinal Implementation

Hierarchical model

$$y_k \sim \text{MVN}((X_\alpha)_k \cdot \alpha + (X_\delta)_k \cdot \delta + (X_\beta)_k \cdot \beta,\ I_{N_k} \otimes \Sigma_k)$$

$$\alpha_{kt} \overset{\text{ind}}{\sim} \text{Normal}(\mu_t, \tau_t^2)$$

$$\mu_t \overset{\text{ind}}{\sim} \text{Normal}(0, s_\mu^2)$$

$$\tau_t \overset{\text{ind}}{\sim} \text{Uniform}(0, s_\tau)$$

$\ldots$

- y_k: vector of observed patient-level outcomes of ISA* k.
- α: vector of α_{kt} parameters.
- α_{kt}: placebo mean response of ISA k time t.
- $(X_\alpha)_k$: indicator matrix to match the correct α_{kt} to each patient and time point.
- μ_t grand mean placebo response at time t.
- τ_t: standard deviation of the placebo means, controls the strength of dynamic borrowing.

*ISA = intervention-specific appendix, a clinical trial within the master protocol.

Hierarchical model

$$y_k \sim \text{MVN}((X_\alpha)_k \cdot \alpha + (X_\delta)_k \cdot \delta + (X_\beta)_k \cdot \beta,\ I_{N_k} \otimes \Sigma_k)$$

$$\ldots$$

$$\delta_{dt} \overset{\text{ind}}{\sim} \text{Normal}(0, s_\delta^2)$$

$$\beta_b \overset{\text{ind}}{\sim} \text{Normal}(0, s_\beta^2)$$

- y_k: vector of observed patient-level outcomes of ISA k.
- δ: vector of δ_{dt} parameters.
- δ_{dt}: group mean response of active arm d time t.
- $(X_\delta)_k$: indicator matrix to match the correct δ_{kt} to each patient and time point.
- β: vector of β_b parameters.
- β_b: baseline covariate fixed effect parameter.
- $(X_\beta)_k$: model matrix of baseline covariates.

Hierarchical model

$$y_k \sim \text{MVN}((X_\alpha)_k \cdot \alpha + (X_\delta)_k \cdot \delta + (X_\beta)_k \cdot \beta,\ I_{N_k} \otimes \Sigma_k)$$

$$\dots$$

$$\Sigma_k = (I_T \sigma_k)\, \Lambda_k \Lambda_k' \,(I_T \sigma_k)$$

$$\sigma_{k1}, \dots, \sigma_{kT} \overset{\text{ind}}{\sim} \text{Uniform}(0, s_\sigma)$$

$$\Lambda_k \Lambda_k' \sim \begin{cases} \text{LKJ}(\text{shape} = s_\lambda,\ \text{order} = T) & m_k = 1 \\ \text{AR}(1)(T, \rho_k) & m_k = 2 \\ I_T & m_k = 3 \end{cases}$$

$$\rho_k \overset{\text{ind}}{\sim} \text{Uniform}(-1, 1) \qquad (\text{only for } m_k = 2)$$

- y_k: vector of observed patient-level outcomes of ISA k.
- N_k: number of patients in ISA k.
- I_{Nk}: identity matrix with N_k rows.
- $\otimes$: Kronecker product.
- Σ_k: longitudinal covariance matrix block of ISA k. Has covariances among time points within patients.
- Λ_k: Cholesky factor of the longitudinal correlation matrix block of ISA k.
- σ_k: vector of σ_{kt} parameters.
- σ_{kt}: residual standard deviation of ISA k time t.
- ρ_k: correlation between adjacent times within patients for ISA k (AR(1) only).
- m_k: choice of covariance structure of ISA k: 1 for unstructured/LKJ, 2 for AR(1), and 3 for diagonal.

Benchmark models to quantify borrowing

Model	Borrowing strength	Model of placebo response	Description
Hierarchical	Dynamic borrowing	$\alpha_{kt} \overset{\text{ind}}{\sim} \text{Normal}\left(\mu_t, \tau_t^2\right)$ $\mu_t \overset{\text{ind}}{\sim} \text{Normal}\left(0, s_\mu^2\right)$ $\tau_t \overset{\text{ind}}{\sim} \text{Uniform}\left(0, s_\tau\right)$	At each time t, the placebo means α_{kt} of each ISA k share a common mean parameter μ_t and common standard deviation τ_t.
Independent	No borrowing	$\alpha_{kt} \overset{\text{ind}}{\sim} \text{Normal}\left(0, s_\alpha^2\right)$	Placebo means α_{kt} are independent.
Pooled	Full borrowing	$\alpha_t \overset{\text{ind}}{\sim} \text{Normal}\left(0, s_\alpha^2\right)$	All studies k share a common placebo mean α_t at time t.

Quantify borrowing

- Want to empirically measure the strength of borrowing of the hierarchical model.
- One approach is to compare the results of the hierarchical model against two benchmark models:
  - Independent: like the hierarchical model, but with independent diffuse priors on the placebo means.
  - Pooled: like the independent model, but with a single shared placebo mean.
- Notation:
  - $u_t^{(m)}$ posterior mean of the placebo mean.
  - $v_t^{(m)}$: posterior variance of the placebo mean.
  - $n_t^{(m)}$: number of observed data points.
  - t: time point.
  - m: 1 for the hierarchical model, 2 for the independent model, and 3 for the pooled model.

Mean shift ratio

$$\frac{u_t^{(1)} - u_t^{(2)}}{u_t^{(3)} - u_t^{(2)}}$$

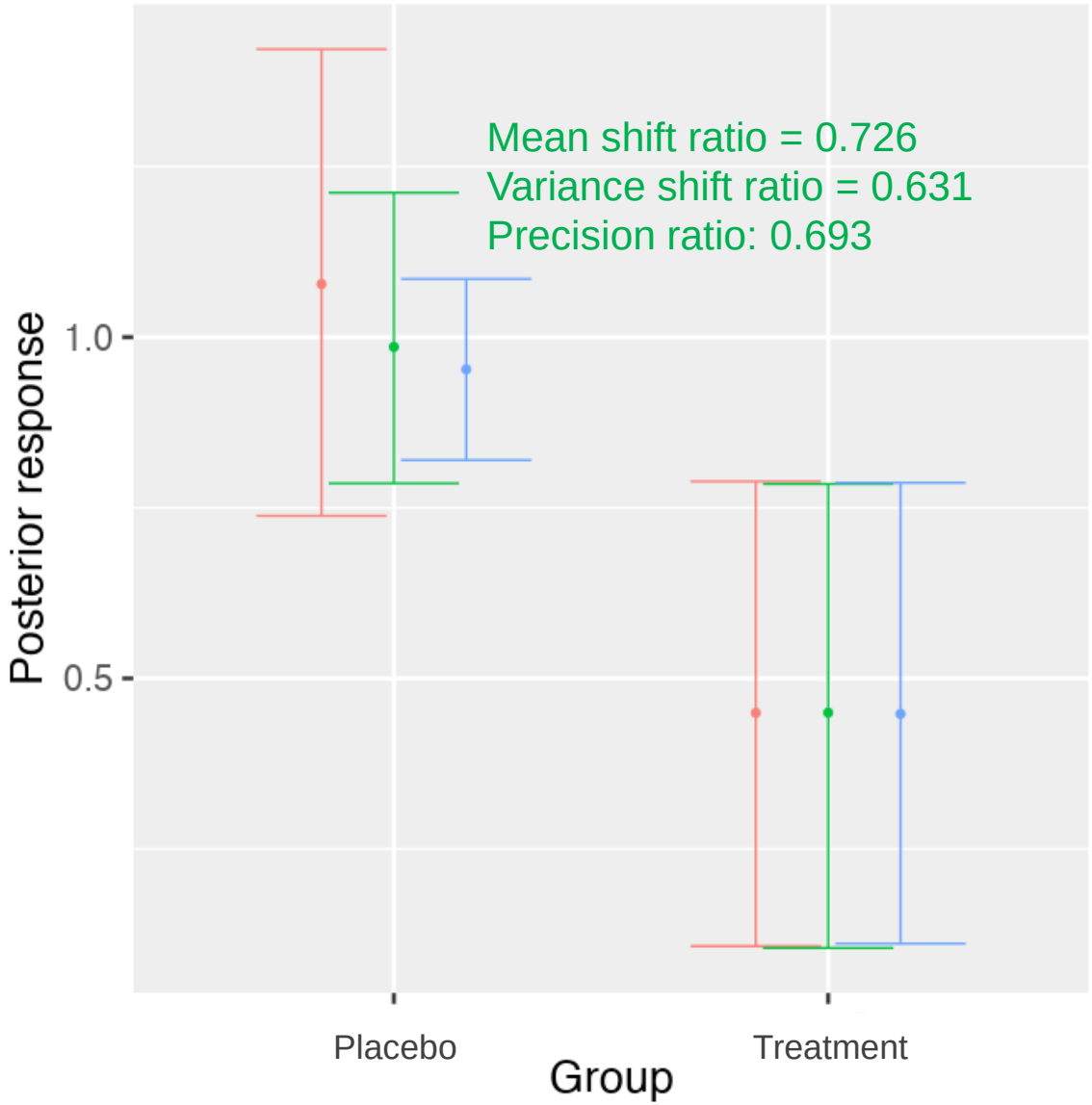
Variance shift ratio

$$\frac{v_t^{(1)} - v_t^{(2)}}{v_t^{(3)} - v_t^{(2)}}$$

Precision ratio

$$\frac{\frac{1}{\tau_t^2}}{\frac{1}{\tau_t^2} + \frac{n_t}{\sigma_t^2}}$$

Example results for a single time point



- Placebo borrowing is about 63%-73% according to the borrowing metrics.
- The mean shift ratio and variance shift ratio are visible in the graph.

Software

- Published R package {historicalborrowlong} on CRAN.*
  - Hierarchical, independent, and pooled models.
- The package has Stan code included using R packages {rstan} and {rstantools}.
- We could not use JAGS or NIMBLE for longitudinal modeling.
  - The data model for each patient is multivariate normal, and neither JAGS nor NIMBLE supports partially missing data in this situation.
- Because of the custom hierarchical priors and unstructured covariance matrices, we could not use existing high-level packages like {MCMCglmm} or {rstanarm} (although the latest version of {brms} would have been an option).

*The {historicalborrow} package implements non-longitudinal versions of these models, as well as a mixture model. Also on CRAN.

**Discussions · wlandau/historicalborrowlong (github.com)

Operational Learnings & Challenges

Clinical operations

- CPMP began enrolling in May 2020
- 9 ISAs completed or ongoing
- 30+ clinical sites across the US
- 1000+ patients enrolled in the program

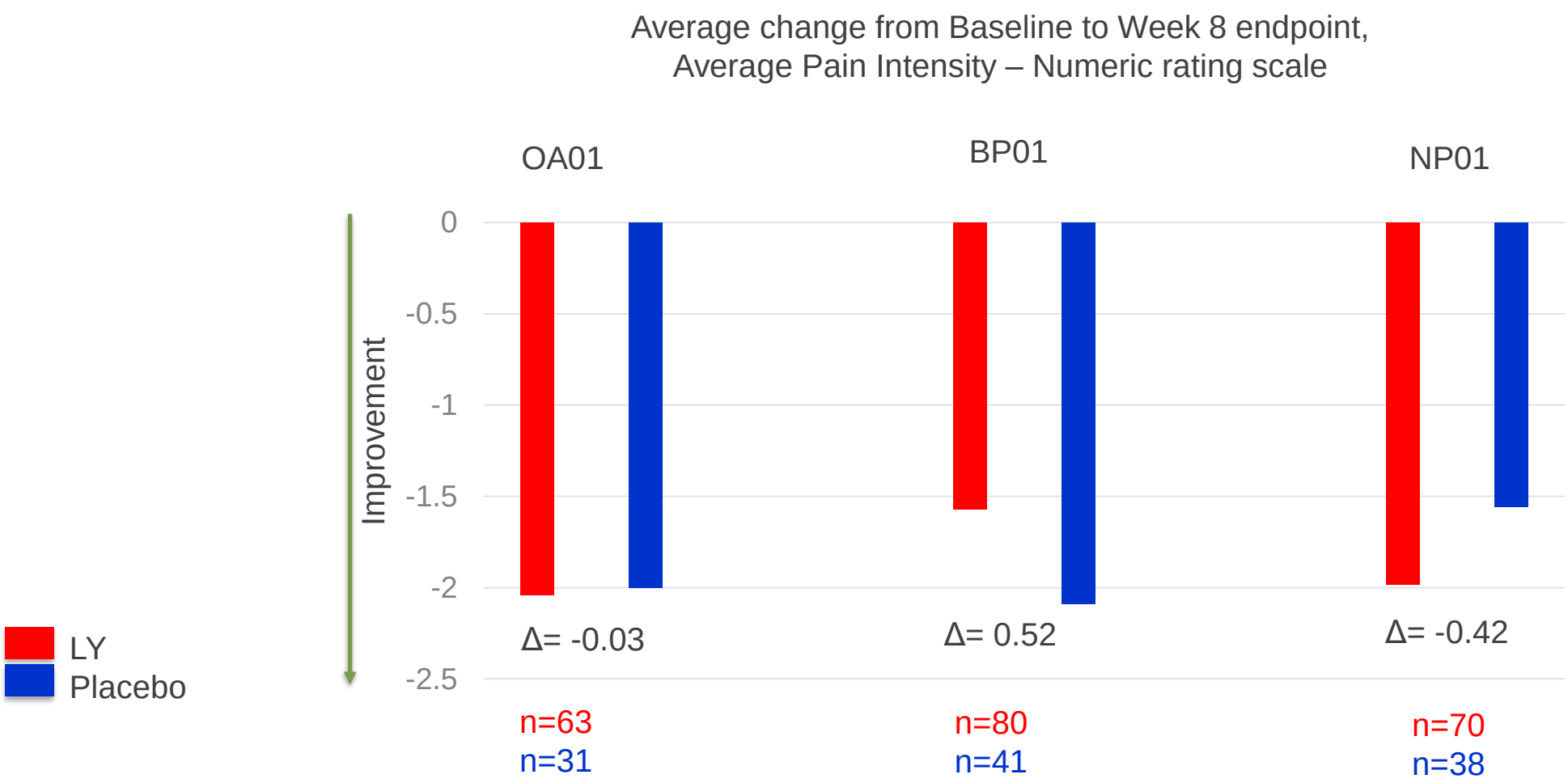
Operational efficiencies realized:

$ **30% Cost Reduction versus a standalone trial**

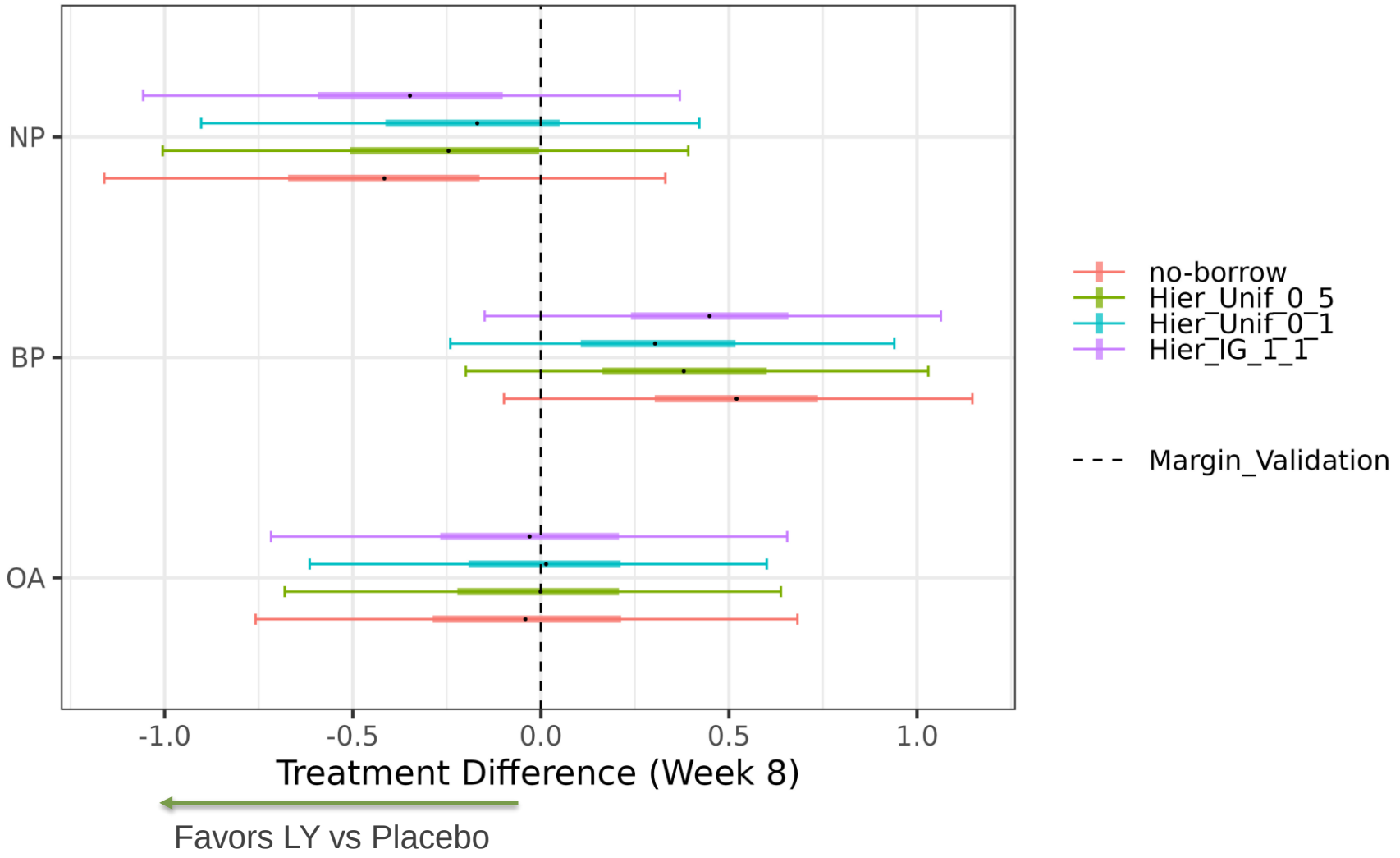
50% less time from Design Lock to First Patient Dosed

Enrollment duration reduced 30%

First asset results



First CPMP Asset TE Borrowing Results



Key Takeaways

1. Borrowing shrinks the estimated TE in the direction observed in the other disease types.
2. The neutral effect in OA does not change much after borrowing, but the shorter credible interval leads to more confidence in the treatment effect estimates.

Key Learnings from CPMP

Benefits:

- Same sites, same monitoring team and single database across multiple disease states/assets
  - Data and Site readiness efficiencies
- Ability to integrate safety data across chronic pain states earlier in development
- Biomarker collection may inform response within asset and across disease states

Challenges:

- Heterogenous Ph3-like population increases enrollment speed, but small sample sizes decrease magnitude of treatment effect and potential responder identification
- Inherent increase in placebo response
  - 2:1 active to PBO for 1st asset
  - Limited ability to control expectation bias and variability
- Limited ability to address asset-specific needs and make adjustments post-data

Additional Challenges

- Integrated dataset requires unblinded support (external to study team) to maintain blinding
- Using data from ongoing blinded studies for borrowing requires blinding considerations
- Study differences (e.g. differences in route of administration) may affect placebo borrowing.
- Repeat enrollers
  - Patients may complete an ISA and enroll in another one. Evaluate potential bias and amend protocol to limit repeat enrollers if needed.
  - Consider impact to placebo borrowing analyses?
- Not everyone loves statistical borrowing?!?!?!

Summary

- The development of the master protocol was not easy
  - But tremendous benefits have been realized
  - We have learned a lot which will improve the process of developing master protocols in the future
- The design introduces numerous statistical challenges, opportunities, and data analysis borrowing decisions
- More consistent data collection should enable better decision making in the drug development process
- Ultimately, a master protocol will enable better medicines to get to patients sooner

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