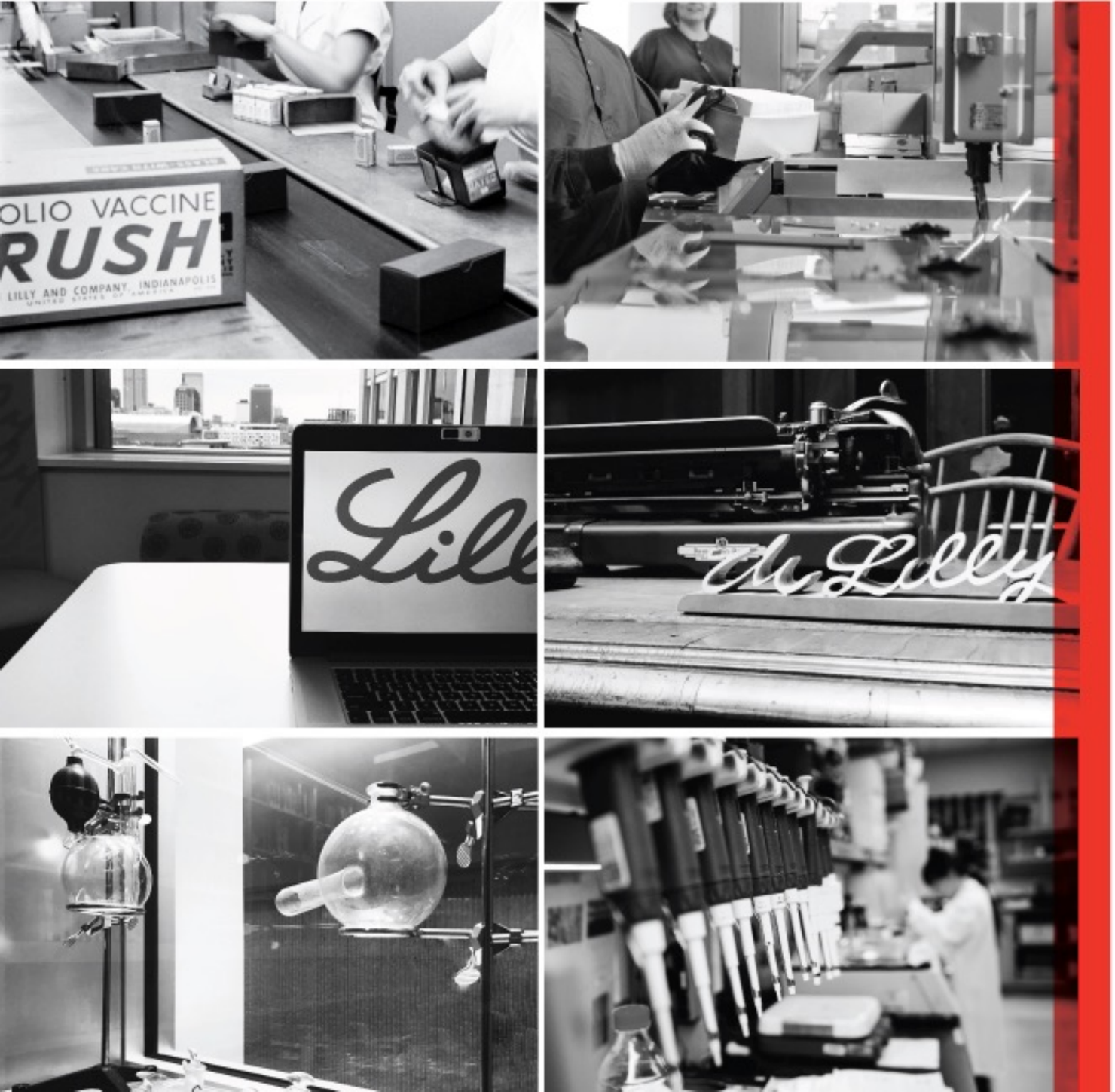


# Accelerating Innovation: A Master Protocol for Patients with Chronic Pain

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# Outline

- Overview of CPMP
- Some Statistical Details
- Interactive Tool
- Moving Forward

# Importance of Case Example

- Chronic pain is a public health crisis
- Pain is one of the main reasons patients seek care
- Over 20% of adults in the United States estimated to live with some form of pain lasting ≥3 months
- Only 0.7% probability of approval of novel analgesics that have completed phase 1 compared with overall probability of 6.5% for novel drugs across all diseases
- Opioids and non-steroidal anti-inflammatory medications (NSAIDs) are most used medications, which lack effectiveness and/or have safety concerns

This example showcases innovation in a very common disease state with continued high unmet need.

# One Solution: Master Protocol

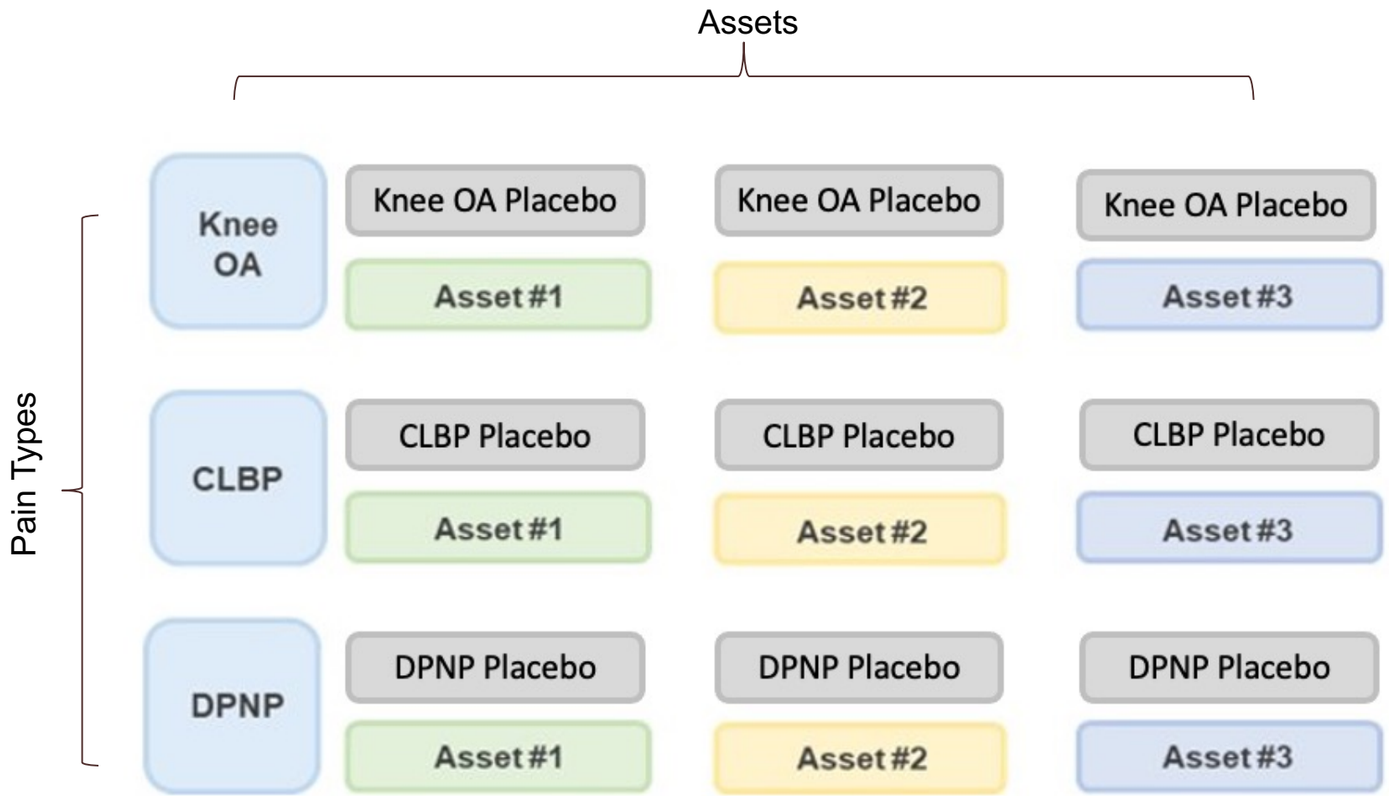
- Phase 2 studies often focused on one clinical pain population

- Chronic Pain Master Protocol (CPMP) tests multiple novel analgesics with different mechanisms of action in:
  - diabetic neuropathic pain (DPNP),
  - chronic low back pain, and
  - osteoarthritis pain

- Innovative statistical approaches allow comparisons of novel analgesics over time reducing the overall size and cost of clinical studies

# 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)

OA: musculoskeletal pain
DPNP: neuropathic pain
CLBP: mixed pain type

# Master Protocol: Structure

## Tier 1: Master Protocol (MP)

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

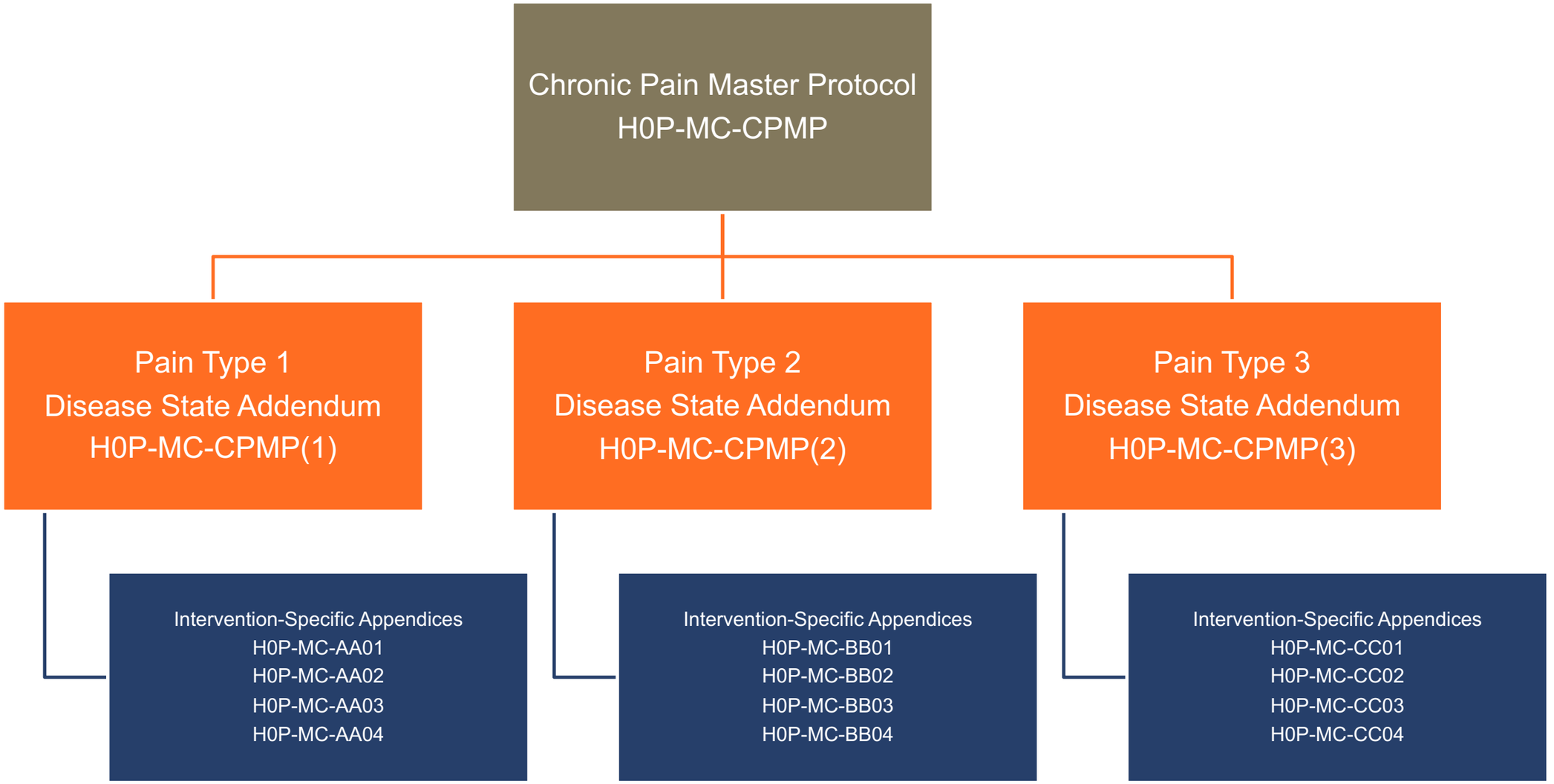
## Tier 2: Disease-state Addenda (DSA)

- 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

# 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
- 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:**

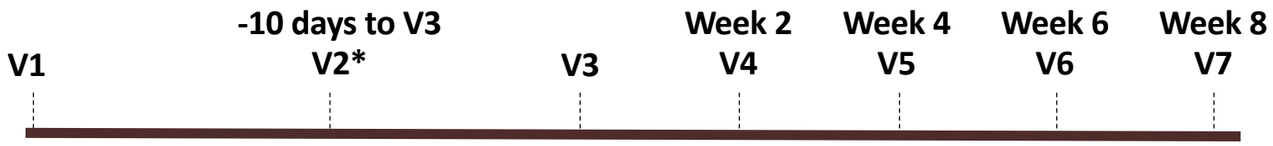
- Pain: Numerical Rating Scale (primary)
- Physical functioning
- Emotional functioning
- Patient global assessment

**Commonalities:**

- Standardized data collection, including similar visit schedules
- Master protocol level team established to analyze efficacy analysis data and to establish key decision rules

# Primary Efficacy Analysis

- Bayesian mixed model repeated measures (MMRM) model is primary efficacy analysis
  - The average of the NRS 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

# How to Balance?

## Standardization

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

VERSUS

## Flexibility

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

# Statistical Benefits

- 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
  - 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

# Significant Impact

- Enabled direct and indirect comparison of different medicines and pain types
- Cost reduction, reduction in time from protocol approval to first patient dosed, time to datalock, time to results/decision, and enrollment time
- Completed 12 proof-of-concept studies in 38 months and have validated three novel targets

# SOME STATISTICAL DETAILS

# Sources of Borrowing

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

# Borrowing Approaches

- Static
  - Pooling
  - Power priors
- Dynamic
  - Hierarchical modeling
  - Mixture priors
  - Commensurate priors

# Some Challenges Encountered

- Necessary changes to inclusion/exclusion for an ISA
- Use pooled placebo or ISA only in safety reviews?
- How to statistically handle repeat enrollers?
- Hesitancy to borrow from some team members
- Best approach to borrow?
- Whether or not to borrow across pain types
- Identifying and measuring placebo expectation bias

# Overview of Simulation Plan

- Simulations necessary to understand potential impact of borrowing on overall performance of trial

- Key factors evaluated via simulation for each ISA:
  1. amount of placebo data available from completed and ongoing ISAs;
  2. understanding of the potential treatment effects between pain types;
  3. any potential placebo “drift” that could occur over the course of the trial; and
  4. the impact of different routes of intervention administration.

- Accounted for fixed and longitudinal time point settings

# Key Elements in CID Simulations

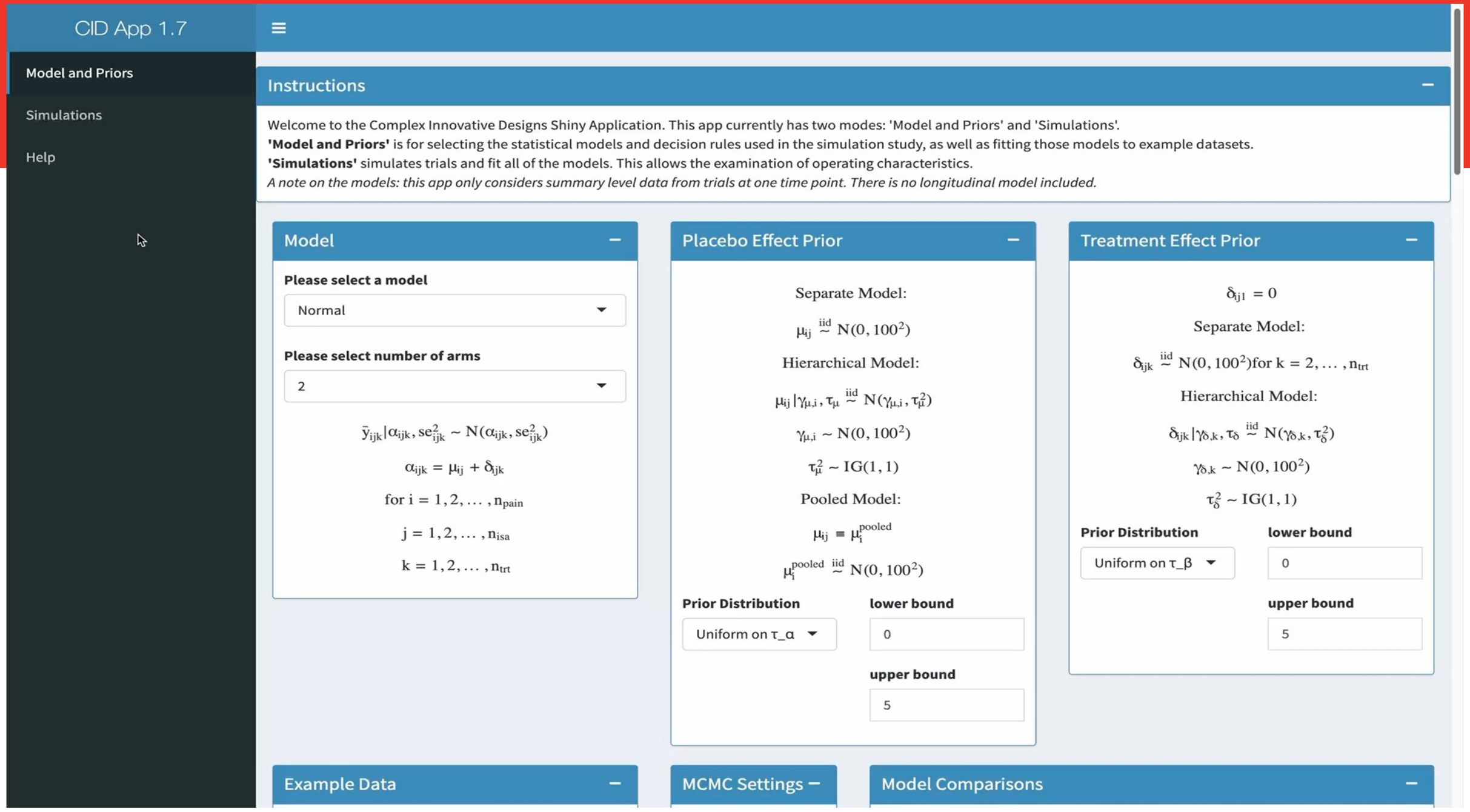
- Power, false positive rate, bias, and standard error of the treatment difference for placebo borrowing methods within a pain type
- Impact to operating characteristics across factors that may affect the underlying true placebo response and for borrowing treatment difference
- Benefits on power increase and/or sample size reduction
- Impact of various ISA initiation and lag times, enrollment/dropout rates
- Impact of quantity of patient-level data available from an ongoing ISA when current ISA has concluded and is evaluating the primary efficacy analysis

# How to speed evaluation of simulations?

- Created an R/Shiny Application to
  - Allow FDA to better evaluate this design
  - Reduce amount of paper sharing required
  - Provide more interactive visualizations
- Goal: modernize collaboration and reporting of simulation results
- Part of broader solution for more flexible simulations

# Key Features of the Application

- Application
  - Fits a user-defined model for single realization of master protocol
  - Simulates multiple trials to evaluate operating characteristics
- User can
  - enter data from completed ISAs, and simulate future ISAs
  - vary analysis model, prior distribution, and critical success factor
- Provides key plots and summary statistics


CID App 1.7
Model and Priors
Simulations
Help
Instructions
Welcome to the Complex Innovative Designs Shiny Application. This app currently has two modes: 'Model and Priors' and 'Simulations'.
'Model and Priors' is for selecting the statistical models and decision rules used in the simulation study, as well as fitting those models to example datasets.
'Simulations' simulates trials and fit all of the models. This allows the examination of operating characteristics.
A note on the models: this app only considers summary level data from trials at one time point. There is no longitudinal model included.
Model
Please select a model
Normal
Please select number of arms
2
$\bar{y}_{ijk}|\alpha_{ijk}, se^2_{ijk} \sim N(\alpha_{ijk}, se^2_{ijk})$
$\alpha_{ijk} = \mu_{ij} + \delta_{jk}$
for $i = 1, 2, \ldots, n_{pain}$
$j = 1, 2, \ldots, n_{isa}$
$k = 1, 2, \ldots, n_{trt}$
Placebo Effect Prior
Separate Model:
$\mu_{ij} \overset{iid}{\sim} N(0, 100^2)$
Hierarchical Model:
$\mu_{ij}|\gamma_{\mu,i}, \tau_\mu \overset{iid}{\sim} N(\gamma_{\mu,i}, \tau^2_\mu)$
$\gamma_{\mu,i} \sim N(0, 100^2)$
$\tau^2_\mu \sim IG(1, 1)$
Pooled Model:
$\mu_{ij} \equiv \mu_i^{pooled}$
$\mu_i^{pooled} \overset{iid}{\sim} N(0, 100^2)$
Prior Distribution
Uniform on τ_α
lower bound
0
upper bound
5
Treatment Effect Prior
$\delta_{ij1} = 0$
Separate Model:
$\delta_{ijk} \overset{iid}{\sim} N(0, 100^2)$ for $k = 2, \ldots, n_{trt}$
Hierarchical Model:
$\delta_{ijk}|\gamma_{\delta,k}, \tau_\delta \overset{iid}{\sim} N(\gamma_{\delta,k}, \tau^2_\delta)$
$\gamma_{\delta,k} \sim N(0, 100^2)$
$\tau^2_\delta \sim IG(1, 1)$
Prior Distribution
Uniform on τ_β
lower bound
0
upper bound
5
Example Data
MCMC Settings
Model Comparisons

# Overall Feedback from CID Program Experience

Positive interactions between Lilly and FDA 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 study design early in process was beneficial.
- CID program progressed how Lilly (Sponsors) & FDA should communicate on Bayesian methods, simulation plans and results.
- Need to have an avenue long-term enabling similar opportunities for statistical discussions between Sponsors/FDA
- 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
- 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

# Moving forward?

- Shared learnings across divisions
- Improved infrastructure
- Interactive simulations
- Meeting schedules that accommodate speed needed
- Improved education of statisticians and medical
- Use of AI/ML, other new technologies
- Use of decentralized trials and digital health technologies

# THANK YOU!