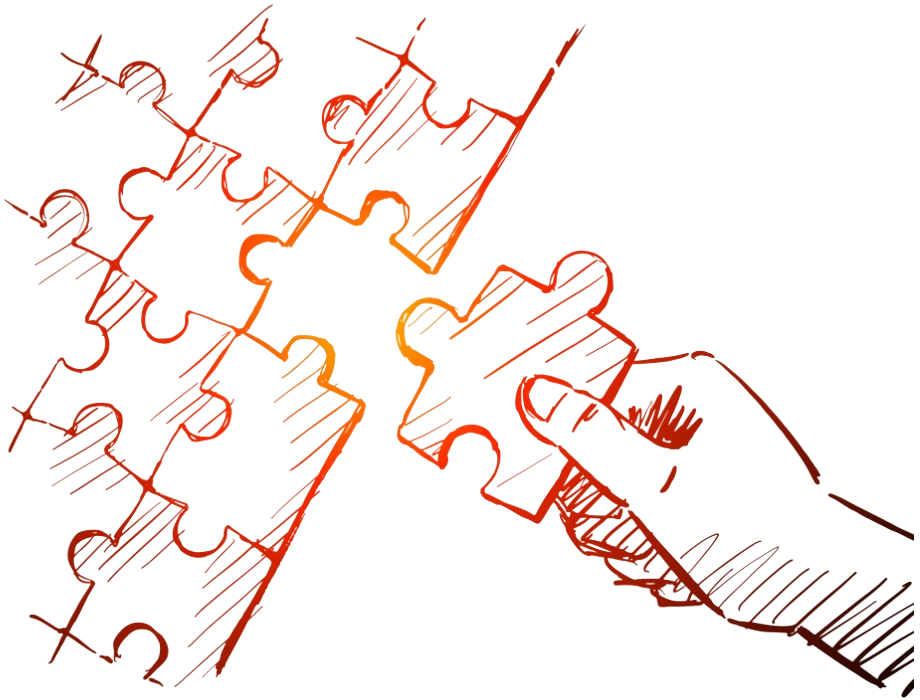
Evaluating Multiple Assets and Disease Types in a Master Protocol

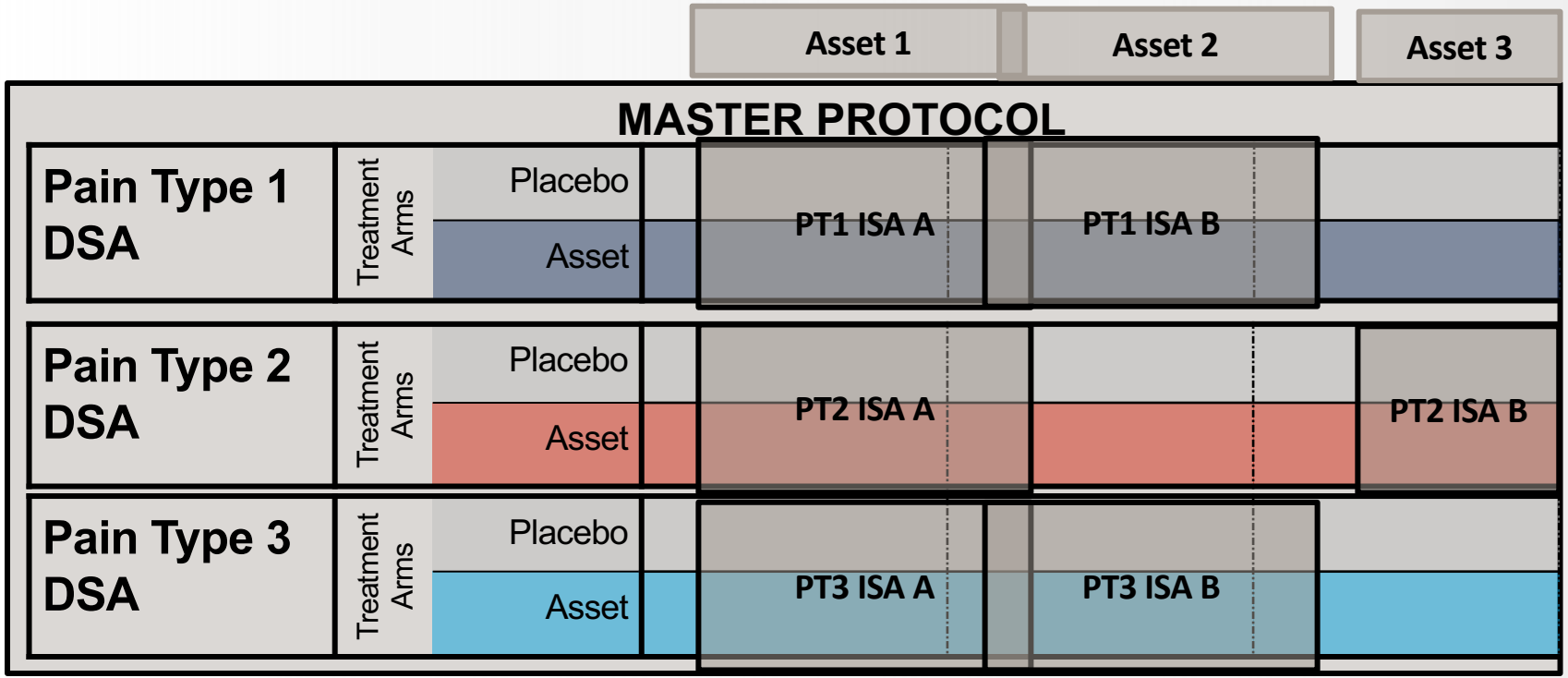
Eric Nantz, Ph.D.
Eli Lilly and Company
Bay Area Biotech-Pharma Statistics Workshop
2022-03-17

The Challenge

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



Pain Master Protocol

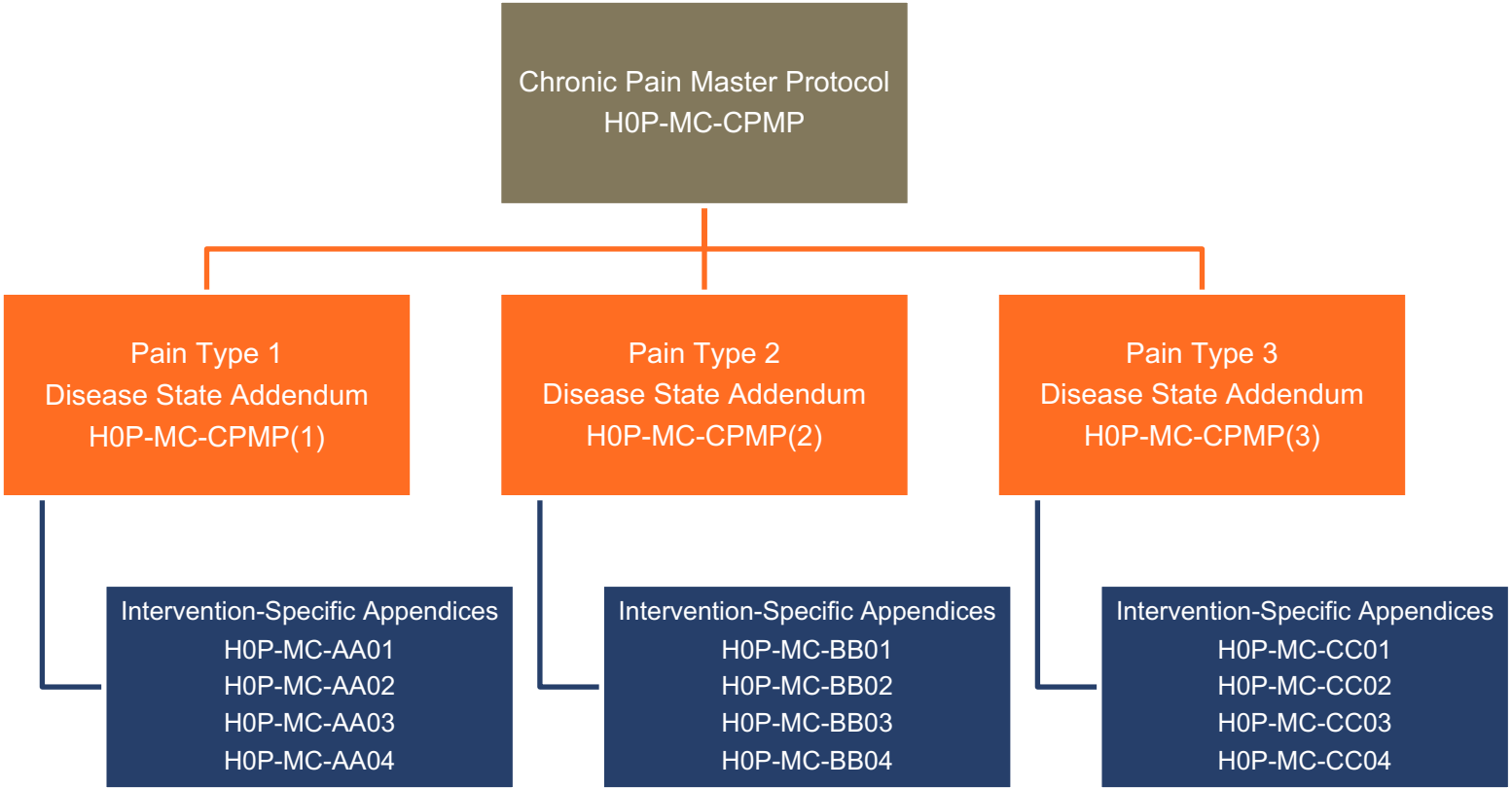


DSA = Disease State Addendum; ISA = Intervention-Specific Appendix

Master Protocol Structure

Tier 1: Master Protocol (MP)	Tier 2: Disease-state Addenda (DSA)	Tier 3: Intervention-specific appendices (ISA)
• 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	• Contain study elements specific to target population and unique scales for assessments • Ability to add additional DSAs	• 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



Complex Innovative Designs Pilot

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

September 5, 2019

Download PDF

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.

Link to Press Release

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

Types of Borrowing

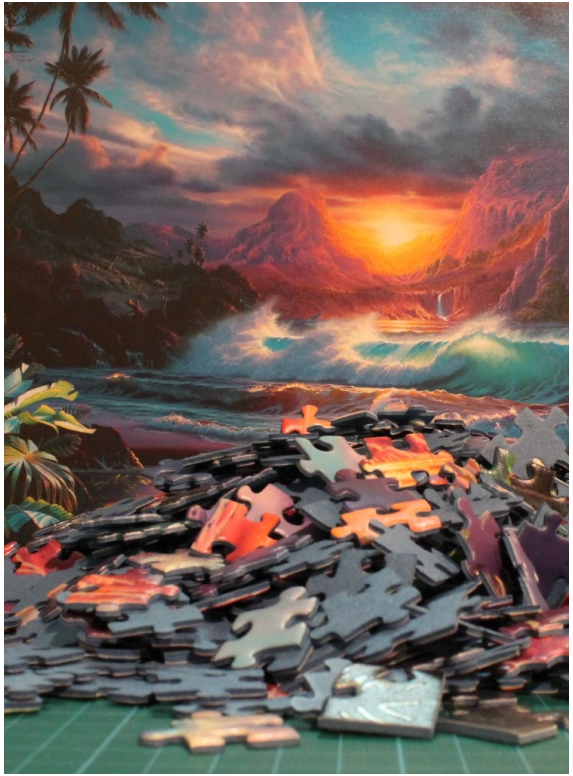
- Static vs Dynamic Borrowing
  - Static
    - Fixed prior
    - Pooling of data
    - Power priors
  - Dynamic
    - Mixture prior
    - Hierarchical modeling
    - Commensurate prior

Appeal of Dynamic borrowing:
- Borrows more when current data are similar to historical data

- Static vs. dynamic borrowing can vary by placebo arm and treatment difference
- FDA comments on Lilly's proposed borrowing approach: "It may be useful to explore additional methods, …., that adapt the level of borrowing based on the similarity of the placebo response."

Opportunities and Questions Abound

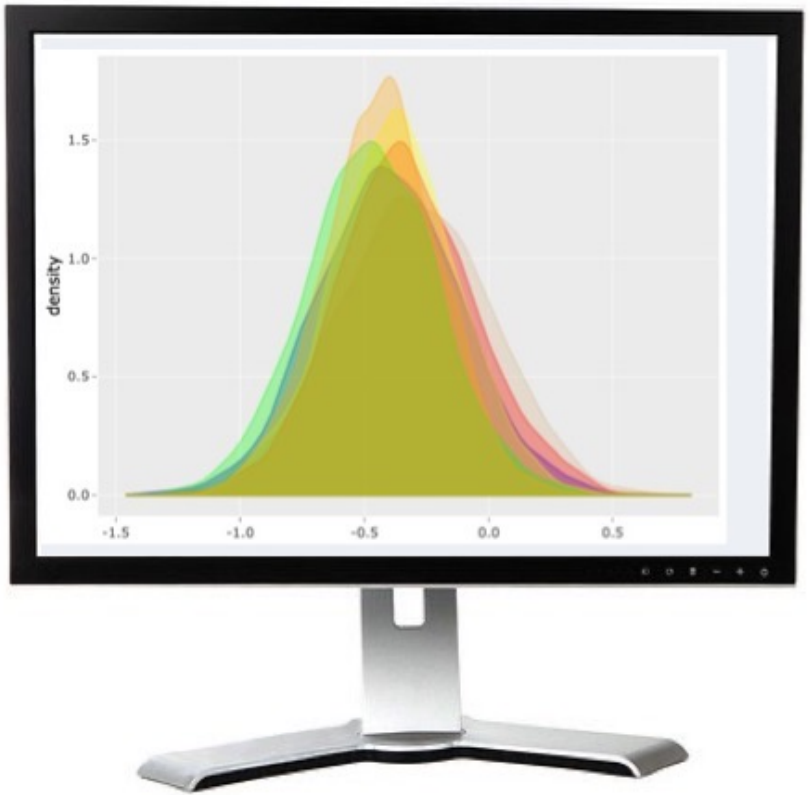
- Leveraging common features to optimize sample size
  - How much placebo or treatment effect should we borrow?
  - Which borrowing methodologies to use?
- Impact of placebo and treatment effect prior distributions?
- Probability of achieving critical success factor under various effect of interest and probability thresholds?



Advantages of using R for Clinical Simulations

- Integrate with multiple “within-node” and “multiple-node” parallel computing paradigms
  - Multiple CPU cores
  - Packages to interface with multiple high-performance computing orchestration tools
- Packages that wrap APIs to common web and cloud platforms
- Ability to manage project and analysis execution environments

Immersive Exploration with Shiny



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

Acknowledgements

- Statistical Innovation Center: Karen Price, JonDavid Sparks, Saptarshi Chatterjee
- Research Information and Delivery Solutions: Andrew Craven, Jeff Kriske, Patty Bragger-Wilkinson