

The Impact of Bayesian Methods in Drug Development: An Industry Perspective

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Outline

- Overview: Bayesian methods at Lilly
- Specific High-Level Examples
- Some Key Challenges and Benefits
- Outlook

Overview

Lilly's Advanced Analytics Hub: 5 Key Areas

- Clinical Trial Optimization
- Tailoring Analytics
- Bayesian Methods
- Data Mining
- Modeling and Simulation

Overview, cont.

Our Bayesian Team at Lilly has the mission to:

- Enable broad use of Bayesian inference in efficient decision making and evaluation of Lilly's portfolio
- Implement Bayesian methods throughout drug development to enhance decision making

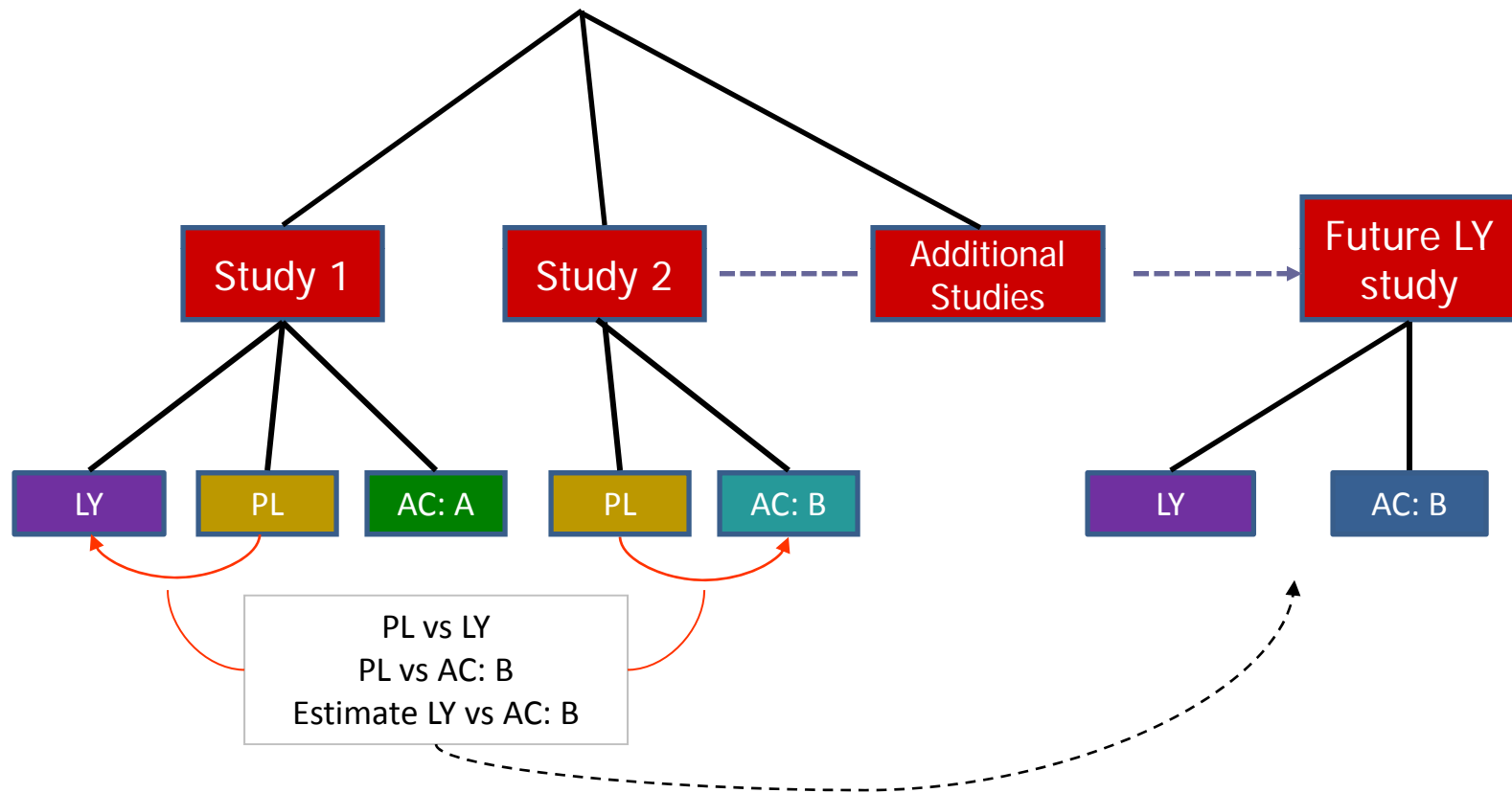
Overview, cont.

- 3 dedicated individuals
- Core team: Additional ~10 members ranging in 10-50% time
- Extended team: Additional ~20 members with approximately 10% time
- Cross-functional forum
 - For example, Global Health Outcomes, Global Patient Safety, cross-therapeutic Clinical Research Physicians, PK/PD, Informatics

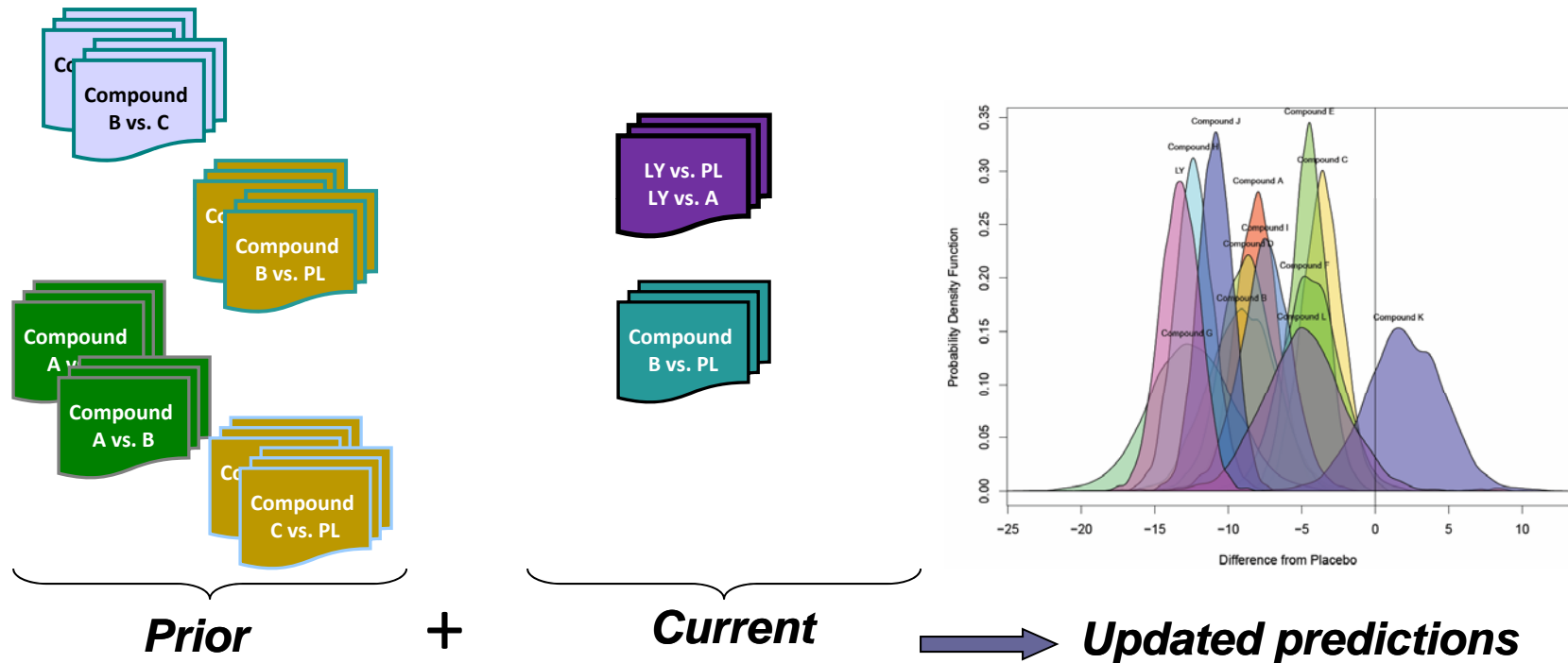
Overview, cont.

- Activities to impact drug development directly
 - Assess competitive landscape
 - Evaluate probability of critical success factors
 - Trial design / Clinical planning
 - Observational studies
- Activities to increase capabilities
- Activities to increase education/awareness
- Activities to collaborate externally

Assessing Competitive Landscape



Basic Framework: Throughout Drug Development



Ref for model: Spiegelhalter, Abrams, Myles 2004

NOTE: Data is from simulated scenario

Predicting Outcomes: Better Trial Designs

Posterior probability of successful study versus comparator B
under a variety of trial options

Trial Options	Posterior Probability of Success
Non-inferiority trial with clinically meaningful margin N = 100 per arm	0.70
Superiority study N = 100 per arm	0.15
Superiority study with increased sample size to N = 300 per arm	0.30

NOTE: Data is from simulated scenario

Assessing Key CSFs

- Critical success factors (CSFs) need to be achieved for a drug to be successful
- Using Bayesian approach, we calculate an updated probability of achieving the CSFs when new data are available
- Provides decision makers with probabilistic statements of success (or failure) for the CSFs of a compound throughout drug development
- Provides guidance on how to define and evaluate the CSFs
- Use framework to predict probability of success in future trials

Power vs. Probability of Success

- Traditionally, we use power to design studies
- As others have pointed out (e.g., Chuang-Stein 2006) a very high statistical power to detect a treatment effect does not translate to a high success probability
- Providing the probability of success is key for the decision-making process
- Can be done at trial level or compound level
- Use of historical data in all cases can provide added benefit



Clinical Design Strategy 2: Improved Design of Randomized Trials with Use of Information from Historical Controls

Specific Aim: To develop **mixture prior models** for use when incorporating **historical control data** with a concurrent control that is part of a randomized controlled trial (RCT).

Flexible Bayesian nonparametric models allows one to include more relevant data sources than is possible when using other models; the **mixture approach will be more robust to data-source-specific departures from a common, exchangeable hierarchical model.**

We will **develop and test this model**, using the RCTs in JANUS and data from other databases. We will carry out **simulation** studies to test these mixture prior models and **compare the method to alternative formulations** for incorporating historical data. We will use patient-level data in FDA database, along with complementary data warehoused in these other databases.

Observational Studies

- Use of observational research, such as with data from claims databases and EMRs, has grown in recent years.
- With large and heterogeneous populations, observational databases are a rich source of data mining.
- The use of such data for comparative effectiveness is challenged by selection bias and potential for unmeasured confounding.
- Statistical adjustment for measured confounders is possible; however, the validity of such methods relies on assumption of no unmeasured confounders.
- While many researchers mention limitations due to unmeasured confounding, few directly assess the impact of unmeasured confounding quantitatively¹.

1 Schneeweiss 2006, Gustafson and McCandless 2010

Observational Studies, cont.

- Bayesian approaches provide a natural solution, as the unmeasured confounder can easily be modeled
- Whether internal or external information exists, Bayesian approach can incorporate this information into the statistical analysis through a prior distribution
- The posterior distribution of the treatment effect then reflects the uncertainty of unmeasured confounding in addition to random error
- Bayesian approach can also help determine how much internal validation data would be necessary to reliably inform the unmeasured confounding

Observational Studies, cont.

- Via external collaboration with Baylor University
 - We have a thorough understanding of the literature
 - Developed tools/methods/etc. to implement unmeasured confounding approaches, including primarily Bayesian methods
 - We can provide guidance to our colleagues regarding the use of the unmeasured confounding approaches
 - Extended available methods to better meet our needs

Specific Projects Conclusion

- There are a number of applications of Bayesian methods utilized at Lilly for decision making
- Bayesian approaches are proving quite useful and are well received by the cross-functional groups who review results
- More work to be done...

Other Internal Non-compound Efforts

- As mentioned, forums for discussing Bayesian approaches (cross-functionally) – external speakers are welcome!
- External collaborations – vital! And, win/win.
- Development of educational modules
- Development of templates for documenting / planning Bayesian applications
- Computational advancements

Clear Benefits

- Bayesian methods allow us to directly answer questions we care about
- They provide flexibility and can easily predict future outcomes
- Results have a straightforward interpretation and enable us to inform decision makers directly the probability of events of interest happening
- Able to better understand risks
- Allows teams to easily evaluate “what if” scenarios and more responsibly discharge risks
- Ultimately, result in better patient outcomes

Some Challenges Across Industry

- Lack of education and tools need to be developed
- Need the right resources to get work done
- Data availability
- Not clear acceptance of approaches, particularly by regulatory in phase 3
- Sometimes people are hesitant to use prior information or cannot agree on how to use it
 - Need knowledge of how to use prior information better
- Need broad input and open communication across regulatory, academia, and industry

Outlook

- Awareness/education is increasing
- Companies are supporting RIGHT resources
- External collaborations are increasing: for example, Bayesian DIA working group officially sanctioned
 - Further allows for the academic, regulatory, and industry communities to communicate regularly and openly

Full References

- Spiegelhalter, Abrams, & Myles (2004) *Bayesian Approaches to Clinical Trails and Health-Care Evaluation* (John Wiley & Sons)
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