The Future of Bayesian Biostatistics in the Regulatory World

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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Bayesian Methods in the Regulatory World (Present)

- We are seeing increasing adoption of Bayesian methods in many different areas, with different purposes and advantages.

https://link.springer.com/article/10.1007/s43441-022-00483-0

Complex Innovative Trial Design Program

- The Complex Innovative Trial Design (CID) which started under PDUFA VI was continued under PDUFA VII.
- The longer, statistician led meanings have been helpful for cultivating and promoting complex, often Bayesian methods in clinical trials.

https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program

CID Case Examples

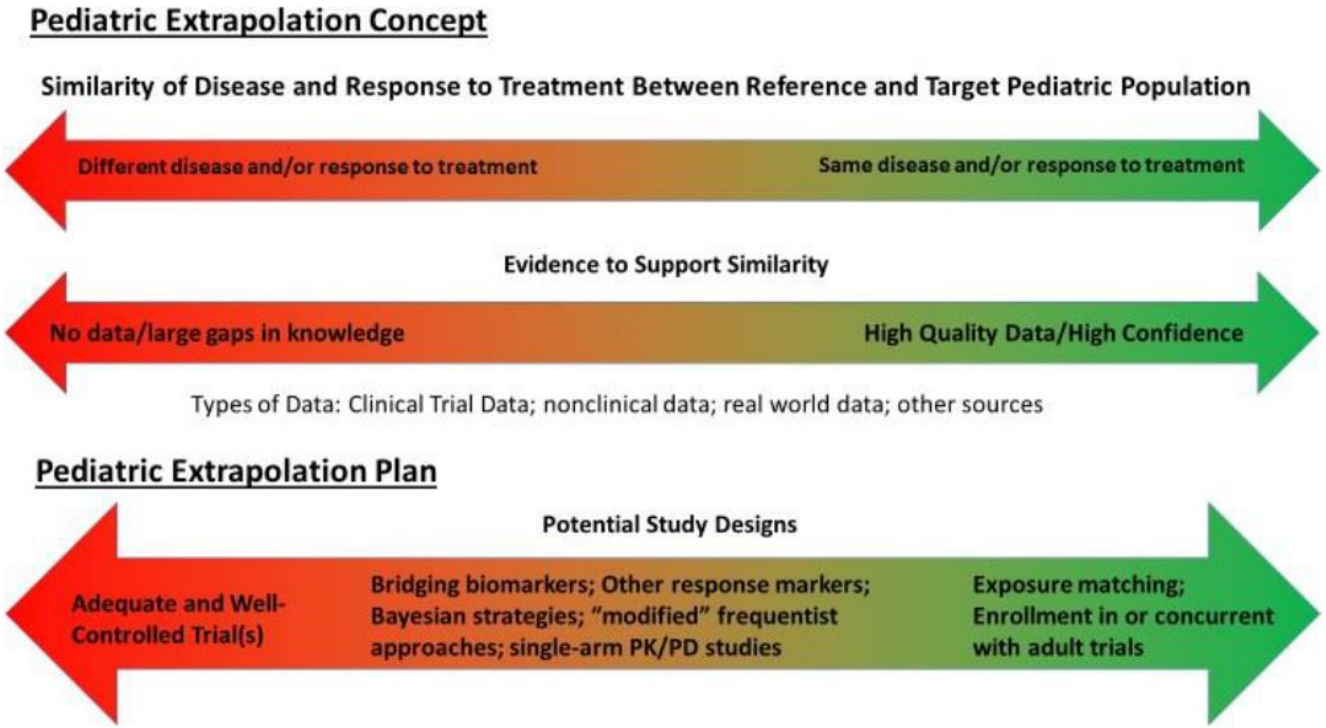
- So far, there are five published case studies, all of which utilize Bayesian approaches in some fashion:
  - EMAS Case Study
  - Multiple Sclerosis Case Study
  - Master Protocol Case Study
  - Lupus Case Study
  - DLBCL Case Study

Pediatric Extrapolation

- The area I am most involved in is the use of Bayesian methods for supporting pediatric extrapolation.
- This was discussed in 2004 at an FDA workshop but use in an actual CDER regulatory review took until 2019.

https://doi.org/10.1191/1740774505cn102oa

ICH E11A (2022) – Figure 1



Pediatric Extrapolation Examples

- Belimumab: https://www.fda.gov/media/127912/download?attachment
- Albuterol and Budesonide Combination https://www.fda.gov/media/167843/download?attachment
- Empagliflozin: https://www.fda.gov/media/172972/download?attachment
- Linagliptin: https://www.fda.gov/media/172630/download?attachment

Subgroup Analyses (Drug Trial Snapshots)

- Since 2015, CDER has published enhanced demographic summaries for new molecular entities and original biologics to make demographic data more available and transparent.
- As part of the initiative, we have used Bayesian hierarchal models to implement shrinkage estimation approaches to improve estimation for the various demographic subgroups.

https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots
https://www.fda.gov/drugs/regulatory-science-action/impact-story-using-innovative-statistical-approaches-provide-most-reliable-treatment-outcomes

Dose Finding (Project Optimus)

- Traditional dose finding trials in oncology were often based on rule-based dose-escalation approaches such as 3+3 designs.
- Recently, efforts have been made move to more informative designs including Bayesian model-based and model-assisted approaches.

https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus

Real-World Data

- In some cases, rather than the ideal placebo-controlled design, it may be necessary to rely on controls that utilize historical real-world data to support the efficacy assessment.
- Bayesian methods have been explored in this case, as they allow the construction of a prior that flexibly integrates evidence from multiple sources.

Adaptive Trials

- Bayesian methods have also been extensively discussed in guidance as a way of implementing adaptive trials.

https://www.fda.gov/media/78495/download

The Future

- How do we want to see Bayesian methods used in the future?
- How do we ensure this happens?

Why Do People Prefer Frequentist Methods?

- Familiar
- Less communication needed
- Fewer decision to be made
- Quicker to review

Issues we Often Face

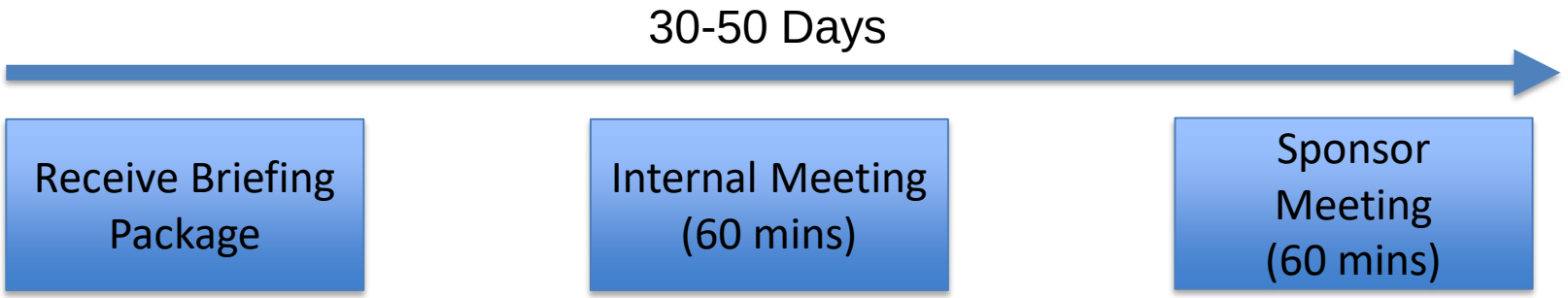
- Clear need for education
- Difficulty communicating the design choices and their implications
- Not always clear how decisions need to be made and by whom
- Additional review time needed

C3TI Demonstration Project

- “C3TI aims to increase experience in Bayesian statistical methods in simple trial settings across sponsors, CDER clinical reviewers, and CDER statisticians, including deepening an understanding of their applicability, opportunities, and challenges.”

https://www.fda.gov/about-fda/cder-center-clinical-trial-innovation-c3ti/bayesian-supplemental-analysis-bsa-demonstration-project

Communicating the Design Choices



- Goal: make the package and methods as easy to explain as possible

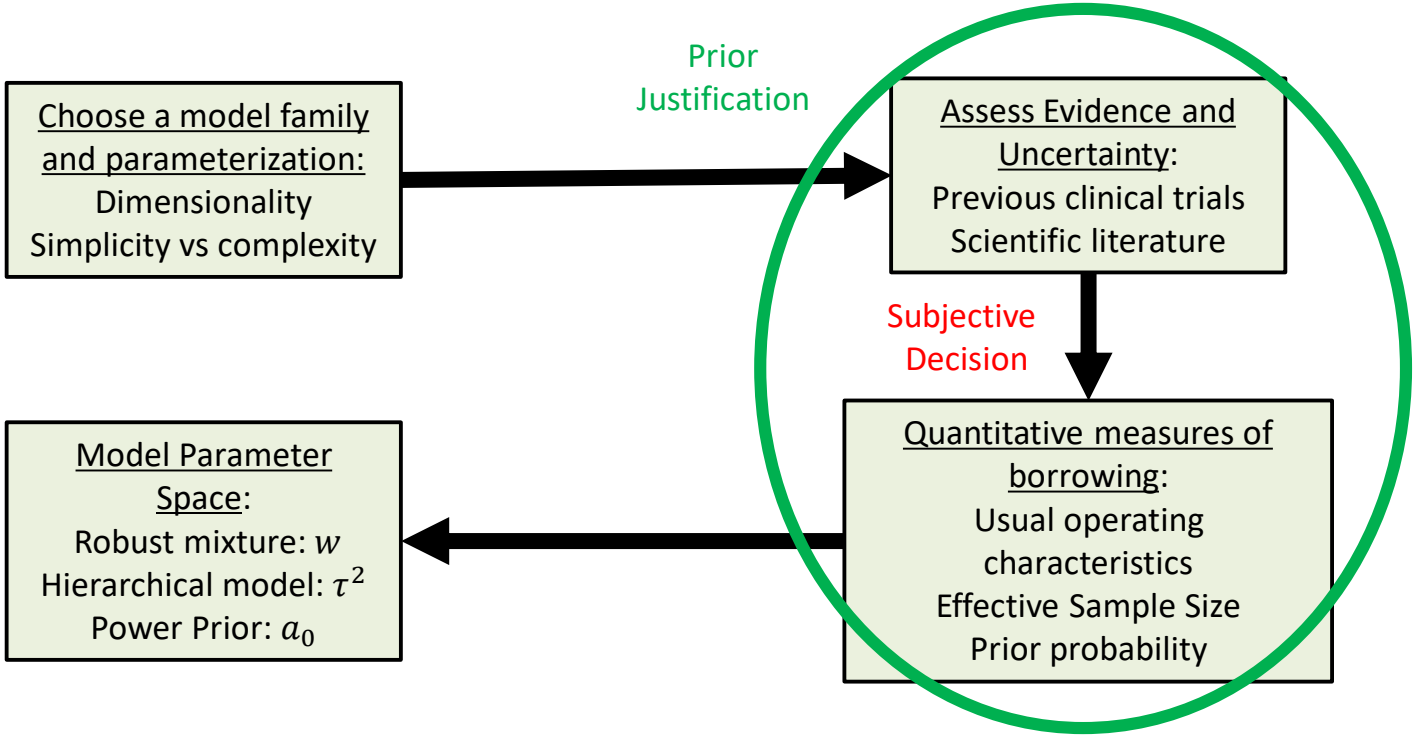
Need For Education

- When using Bayesian methods there are many educational hurdles that often occur:
  - Change in decision paradigm
  - Change in terminology

Communication Goals

- Goal #1: Transparency
  - Explain what the key modelling choices were
  - Be transparency in how the data influenced the decisions for these choices
- Goal #2: Plain language
  - Statisticians have to ‘translate’ methods for clinicians
  - Often takes several attempts for necessary details to be absorbed, which is challenging in a typical review cycle

Example – How Much to Borrow?



Mathematical Levers and Prior Justifications

- Each method has mathematical levers that are used to control the degree of reliance on the source information (w, δ, τ, a_0).
- To determine meaningful parameters values, we must translate these to terms that are meaningful and determinable using clinical judgment.
- Helpful to consider alternative metrics that can serve as more meaningful and familiar intermediaries.

Guidance

- By the end of FY 2025, FDA will publish draft guidance on the Use of Bayesian Methodology in Clinical Trials of Drugs and Biologics. FDA will work towards the goal of publishing final guidance within 18 months after the close of the public comment period on the draft guidance.
- If, after receiving comments on the draft guidance, FDA determines that the guidance requires substantive changes on which further public comments are warranted, FDA will issue a revised draft guidance within those 18 months instead.
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Conclusion

- Goals:
  - Make the advantages clear
  - Share success stories
  - Give people a road map and how to navigate
    - How did we make decisions
    - How did we justify those decisions


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