The Role of Bayesian Dynamic Borrowing Methods in Rare Disease Clinical Trials

Lei Nie, joint work with Ying Yuan

Disclaimer

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

Outline

- Rare Diseases: background, current approaches, and challenges
- One Possible Alternative to the Traditional Development Strategy: Basket trials
- Bayesian Dynamic Borrowing Methods
- Considerations

Rare Diseases: Background

- Scientists have identified nearly 7,000 rare diseases. In the United States, more than 30 million people have at least one rare disease, and more than half of these people are children.

- The Orphan Drug Act, enacted in 1983, provides financial incentives and other inducements to industry for developing treatments for rare diseases and conditions.
  - In 1983, the FDA approved the first-ever two treatments for rare diseases.
  - Until 2022, the FDA had 1093 approvals for rare diseases

References: https://www.fda.gov/patients/rare-diseases-fda; Rare Disease Day 2019, 2020, 2021 and 2022; https://www.accessdata.fda.gov/scripts/opdlisting/oopd/

Rare Diseases: Current Approaches

- Approvals of treatments for rare diseases meet the same statutory standards for efficacy and safety.

- The FDA exercises flexibility, e.g.
  - Considering treatment for a serious disease with no available therapy, or for a rare disease with limited sample size
  - Utilizing RWD/RWE, historical controls, and/or natural history studies

Rare Diseases: Continuing Challenges

- Limited patients available for trials
- Poorly characterized natural history
- Lack of consensus on endpoints
- Delayed and mistaken diagnosis
- Phenotypic diversity within a disorder
- The burden on the patient to participate
- The collective amount of 7,000 rare diseases leads to resource constraints
- Noninferiority trials

Modernization of Drug Development

- The 21st Century Cures Act emphasizes modernization of drug development.

- To satisfy a mandate of the Cures Act on the use of novel clinical trial designs including the Bayesian design, the FDA published
  - A guidance on adaptive design in 2019
  - A guidance on complex innovative design in 2020

- Both guidance documents include Bayesian designs

One Possible Alternative to the Traditional Development Strategy

- Thousands of rare diseases, far fewer etiologies/mutations

- Basket trials
  - Enroll patients based on their genetic alteration or biomarkers, regardless of diseases
  - Determine if a new drug can successfully treat disease conditions based on genetic alteration

Bayesian Dynamic Borrowing methods

- Data driven

- Dynamic Borrowing
  - Strongly borrow if external data are congruent to the internal data
  - Barely borrow if they are incongruent

Bayesian Methods for Dynamic Borrowing

- Informative prior based approaches
  - Power Prior (Ibrahim and Chen, 2000)
  - Commensurate Prior (Hobbs, et al., 2011)
  - Robust Meta Analytic Predictive Prior (Schmidli, et al., 2014)
  - Elastic Prior (Jiang, et al., 2021)
  - ……
- Model based approaches
  - Bayesian hierarchical model (BHM, Bernardo and Smith, 1994, Thall, et al., 2003)
  - Multisource exchangeability model (Kaizer**,** Koopmeiners, and Hobbs, 2018)
  - Calibrated BHM (Chu and Yuan, 2018)
  - Clustered BHM (Jiang, et al., 2021)
  - ……

Bayesian Hierarchical Model (BHM)

Pros

- Intuitive when there are multiple sources of data to borrow
- Appealing mechanism to account for study heterogeneity for dynamic borrowing

Cons

- Challenging to estimate the shrinkage parameter to achieve dynamic information borrowing
- Relying on the exchangeability assumption

Power Prior

Pros

- Intuitive
- An explicit mechanism to account for the incongruence between data

Cons

- Determination of power parameter is challenging, and assigning it a prior does not provide satisfactory adaptation on information borrowing
- Additional complication when we borrow from multiple sources

Commensurate Prior

Pros

- The idea of the specific shrinking is appealing
- An explicit mechanism (commensurability parameter) to account for the incongruence between data

Cons

- Estimation of commensurability parameter is challenging
- Integrating out nuisance parameters can be strenuous
- Less straightforward to accommodate data from multiple sources

Robust Meta Analytic Predictive Prior

Pros

- Intuitive
- An explicit mechanism to acknowledge potential incongruence between data

Cons

- Specification and interpretation of the weight is challenging,
- Does not necessarily provide satisfactory adaptation on information borrowing

Elastic Prior

Pros

- Actively control information borrowing based on the congruence between data
- Incorporate clinical knowledge to shape the behavior of borrowing (e.g., preventing borrowing when the difference between data exceeds a clinically significant difference)
- Achieve a high degree of dynamic borrowing because of the active adaptation on information borrowing

Cons

- Simulation calibration is needed to determine the elastic function

Consideration 1: Starting With Estimand

- Principles and thinking process outlined in ICH E9(R1) are relevant whenever a treatment effect is estimated, or a hypothesis related to a treatment effect is tested. Thus, ICH E9(R1) therefore remains applicable to basket trials.

- It is important to clearly define the estimands depending on the study objectives, which can be complex in basket trials.

- We will distinguish different study objectives and define corresponding estimands, which form the basis of operational characteristics.

Consideration 2: Incorporating Clinical Expertise

- The operational characteristics of the dynamic borrowing may rely on an adequate sample size for every disease under consideration, which however, could be lacking.

- Incorporate expertise from other disciplines
  - Science
  - Clinical knowledge and judgement
  - Potentially mechanistic model

Consideration 3: Addressing Issues

- Different disorders may use different endpoints
- Treatments may be efficacious in some but not all diseases under consideration
- Treatments may be efficacious in all diseases under consideration but with different treatment effect sizes

Statistical Thinking Guides Statistical Inference

For the challenges we are facing, statistical thinking helps us to develop new methods and solutions.

- Statistical thinking starts with a question of interest
- Every statistical inference method has its own limitation.
- Current resources and methods may not be enough to address the challenges in a timely fashion
- Statistical inference executes statistical thinking into a specific drug development

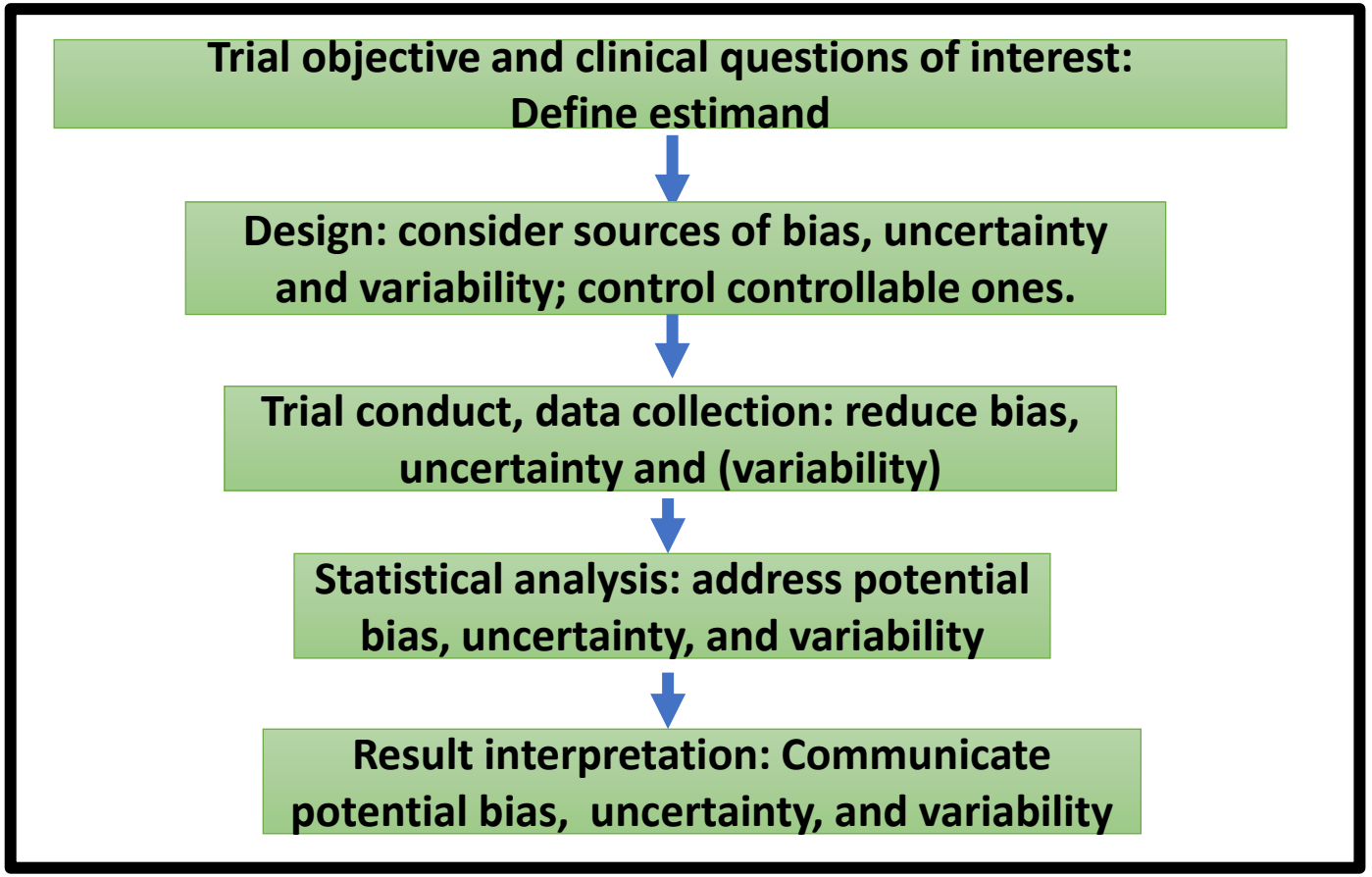
"Based on results from cognitive sciences, an expert follows four general steps in problem solving:

a) they represent the problem
b) determine the solution strategy
c) execute the strategy, and
d) evaluate the results."

Bretz and Greenhouse, ASA RISW 2021

"at the heart of our subject are core issues about uncertainty and variability that have both a permanent value and an exciting continuing challenge that is conceptual, mathematical, and computational" by Cox and Efron B. (2017). Statistical thinking for 21st century scientists. *Science advances*

One Statistical Thinking Process



Collaboration

- FDA
  - has an excellent and comprehensive training and education program
  - is transitioning into drug review modernization
  - has many internal research programs to promote innovation and exploration
  - has external collaboration programs, such as
    - Centers of Excellence and Regulatory Science Education (CERSI)
    - Broad Agency Announcement for solicitation of research to advance regulatory science
- Challenges and opportunities span the development process, demanding innovative approaches and collaboration
  - success will rely on collaboration among statisticians, clinicians, and other scientists, between sponsors and FDA.

Opportunities for YOU at the FDA

- Attend an Advisory Committee meeting
- ORISE Fellowship
- Commissioner's Fellowship (2-year program)
  - Regulatory science training and research with mentor
- Apply for job (OB is actively recruiting)
  - Mathematical statisticians and Statistical analysts
  - Regardless of citizenship or visa status
  - Inquire at OTSHires@fda.hhs.gov.

References

- Ibrahim, J.G.& Chen, M.H. (2000) Power prior distributions for regression models. *Statistical Science*, **15**, 46– 60.
- Hobbs, B.P., Carlin, B.P., Mandrekar, S.J.& Sargent, D.J. (2011) Hierarchical commensurate and power prior models for adaptive incorporation of historical information in clinical trials. *Biometrics*, **67**, 1047– 1056.
- Schmidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D.& Neuenschwander, B.(2014) Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, **70**, 1023– 1032.
- Jiang L, Nie L and Yuan Y (2021) Elastic priors to dynamically borrow information from historical data in clinical trials, *Biometrics*, https://doi.org/10.1111/biom.13551
- Thall P.F., Wathen J.K., Bekele B.N., Champlin R.E., Baker L.H., Benjamin R.S., (2003) Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes, Stat. Med. 22 (5) 763–780.
- Kaizer, A. M., Koopmeiners, J. S., & Hobbs, B. P. (2018). Bayesian hierarchical modeling based on multisource exchangeability. *Biostatistics*, *19*(2), 169-184.
- Chu, Y.& Yuan, Y. (2018a) A Bayesian basket trial design using a calibrated Bayesian hierarchical model. *Clinical Trials*, **15**, 149– 158. [an extension of BHM to improve dynamic information borrowing]
- Jiang L, Li R, Yan F, Yap TA, Yuan Y. (2021) Shotgun: A Bayesian seamless phase I-II design to accelerate the development of targeted therapies and immunotherapy. *Contemp Clin Trials*. 2021 May;104:106338. doi: 10.1016/j.cct.2021.106338. [clustered BHM to relax the exchangeablity assumption]