Communicating Bayesian Design and Analysis to Statisticians

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Disclaimers

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.
- I have nothing to disclose

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Outline

How to Align on Bayesian Design and Analysis?

1. Dispel myths
2. Align on estimands with key stakeholders early
3. Provide well-structured documentation
   - Prior Distribution
   - Sample Size
   - Decision Criteria
   - Simulations

Dispel Myths

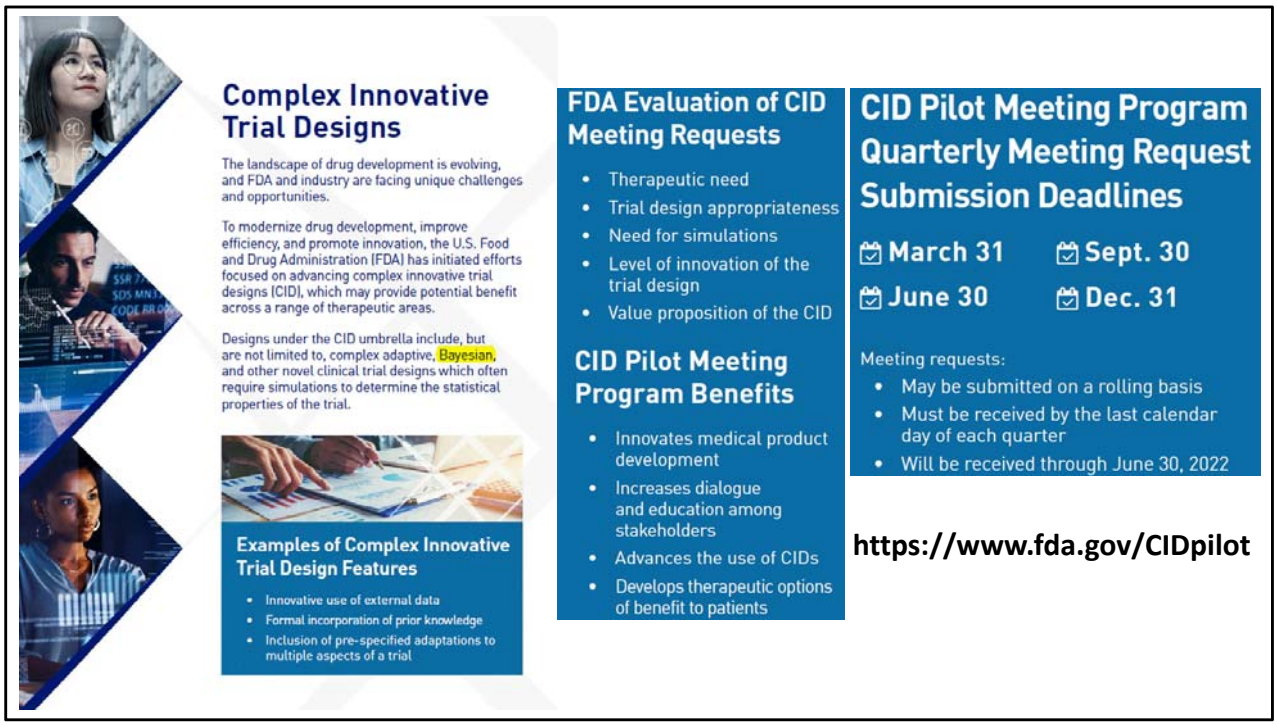
Demonstrating
Substantial Evidence of
Effectiveness for
Human Drug and
Biological Products
Guidance for Industry

DRAFT GUIDANCE

C. Statistical considerations

The strength of evidence in each trial contributing to meeting the substantial evidence standard should be assessed by appropriate statistical methods. The uncertainty about the findings from each trial should be sufficiently small and the findings should be unlikely to result from chance alone, as demonstrated by a statistically significant result or a high posterior probability of effectiveness.[18] Statistical approaches should be specified in advance, to limit erroneous conclusions resulting from multiplicity.

https://www.fda.gov/media/133660/download



https://www.fda.gov/CIDpilot
https://www.fda.gov/media/129256/download

Labeling Example

Table 2: Primary Efficacy Endpoint Results (Study 2)

Primary Endpoints	Ages 6 months – 4 years	Ages 5 – 12 years
Procedural Success (rate)[a]	86% (103/120) (95% credible interval: 80%, 91%)	89% (91/102) (95% credible interval: 82%, 93%)
Tube Placement Tolerability (mean FPS-R score) [b]	N/A	3.3 (out of 10) (95% confidence interval: 2.6, 4.0)

[a]The Procedural Success endpoint was evaluated using a Bayesian Hierarchical framework. The success rate in each age group was compared to the performance goal of a 68% success rate. Success was declared for each age group if the lower bound of the 95% credible interval exceeded the performance goal of a 68% success rate. The study was designed to evaluate each age group separately, with data borrowing between groups.

[b]The mean Tube Placement Tolerability score was compared to a performance goal of 4.2. Success was declared if the upper bound of the 95% confidence interval was less than 4.2 on the FPS-R.

https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190016C.pdf

Sessions Featuring Bayesian Methods

PS1a - Experience of Bayesian Approach and Its Applications in Studies of Stem Cell Products, Medical Devices, and Drugs
Wed, Sep 23, 11:00 AM - 12:45 PM
Virtual

PS4a - Bayesian Methods in Clinical Trials: Making Better Decisions via Synthesizing Evidence
Parallel Session
Thu, Sep 24, 3:00 PM - 4:15 PM
Virtual

Application of Bayesian Methods in Regulatory Decisions
Lei Nie, FDA

PS6a - Utility of Bayesian Approaches in Design and Analysis for Regulatory Approval of Medical Products
Parallel Session
Fri, Sep 25, 3:30 PM - 4:45 PM
Virtual

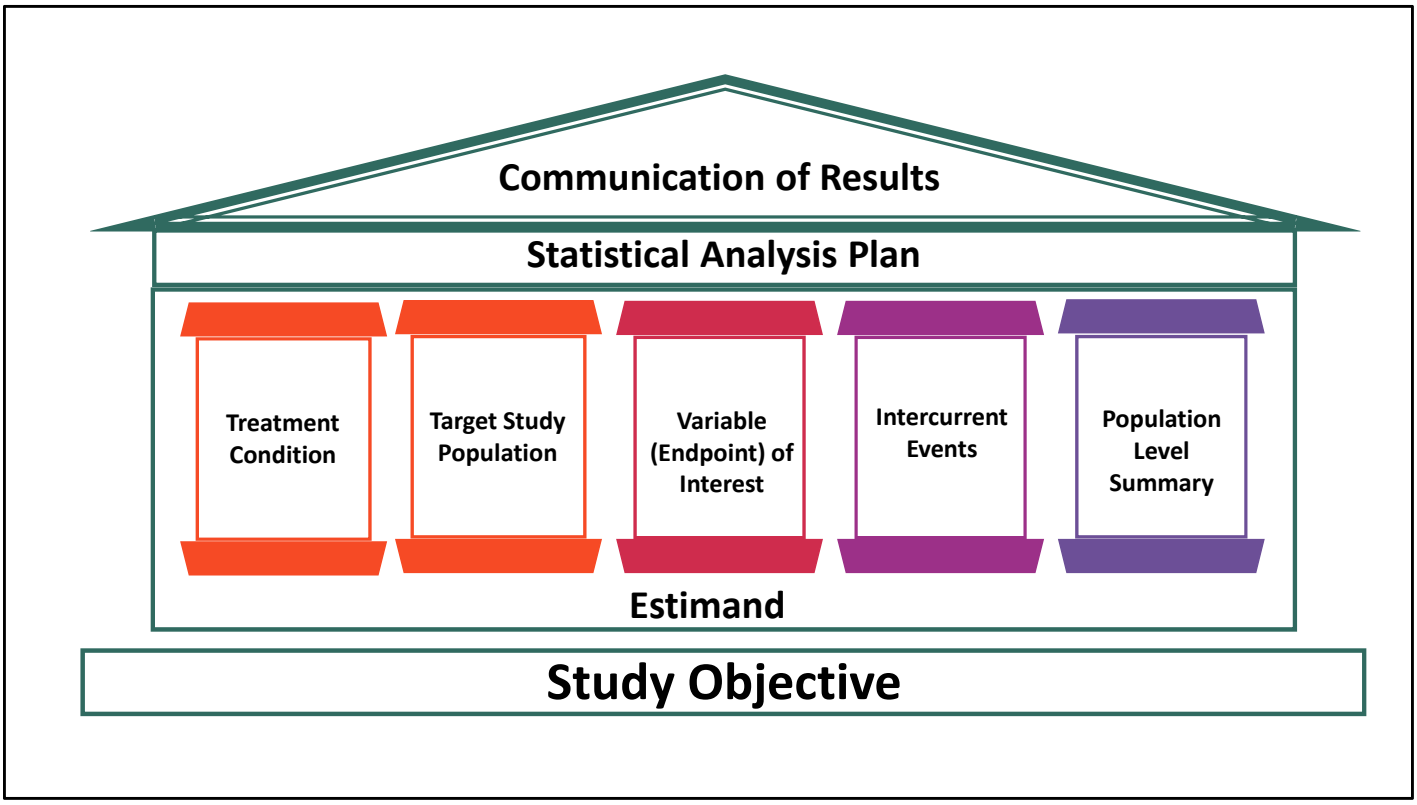
Applications of Bayesian Methods Within CDER
James Travis, CDER,Office of Biostatistics, Division of Biometrics II ,FDA

PS6d - The FDA Complex Innovative Trial Design Pilot Program: Case Examples
Parallel Session
Fri, Sep 25, 3:30 PM - 4:45 PM
Virtual

Bayesian Adaptive Clinical Trial in Duchenne Muscular Dystrophy
Stephen Lake, Wave Life Sciences

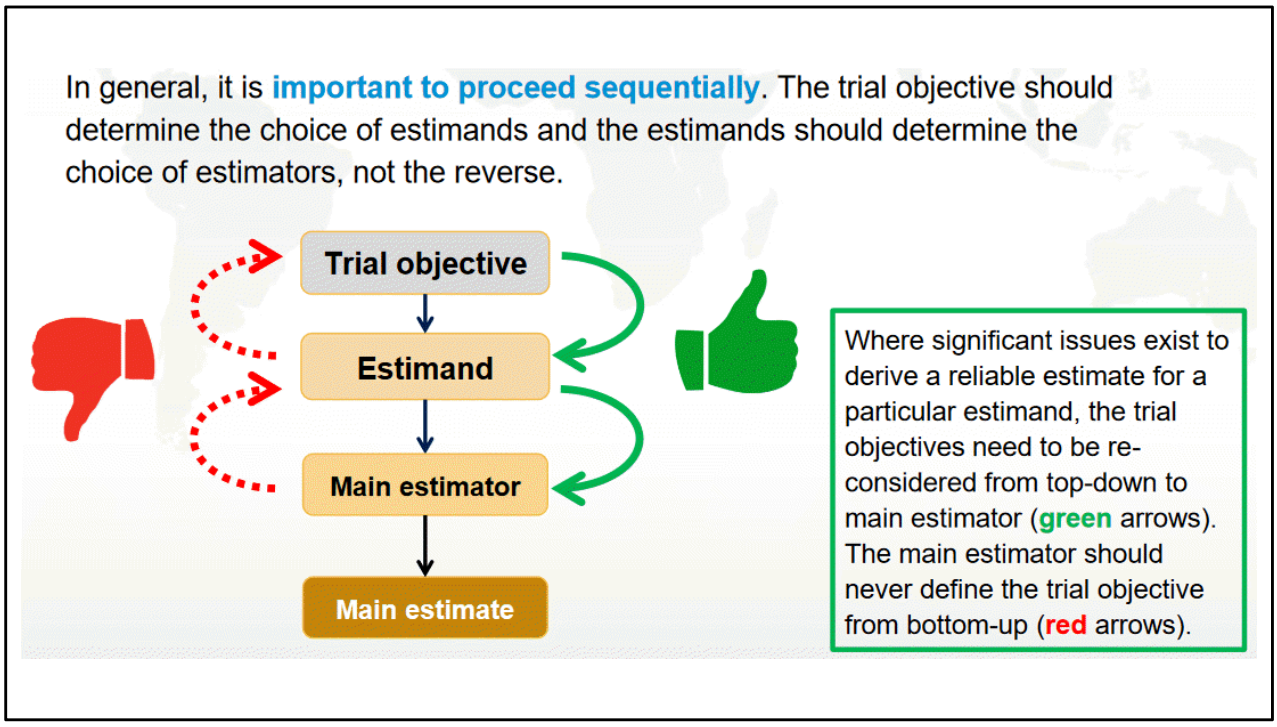
https://ww2.amstat.org/meetings/biop/2020/onlineprogram/index.cfm

Align on Estimands Early



This house with estimand elements rests on a strong foundation, the study objective. Clearly defining the objective is essential.

Adapted from 2019 FDA-ASCO public workshop: Mallorie Fiero, Chana Weinstock, Madeline Pe. COA-CCT Session III Using a standardized estimand framework for medical product review and labeling: a case study. FDA-ASCO Public Workshop: 2019 Clinical Outcome Assessments in Cancer Clinical Trials Fourth Annual Workshop



ICH E9(R1) Step 2 Training MaterialModule 2.2 –Framework
https://www.ich.org/

Relevant Information for a Meeting Request

- Description of study design, including study schema with treatment arms, randomization strategy, and endpoints.
- Key features of the statistical analysis plan, including, but not limited to, the analyses, models, analysis population, approach to handling missing data, and decision criteria. These key features should include aspects of the design that may be modified and the corresponding rules for decisions, if adaptive.
- Simulation plan, including the set of parameter configurations that will be used for the scenarios to be simulated and preliminary evaluation and discussion of design operating characteristics. Preliminary simulation results of the operating characteristics (e.g., type I error, power) should include several plausible hypothetical scenarios.

https://www.fda.gov/CIDpilot

Provide Well-Structured Documentation

Prior Distribution

Prior Distribution Documentation

- Include any data or other external information used to specify the prior distribution. Describe the source and completeness of the external information, its relevance, and the quality and reliability of the data.
- Prior distributions should generally be based on a thorough evaluation of all relevant evidence, including evidence that may suggest skepticism of the existence or magnitude of a treatment effect. Discuss steps taken to ensure information was not selectively obtained or used.
- In cases where down-weighting or other non-data-driven features are incorporated in a prior distribution, include a rationale for the use and magnitude of these features.
- When external data are used to define a prior, write a protocol that pre-specifies and documents the processes used to generate the prior distribution. To mitigate the potential for error, the protocol should follow the process laid out in the meta-analysis draft guidance.
- Explicitly specify prior parametrization, assumptions (e.g., independence), and justification for each (hyper-)parameter and prior functional form, including simulations studies. Include any special considerations for software-specific coding (e.g., variance vs. precision).
- A function of parameter(s) may be of interest. Explicitly specify and describe any induced priors.

Sample Size

Sample Size Documentation

- Statistical model (prior and likelihood)
- All assumptions
- Decision criteria used in optimizing the sample size
- Justifications for any minimum and maximum sample sizes
- Sample size updating criteria, if applicable, and any potential issues associated with sample size updating
- Trial stopping criteria for efficacy, futility, and safety
- Other additional information used in sample size determination, including executable, well-structured, and well-commented code and simulations results

Decision Criteria

Patient Objective

Treatment outcomes with adequate utility

- Therapy efficacy and safety
- Quality-of-life
- Physical, psychological, and social functioning
- Financial toxicity

Patients need treatment outcomes with adequate utility. I use the word utility because of multiple input factors and variability among patient preferences. Beyond quality, safety, and efficacy, quality-of-life and financial toxicity are important considerations. Therapy price is not considered in FDA decision-making.

Regulatory Objective

Substantial evidence

- adequate and well-controlled investigations
- drug will have the effect… prescribed, recommended, or suggested in the labeling

Structured risk-benefit assessment framework

- a consistent and systematic approach to the discussion and regulatory decision-making
- communication of the benefits and risks of new drugs

Title 21. FOOD AND DRUGS Chapter 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT Subchapter V. DRUGS AND DEVICES Part A. Drugs and Devices Section 355. New drugs

Regulations. We need substantial evidence from adequate and well-controlled investigations and substantial evidence that drug will have an effect "prescribed, recommended, or suggested in the labeling." Structured risk-benefit assessment framework is also explicitly mentioned.

The term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof… The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.
Title 21. FOOD AND DRUGS Chapter 9. FEDERAL FOOD, DRUG, AND COSMETIC ACT Subchapter V. DRUGS AND DEVICES Part A. Drugs and Devices Section 355. New drugs

Quantification of Uncertainty

- *The uncertainty about the findings from each trial should be sufficiently small… as demonstrated by… a high posterior probability of effectiveness*[1].
- Depends on clinical context: Unmet medical need, disease severity (serious and life-threatening), available therapy, disease rarity, patient input.
- How do the design features relate to the clinical questions?
- Treatment effect magnitude and benefit-risk must be meaningful.

Examples:
Ye J, Reaman G, De Claro RA, Sridhara R. A Bayesian approach in design and analysis of **pediatric cancer** clinical trials [published online ahead of print, 2020 Jun 14]. Pharm Stat. 2020;10.1002/pst.2039. doi:10.1002/pst.2039
Proschan MA, Dodd LE, Price D. Statistical considerations for a trial of **Ebola** virus disease therapeutics. Clin Trials. 2016;13(1):39-48. doi:10.1177/1740774515620145

[1] **Guidance for Industry** (draft): Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry
Draft, December 2019
https://www.fda.gov/media/133660/download

Simulations

Transparent Subjectivity

(a) statistical work in which the assumptions and judgments are fully in view, for everyone to consider and critique, and in which sensitivity analysis reveals stability or fragility of conclusions with respect to the assumptions and judgments.

(b) analyses disciplined by both coherence and calibration in a way that helps us, and others working with us, to make good predictions of observables.

Draper, D (2006). Coherence and calibration: comments on subjectivity and "objectivity'' in Bayesian analysis (comment on articles by Berger and by Goldstein), Bayesian Anal., 1(3):423-428. doi:10.1214/06-BA116B. https://projecteuclid.org/euclid.ba/1340371038

Careful assessment of assumptions and accurate quantification of uncertainty are essential.

Draper, D (2006). Coherence and calibration: comments on subjectivity and "objectivity'' in Bayesian analysis (comment on articles by Berger and by Goldstein), Bayesian Anal., 1(3):423-428. doi:10.1214/06-BA116B. https://projecteuclid.org/euclid.ba/1340371038

Simulation Report

Section	Description
1. Introduction	Description and rationale for the simulation experiment and its alignment with the study objectives.
2. Design	Overview and rationale for the proposed designs, followed by descriptions and justifications for the settings in the simulation experiment, including data generating model (prior and likelihood); parameter configurations used for the simulation scenarios; missing data patterns; the number of simulated trials (iterations) evaluated for each scenario; departures from and robustness to assumptions; operating characteristics; decision criteria. Cite and discuss literature references to support the design proposal.
3. Results	Concise presentation of operating characteristics and decisions per proposed design and simulation scenario.
4. Recommendations	Description of the chosen design and design choice justification.
5. Examples	Examples applying the chosen design, analysis, and decision criteria on data generated under various scenarios.
6. References	Cited literature
7. Appendix	Documentation of derivations, proofs, software, and other technical details; simulation code (could be a link to a folder with the code) and its validation.

FDA Guidances

- Guidance for Industry: **Adaptive Designs** for Clinical Trials of Drugs and Biologics, November 2019, https://www.fda.gov/media/78495/download
- Draft Guidance for Industry: Interacting with the FDA on **Complex Innovative Trial Designs** for Drugs and Biological Products, September 2019*, https://www.fda.gov/media/130897/download
- Guidance for Industry and FDA Staff: Guidance for the Use of **Bayesian Statistics in Medical Device Clinical Trials**, February 2010, https://www.fda.gov/media/71512/download
- Draft Guidance for Industry: General Clinical Pharmacology Considerations for **Pediatric Studies** for Drugs and Biological Products, December 2014*, https://www.fda.gov/media/90358/download
- Draft Guidance for Industry: **Meta-Analyses** of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry, November 2018*, https://www.fda.gov/media/117976/download

* When finalized, this guidance will represent FDA's current thinking on this topic.

Some Relevant Literature

- Ye J, Reaman G, De Claro RA, Sridhara R. A Bayesian approach in design and analysis of **pediatric cancer clinical trials** [published online ahead of print, 2020 Jun 14]. Pharm Stat. 2020;10.1002/pst.2039. doi:10.1002/pst.2039
- Proschan MA, Dodd LE, Price D. Statistical considerations for **a trial of Ebola virus disease therapeutics**. Clin Trials. 2016;13(1):39-48. doi:10.1177/1740774515620145
- Mayer, C., Perevozskaya, I., Leonov, S., Dragalin, V., Pritchett, Y., Bedding, A., Hartford, A., Fardipour, P. and Cicconetti, G. **Simulation Practices** for Adaptive Trial Designs in Drug and Device Development. Statistics in Biopharmaceutical Research, 2019;11(4): 325-335. doi:10.1080/19466315.2018.1560359

Supplementary Information

Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure

https://www.fda.gov/media/114862/download (.xlsx file)

BENEFIT-RISK ASSESSMENT IN DRUG REGULATORY DECISION-MAKING

Draft PDUFA VI Implementation Plan (FY 2018-2022)

Enhancing Benefit-Risk Assessment in Regulatory Decision-Making
https://www.fda.gov/media/112570/download