# 第4回 DSRT
# ベイズ統計学の医薬品の臨床開発での活用について

## 議題1-2：ベイズ統計学の導入と，FDAの医療機器ガイダンスから学べること

# はじめに

- 本議題の内容
  - FDAのガイダンス”**Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials** “（以下，FDAガイダンス）の中で**「どういう状況でベイズ統計学が使えるか」「ベイズ統計学を使うことのメリット」**について記載された箇所の内容を整理し，FDAガイダンスに基づいた医薬品開発での使用可能性や，使用が難しい状況について議論する

# 本議題の予習資料（参考のみ）

- Food, U., Administration, D., et al. (2010). Guidance for the use of bayesian　statistics in medical device clinical trials. Silver Spring, Maryland: FDA.
  - http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071121.pdf
    - 日本語訳：手良向聡，大門貴志（訳）(2010). 医療機器の臨床試験におけるBayes流統計学の利用に関するガイダンス．臨床評価．38(2). 291-326.

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# 1. Introduction

- This document provides guidance on statistical aspects of the design and analysis of clinical trials for medical devices that use Bayesian statistical methods.
- The purpose of this guidance is to discuss important statistical issues in Bayesian clinical trials for medical devices.
  - The purpose is not to describe the content of a medical device submission.
  - Further, while this document provides guidance on many of the statistical issues that arise in Bayesian clinical trials, it is not intended to be all-inclusive.
  - The statistical literature is rich with books and papers on Bayesian theory and methods; a selected bibliography has been included for further discussion of specific topics.
- FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities.
  - Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.
  - The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

# 2.1 What is Bayesian statistics?

- **Bayesian statistics** is an approach for learning from evidence as it accumulates.
  - In clinical trials, traditional (frequentist) statistical methods may use information from previous studies only at the design stage. Then, at the data analysis stage, the information from these studies is considered as a complement to, but not part of, the formal analysis.
  - In contrast, **the Bayesian approach uses Bayes' Theorem to formally combine prior information with current information on a quantity of interest**.
    - The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available.

# 2.2 Why use Bayesian statistics for medical devices?
# -With prior information

- **When good prior information on clinical use of a device exists**, the Bayesian approach may enable this information to be incorporated into the statistical analysis of a trial.
  - In some circumstances, the prior information for a device may be a justification for a smaller-sized or shorter-duration pivotal trial.

# 2.2 Why use Bayesian statistics for medical devices?
# -With prior information

- Good prior information is often available for medical devices because of their mechanism of action and evolutionary development.
  - The mechanism of action of medical devices is typically physical. As a result, device effects are typically local, not systemic.
    - Local effects can sometimes be predictable from prior information on the previous generations of a device when modifications to the device are minor.
- Good prior information can also be available from studies of the device overseas.
- In a randomized controlled trial, prior information on the control can be available from historical control data.

# 2.2 Why use Bayesian statistics for medical devices?
# -With prior information

- Our experience is that Bayesian methods are usually less controversial when the prior information is based on empirical evidence such as data from clinical trials.
- However, Bayesian methods can be controversial when the prior information is based mainly on personal opinion (often derived by elicitation from “experts”).

# 2.2 Why use Bayesian statistics for medical devices?
# -Without prior information

- **The Bayesian approach is also frequently useful in the absence of prior information**.
  - First, the approach can accommodate adaptive trials (e.g., interim analyses, change to sample size, or change to randomization scheme) and even some unplanned, but necessary trial modifications.
  - Second, the Bayesian approach can be useful for analysis of a complex model when a frequentist analysis is difficult to implement or does not exist.
  - Other potential uses include adjustment for missing data, sensitivity analysis, multiple comparisons, and optimal decision making (Bayesian decision theory).

# 2.2 Why use Bayesian statistics for medical devices?
# -Least burdensome

- **The Bayesian approach, when correctly employed, may be less burdensome than a frequentist approach**.
- Section 513(a)(3) of the Federal Food, Drug, and Cosmetic Act (FFDCA) mandates that FDA shall consider the least burdensome appropriate means of evaluating effectiveness of a device that would have a reasonable likelihood of resulting in approval (see 21 U.S.C. 360c(a)(3)).

# 【論点1】ベイズ統計学の利用可能性

- **FDAガイダンスの主張を一旦認めた上で**，以下の各論点について議論してください.
  - **論点1-1**
    - 医薬品・医療機器問わず，ベイズ統計学を用いる際に議論となりそうな点を挙げてください
    - 医薬品開発で，医療機器と比較してベイズ統計学の適用が難しいと考えられる理由を考えてください
  - **論点1-2**
    - 医薬品と医療機器の違いに注意しつつ，以下の状況の具体例をそれぞれ考えてください
      - 医薬品開発で，事前情報を用いたベイズ統計学が使えそうな状況の例
      - 医薬品開発で，事前情報を用いたベイズ統計学が使えなさそうな状況の例
  - **論点1-3**
    - 事前情報がない場合の活用方法は，どういう場合に利用可能性が高そうでしょうか？

# 2.3 Why are Bayesian methods more commonly used now?

- Bayesian analyses are often computationally intense.
- However, recent breakthroughs in computational algorithms and computing speed have made it possible to carry out calculations for very complex and realistic Bayesian models.
  - These advances have resulted in a huge increase in the popularity of Bayesian methods (cf. Malakoff, 1999).
  - A basic computational tool is a method called Markov Chain Monte Carlo (MCMC) sampling, a method for simulating from the distributions of random quantities.

# 2.4 When should FDA participate in the planning of a Bayesian trial?

- With any clinical trial, **we recommend you schedule meetings to discuss experimental design and models**.
- For a Bayesian design **we recommend you discuss your prior information with FDA before the study begins**.
- If an investigational device exemption (IDE) is required, we recommend you meet with FDA before you submit the IDE. s

# 2.5 The Bayesian approach is not a substitute for sound science.

- **Scientifically sound clinical trial planning and rigorous trial conduct are important** regardless of whether you use a Bayesian or frequentist approach.
- We recommend you remain vigilant regarding randomization, concurrent controls, prospective planning, blinding, bias, precision, and all other factors that go into a successful clinical trial.
  - See **Section 4.1: Bayesian trials start with a sound clinical trial design**.

# 2.6 What are potential benefits of using Bayesian methods?

## 2.6.1 More Information for Decision Making

- **The information from a current trial is augmented and the precision may be increased by the incorporation of prior information in a Bayesian analysis**.
- The Bayesian analysis brings to bear the extra, relevant, prior information, which can help FDA make a decision.

# 2.6 What are potential benefits of using Bayesian methods?

# 2.6.2 Sample size reduction via prior information

- In some instances, the use of prior information may alleviate the need for a larger sized trial.
- However, **a decrease in the sample size for the current trial may not be warranted by a Bayesian analysis incorporating prior information**.
  - See section 4.7 for further discussion on sample size issues in a Bayesian clinical trial.
  - Additionally, if the prior information does not agree sufficiently with trial results, then the Bayesian analysis may actually be conservative relative to a frequentist or Bayesian analysis that does not incorporate the prior information.

# 2.6 What are potential benefits of using Bayesian methods?

# 2.6.3 Sample size reduction via Adaptive Trial Design

- Adaptive designs use accumulating data to decide on how to modify certain aspects of a trial according to a pre-specified plan. They are often used to potentially reduce the size of a trial by stopping the trial early when conditions warrant. Adaptive trial designs can sometimes be easier to implement using Bayesian methods than frequentist methods. By adhering to the Likelihood Principle, a Bayesian approach can offer flexibility in the design and analysis of adaptive trials (see Sections 3.8 and 4.10).

# 2.6 What are potential benefits of using Bayesian methods?
# 2.6.4. Midcourse changes to the trial design

- With appropriate planning, the Bayesian approach can also offer the flexibility of midcourse changes to a trial. Some possibilities include dropping an unfavorable treatment arm or modifications to the randomization scheme. Modifications to the randomization scheme are particularly relevant for an ethically sensitive study or when enrollment becomes problematic for a treatment arm. Bayesian methods can be especially flexible in allowing for changes in the treatment to control randomization ratio during the course of the trial. See Kadane (1996) for a discussion.

# 2.6 What are potential benefits of using Bayesian methods?

# 2.6.5 Other Potential Benefits

- **Exact analysis**
  The Bayesian approach can sometimes be used to obtain an exact analysis when the corresponding frequentist analysis is only approximate or is too difficult to implement.
- **Missing Data**
  Bayesian methods allow for great flexibility in dealing with missing data. See section 5.4 for a discussion of the use of these Bayesian methods.
- **Multiplicity**
  Multiplicity is pervasive in clinical trials. For example, inferences on multiple endpoints or testing of multiple subgroups (e.g., race or sex) are examples of multiplicity. Bayesian approaches to multiplicity problems are different from frequentist ones, and may be advantageous. See section 4.9 for a discussion of Bayesian multiplicity adjustments.

# 【論点2】ベイズ統計学の利用可能性

- FDAガイダンス2.6節を踏まえ，以下の論点について議論してください.
  - **論点2-1**
    - ベイズ統計学をどういう状況で使用することに興味がありますか？その場合に，どういう点が検討事項となりそうでしょうか.

# 2.7 What are potential challenges using the Bayesian approach?

- **Extensive preplanning**
  - Planning the design, conduct, and analysis of any trial is always important from a regulatory perspective, but is especially crucial for a Bayesian trial. In a Bayesian trial, decisions have to be made at the design stage regarding:
    - the prior information,
    - the information to be obtained from the trial, and
    - the mathematical model used to combine the two.
  - Different choices of prior information or different choices of model can produce different decisions. As a result, in the regulatory setting, the design of a Bayesian clinical trial involves pre-specification of and agreement on both the prior information and the model. Since reaching this agreement is often an iterative process, we recommend you meet with FDA early to obtain agreement upon the basic aspects of the Bayesian trial design.

# 2.7 What are potential challenges using the Bayesian approach?

- **Extensive preplanning**
  - A change in the prior information or the model at a later stage of the trial may imperil the scientific validity of the trial results. For this reason, formal agreement meetings may be appropriate when using a Bayesian approach. Specifically, the identification of the prior information may be an appropriate topic of an agreement meeting.

# 2.7 What are potential challenges using the Bayesian approach?

- **Extensive model-building**
  - The Bayesian approach can involve extensive mathematical modeling of a clinical trial, including:
    - the probability distributions chosen to reflect the prior information,
    - the relationships between multiple sources of prior information,
    - the influence of covariates on patient outcomes or missing data, and
    - sensitivity analyses on the model choices.
  - We recommend you make your modeling choices through close collaboration and agreement with FDA and your statistical and clinical experts.

# 2.7 What are potential challenges using the Bayesian approach?

- **Specific statistical and computational expertise**
  - The Bayesian approach often involves specific statistical expertise in Bayesian analysis and computation. Special computational algorithms like MCMC are often used to
    - analyze trial data,
    - check model assumptions,
    - assess prior probabilities at the design stage,
    - perform simulations to assess probabilities of various outcomes, and
    - estimate sample size.

  - The technical and statistical costs involved in successfully designing, conducting, and analyzing a Bayesian trial may be offset by the increased precision on device performance that can be obtained by incorporating prior information, or in the absence thereof, by the benefits of a flexible Bayesian trial design (e.g., smaller expected sample size resulting from interim analysis).

# 2.7 What are potential challenges using the Bayesian approach?

- **<u>Choices regarding prior information</u>**
  - An FDA advisory panel may question prior information you and FDA agreed upon beforehand. We recommend you be prepared to clinically and statistically justify your choices of prior information. In addition, we recommend that you perform sensitivity analysis to check the robustness of your models to different choices of prior distributions.

# 2.7 What are potential challenges using the Bayesian approach?

- **Device labeling**
  - Results from a Bayesian trial are expressed differently from the way trial results are usually described in device labels. Bayesian terminology is not yet commonly seen in device labeling3. As always, we recommend you ensure trial results reported on the device label are easy to understand.

- **Checking calculations**
  - The flexibility of Bayesian models and the complexity of the computational techniques for Bayesian analyses create greater possibility for errors and misunderstandings. As with any submission, FDA will carry out a detailed statistical review, including verifying results using the same or alternate software. FDA recommends you submit your data and any instruction set used by the statistical analysis program in electronic form.

# 2.7 What are potential challenges using the Bayesian approach?

- **Bayesian and frequentist analyses approaches may differ in their conclusions**
  - Two investigators, each with the same data and a different preplanned analysis (one Bayesian and one frequentist), could conceivably reach different conclusions that are both scientifically valid. While the Bayesian approach can often be favorable to the investigator with good prior information, the approach can also be more conservative than a frequentist approach (e.g., see **Section 4: Planning a Bayesian Clinical Trial**).
  - **We recommend you do not switch from a frequentist to a Bayesian analysis (or vice versa) once a trial has been initiated**.
    - Such *post hoc* analyses are not scientifically sound and tend to weaken the validity of the submission.

# 【論点3】

- 以下の論点について議論してください.
  - 論点3-1
    - 医薬品の開発計画全体の中で，ベイズ統計学が有効に活用できそうな状況はどういうときでしょうか？メリットと注意点をともに意識しつつ，議論してください
    - 実務でベイズ統計学を用いた方法を使用しようとする際に大きな課題となりそうな点（なった点）について，議論してください
  - 論点3-2
    - PMDA申請でベイズ統計学を用いる方法を使用したいと考えた場合，どういうタイミングで，何について相談することが必要そうでしょうか？