Bayes Bayesian Biostatistics Utrecht 2023

Application of Bayesian approaches in drug development: starting a virtuous cycle

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Perspective | Published: 15 February 2023

Application of Bayesian approaches in drug development: starting a virtuous cycle

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Nature Reviews Drug Discovery **22**, 235–250 (2023) | Cite this article

16k Accesses | **6** Citations | **59** Altmetric | Metrics

Outline

1. Motivation
2. Barriers to widespread adoption
3. Framework to guide use
4. Recent progresses

- 96th percentile of the ~0.5Mio tracked articles of a similar age in all journals
- 88th percentile (ranked 7th) of the 53 tracked articles of a similar age in *Nature Reviews Drug Discovery*

Motivation

- PDUFA
- Openness to different thinking
- Epistemological & Interpretation benefits
- How to pursue the journey from early to more late application?

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2023 THROUGH 2027

L. ENHANCING REGULATORY DECISION TOOLS TO SUPPORT DRUG DEVELOPMENT AND REVIEW

Delivering new medicines to patients through biomedical innovation requires advances in regulatory decision tools to support drug development and review. FDA will build on the successes of its efforts on Patient Focused Drug Development (PFDD), benefit-risk assessment in regulatory decision-making, and the drug development tools qualification pathway for biomarkers. FDA will also continue to advance modern approaches to enhance the efficiency of the drug development and review processes, such as complex adaptive, Bayesian, and other novel clinical trial designs and model-informed drug development (MIDD).

e. By the end of 2nd Quarter FY 2024, FDA will convene a public workshop to discuss aspects of complex adaptive, Bayesian, and other novel clinical trial designs. Discussion topics will include considerations for external data sources, Bayesian statistical methods, simulations, and clinical trial implementation (e.g. examples of defining and mitigating bias when using select trial design methods) and will be based on FDA accumulated experience both within and outside of the paired meeting program.

f. By the end of FY 2025, FDA will publish draft guidance on the Use of Bayesian Methodology in Clinical Trials of Drugs and Biologics.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. It then will work towards publishing a final guidance within 18 months after the close of the public comment period on the revised draft guidance.

https://www.fda.gov/media/151712/download

Motivation

- PDUFA
- Openness to different thinking
- Epistemological & Interpretation benefits
  - Closer to the way scientists and decision makers are thinking
  - Probabilistic statements about the biological process

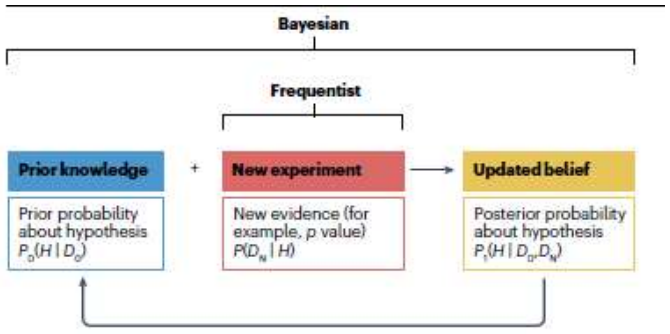


Fig. 1 | Comparison between Bayesian and frequentist approaches. The

Therapeutic Innovation & Regulatory Science (2023) 57:426–435
https://doi.org/10.1007/s43441-022-00482-1

ORIGINAL RESEARCH

Why are There not More Bayesian Clinical Trials? Ability to Interpret Bayesian and Conventional Statistics Among Medical Researchers

The Medical Outreach Team of the Drug Information Association Bayesian Scientific Working Group · Ross Bray[1] · Andrew Hartley[2] · Deborah Wenkert[3] · Natalia Muehlemann[4] · Fanni Natanegara[1] · Frank E. Harrell Jr[5,7] · Fei Wang[6] · Jennifer Clark[7]

Received: 22 July 2022 / Accepted: 22 November 2022 / Published online: 10 December 2022

Abstract

Objective and Background We assessed current understandings in interpretation of Bayesian and traditional statistical results within the clinical researcher (non-statistician) community.

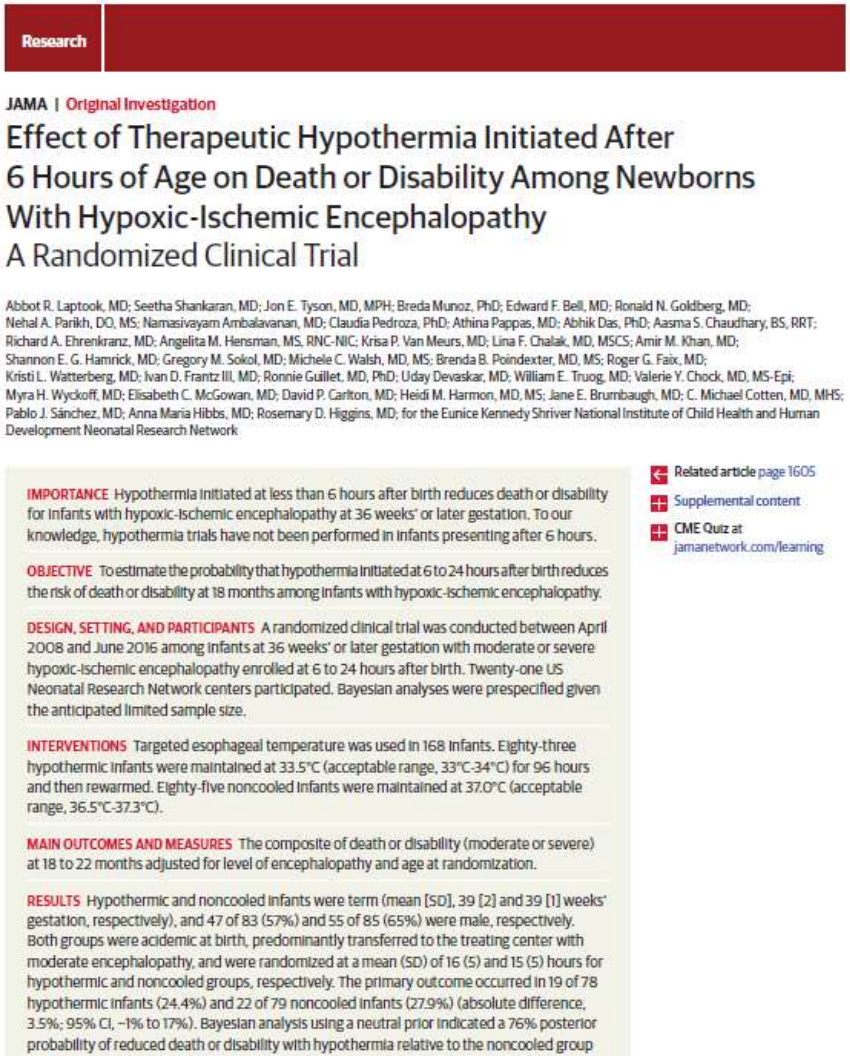
Methods Within a 22-question survey, including demographics and experience and comfort levels with Bayesian analyses, we included questions on how to interpret both Bayesian and traditional statistical outputs. We also assessed whether Bayesian or traditional interpretations are considered more useful.

Results Among the 323 respondent clinicians, 42.4% and 36.5% chose the correct interpretations of the posterior probability and 95% credible interval, respectively. Only 11.5% of respondents interpreted the *p*-value correctly and 23.5% interpreted the 95% confidence interval correctly.

Conclusions Based on these survey results, we conclude that most of these clinicians face uncertainty when attempting to interpret results from both Bayesian and traditional statistical outputs. When presented with accurate interpretations, clinicians generally conclude that Bayesian results are more useful than conventional ones. We believe there is a need for education of clinicians in statistical interpretation in ways that are customized to this audience.

Keywords Bayesian methods · Clinical trials · Bayesian perceptions · Bayesian education · Medical school training

Motivation: A useful illustrative example



Research

JAMA | Original Investigation

Effect of Therapeutic Hypothermia Initiated After 6 Hours of Age on Death or Disability Among Newborns With Hypoxic-Ischemic Encephalopathy
A Randomized Clinical Trial

Abbot R. Laptook, MD; Seetha Shankaran, MD; Jon E. Tyson, MD, MPH; Breda Munoz, PhD; Edward F. Bell, MD; Ronald N. Goldberg, MD; Nehal A. Parikh, DO, MS; Namasivayam Ambalavanan, MD; Claudia Pedroza, PhD; Athina Pappas, MD; Abhik Das, PhD; Aasma S. Chaudhary, BS, RRT; Richard A. Ehrenkranz, MD; Angelita M. Hensman, MS, RNC-NIC; Krisa P. Van Meurs, MD; Lina F. Chalak, MD, MSCS; Amir M. Khan, MD; Shannon E. G. Hamrick, MD; Gregory M. Sokol, MD; Michele C. Walsh, MD, MS; Brenda B. Poindexter, MD, MS; Roger G. Faix, MD; Kristi L. Watterberg, MD; Ivan D. Frantz III, MD; Ronnie Guillet, MD, PhD; Uday Devaskar, MD; William E. Truog, MD; Valerie Y. Chock, MD, MS-Epi; Myra H. Wyckoff, MD; Elisabeth C. McGowan, MD; David P. Carlton, MD; Heidi M. Harmon, MD, MS; Jane E. Brumbaugh, MD; C. Michael Cotten, MD, MHS; Pablo J. Sánchez, MD; Anna Maria Hibbs, MD; Rosemary D. Higgins, MD; for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

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IMPORTANCE Hypothermia initiated at less than 6 hours after birth reduces death or disability for infants with hypoxic-ischemic encephalopathy at 36 weeks' or later gestation. To our knowledge, hypothermia trials have not been performed in infants presenting after 6 hours.

OBJECTIVE To estimate the probability that hypothermia initiated at 6 to 24 hours after birth reduces the risk of death or disability at 18 months among infants with hypoxic-ischemic encephalopathy.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial was conducted between April 2008 and June 2016 among infants at 36 weeks' or later gestation with moderate or severe hypoxic-ischemic encephalopathy enrolled at 6 to 24 hours after birth. Twenty-one US Neonatal Research Network centers participated. Bayesian analyses were prespecified given the anticipated limited sample size.

INTERVENTIONS Targeted esophageal temperature was used in 168 infants. Eighty-three hypothermic infants were maintained at 33.5°C (acceptable range, 33°C-34°C) for 96 hours and then rewarmed. Eighty-five noncooled infants were maintained at 37.0°C (acceptable range, 36.5°C-37.3°C).

MAIN OUTCOMES AND MEASURES The composite of death or disability (moderate or severe) at 18 to 22 months adjusted for level of encephalopathy and age at randomization.

RESULTS Hypothermic and noncooled infants were term (mean [SD], 39 [2] and 39 [1] weeks' gestation, respectively), and 47 of 83 (57%) and 55 of 85 (65%) were male, respectively. Both groups were acidemic at birth, predominantly transferred to the treating center with moderate encephalopathy, and were randomized at a mean (SD) of 16 (5) and 15 (5) hours for hypothermic and noncooled groups, respectively. The primary outcome occurred in 19 of 78 hypothermic infants (24.4%) and 22 of 79 noncooled infants (27.9%) (absolute difference, 3.5%; 95% CI, −1% to 17%). Bayesian analysis using a neutral prior indicated a 76% posterior probability of reduced death or disability with hypothermia relative to the noncooled group

- Rare condition, enrolment was of concern (8 years)
- To estimate the probability that hypothermia initiated at 6 to 24 hours after birth reduces the risk of death or disability at 18 months among infants with hypoxic-ischemic encephalopathy.
- Bayesian approach with 3 priors: sceptical, neutral, enthusiastic

Therapeutic Hypothermia

Non-cooling standard of care

- Group level summary: RR
  - Frequentist: RRf = 0.81 [0.44 – 1.51, 95% CoI]
  - Bayesian : RRb = 0.86 [0.58 – 1.29, 95% CrI]
    Pr[TH improves outcome vs non-cooling | data] ~76%
    Pr[2% reduction in outcome | data] ~ 64%

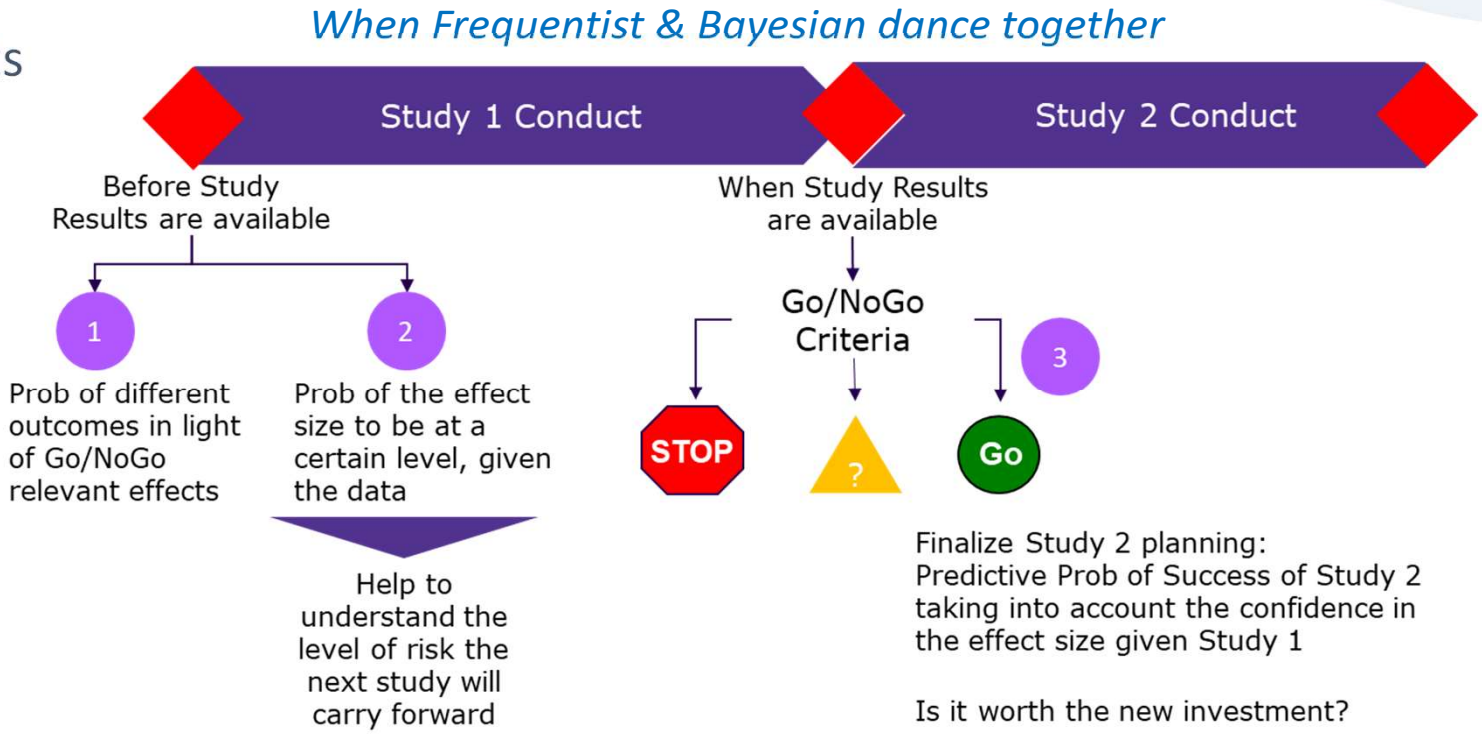
Note: RRf < RRb

….Bayesian not always provide more “favorable” estimate

https://jamanetwork.com/journals/jama/fullarticle/2658322

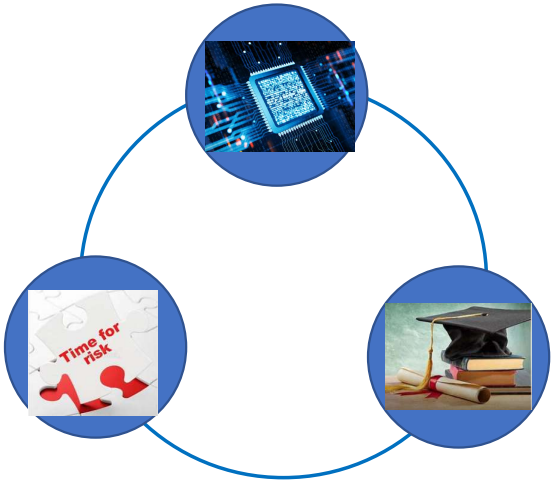
Motivation

- PDUFA
- Openness to different thinking
- Epistemological benefits



Barriers to widespread adoption

1. Computational power
2. Appetite to innovate
   - Lack of acceptance and familiarity
   - Lack of experience & guidance
     - Prior
     - Posterior Probability threshold for decision making
3. Education



Barriers to widespread adoption

1. Computational power
2. Appetite to innovate
   - Lack of acceptance and familiarity
   - Lack of experience & guidance
3. **Education**
   - Training biases: statisticians, scientists
   - No longer about theory but practice

We all know the 70/20/10 Learning & Development Model…same here!

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Why are not There More Bayesian Clinical Trials? Perceived Barriers and Educational Preferences Among Medical Researchers Involved in Drug Development

The Medical Outreach Subteam of the Drug Information Association Bayesian Scientific Working Group · Jennifer Clark, PhD[1] · Natalia Muhlemann[2] · Fanni Natanegara[3] · Andrew Hartley[4] · Deborah Wenkert[5] · Fei Wang[6] · Frank E. Harrell Jr.[7] · Ross Bray[3]

Received: 23 June 2021 / Accepted: 8 November 2021 / Published online: 3 January 2022

Abstract

Objective and Background The clinical trials community has been hesitant to adopt Bayesian statistical methods, which are often more flexible and efficient with more naturally interpretable results than frequentist methods. We aimed to identify self-reported barriers to implementing Bayesian methods and preferences for becoming comfortable with them.

Methods We developed a 22-question survey submitted to medical researchers (non-statisticians) from industry, academia, and regulatory agencies. Question areas included demographics, experience, comfort levels with Bayesian analyses, perceived barriers to these analyses, and preferences for increasing familiarity with Bayesian methods.

Results Of the 323 respondents, most were affiliated with pharmaceutical companies (33.4%), clinical research organizations (29.7%), and regulatory agencies (18.6%). The rest represented academia, medical practice, or other. Over 56% of respondents expressed little to no comfort in interpreting Bayesian analyses. "Insufficient knowledge of Bayesian approaches" was ranked the most important perceived barrier to implementing Bayesian methods by a plurality (48%). Of the approaches listed, in-person training was the most preferred for gaining comfort with Bayesian methods.

Conclusions Based on these survey results, we recommend that introductory level training on Bayesian statistics be presented in an in-person workshop that could also be broadcast online with live Q&A. Other approaches such as online training or collaborative projects may be better suited for higher-level trainings where instructors may assume a baseline understanding of Bayesian statistics. Increased coverage of Bayesian methods at medical conferences and medical school trainings would help improve comfort and overcome the substantial knowledge barriers medical researchers face when implementing these methods.

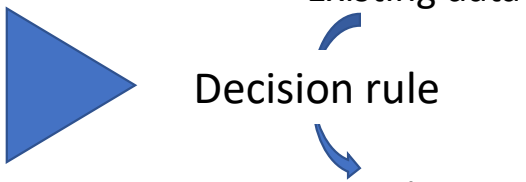
Recommendation for action

1. Increase communication & knowledge exchange
   - Publish findings and learnings: the good, the bad and the ugly
   - Promote the practice
2. Create transparency
   - Pre-specified decision framework
   - Principles & Standards for reporting Bayesian design and analysis (build up Lee et al, 2021)
   - Publicly sharing algorithms <> “black-box”
3. Create structure that build confidence
   - Specific Guidance on how to
     - determine relevant prior distribution (build up Med Device)
     - build the decision criteria (build up NI margins)
   - Stakeholders' agreement on when and how
4. Build and maintain capabilities
   - Education in the practice
5. Foster open mindset

Framework to guide use

Research Question

Totality of evidence



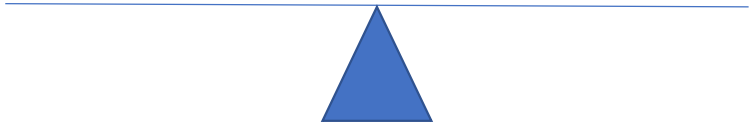
Existing data

Decision rule

New data

Fig. 4 | Recommended stepwise process for deciding whether a frequentist or Bayesian approach is most applicable for design, analysis and interpretation for the test of an experimental hypothesis. Information may consist of quantitative data, qualitative knowledge such as theories about a biological mechanism, or other subjective inputs such as expert opinion.

Risk of bias
Decision risks



Benefit
Efficiency

Recent Progresses

Learning development → Confirming development → Life Cycle Management

- Learning development
  - Bayesian model-based design (CRM, EWOC,…)
  - Platform Trial Design(s)
  - PoC leveraging prior knowledge
  - Bayesian borrowing from earlier trials
  - “Posterior Probability of Success to Confirm”
- Confirming development
  - Rebyota
  - Covid-19
- Life Cycle Management
  - Extrapolation in Pediatric Population
    - Belilumab (descriptive, retrospective Bayesian in Lupus)
    - Ofatumumab (<10 years, prospective Bayesian NI in MS, FDA CID Pilot Meeting Program)
  - Geographical Bridging
    - dTaP vaccine US label extension

Recent Progresses

- Rebyota (Nov 30, 2022)
  - Fecal transplant treatment for C. difficile
  - Treatment options for rCDI are limited, and the current standard of care (SoC) antibiotic treatment regimens can be complex and prolonged
  - Bayesian hierarchical model leveraging the Phase 2 results
  - Bayesian analysis provided the primary evidence of effectiveness
    - model-estimated difference in treatment success rates: 0.13 [0.02-0.24, 95% CrI]
    - Posterior probability that RBX2660 was superior to placebo was 0.991 vs

      > 0.9750338…"equivalent to a frequentist one-sided Type 1 error rate <0.025" (pre-defined second threshold)

      < 0.9993275… "equivalent to a frequentist one-sided Type 1 error rate <0.00125"

Table 25. Posterior Probability for Superiority and Posterior Estimates from the Bayesian Hierarchical Model With Study 2017-01 Analysis Population Definitions Applied to Study 2014-01

Population	Placebo Success Rate	RBX2660 (blinded) Success Rate	Treatment Effect
mITT	--	--	--
Mean	0.57	0.71	0.13
95% Credible Interval	0.48, 0.67	0.64, 0.77	0.02, 0.24
Posterior Probability	--	--	0.991
ITT	--	--	--
Mean	0.57	0.69	0.12
95% Credible Interval	0.47, 0.67	0.62, 0.76	0.01, 0.23
Posterior Probability			0.986
PP	--	--	--
Mean	0.56	0.72	0.15
95% Credible Interval	0.47, 0.66	0.65, 0.78	0.04, 0.26
Posterior Probability	--	--	0.997

Source: Adapted from STN 125739/0, Amendment 25, Final efficacy result Table 7
mITT=Modified Intent to Treat, ITT=Intent to Treat, PP=Per-Protocol
Note: This statistical analysis includes data from Phase 2 study (Protocol 2014-01) and Phase 3 (2017-01) studies

https://www.fda.gov/vaccines-blood-biologics/vaccines/rebyota

Conclusions

- Need to pursue the educational switch and expand use in early development
- While regulators are clearly more open to the use of Bayesian methods, we need to pursue engagement and promote use:
  - As complementary analysis to support benefits evaluation
  - As a mechanism to address unmet needs, especially where:
    - Sample size is a challenge (significant public need) in efficacy evaluation
    - Prior evidences can help being more efficient (incl. subgroup analyses)
  - Sensitivity analyses are always of value
  - …and ultimately gain efficiency where it makes sense

Using Bayesian statistical approaches to advance our ability to evaluate drug products

CDER Small Business and Industry Assistance (SBIA) Chronicles

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Bayesian Statistics is a particular approach of applying probability to statistical problems. This approach starts with a summary of our prior beliefs based on the relevant, available information. When we collect new data, for example in the course of a clinical trial, information from these data is combined with our prior beliefs to provide our current beliefs in terms of probabilities. In contrast, traditional or classical statistical approaches to decision-making are based on only the new data and do not incorporate any prior beliefs. Bayesian statistics can be used in practically all situations in which traditional

https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/using-bayesian-statistical-approaches-advance-our-ability-evaluate-drug-products

Thank you!

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