PERSPECTIVE

Embracing Bayesian Methods in Clinical Trials
FDA's Long-Awaited Draft Guidance

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In January 2026, US Food and Drug Administration (FDA) Centers for Drug Evaluation and Research and Biologics Evaluation and Research issued a long-awaited draft guidance on the use of bayesian methodology in clinical trials of therapeutic agents.[1] This is an exciting and welcome guidance for therapeutic trial design and analysis that we expect to contribute significantly to the rigor, efficiency, and flexibility of clinical trials. Although bayesian methods have been used increasingly in clinical trials over at least the past 30 years,[2] regulatory acceptance has been mixed.[3] The FDA Center for Devices and Radiological Health finalized Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials in 2010 and has approved a variety of medical devices using bayesian approaches. With respect to the regulation of drugs, the sixth iteration of the Prescription Drug User Fee Act and the 21st Century Cures Act, both enacted by the US Congress in 2016, included a call for innovative trial designs, including bayesian designs, and led to the establishment of the Complex Innovative Design pilot program in the Centers for Drug Evaluation and Research and Biologics Evaluation and Research.[4] Although an adaptive design guidance finalized in 2019 left the door open for bayesian trials, their use in drug development has to date been limited,[4] such as in Ebola and SARS-CoV-2 epidemics and in pediatric and rare disease trials. This new draft guidance lays out fundamental concepts and approaches to applying bayesian methods in therapeutics and dispels the misconception that FDA opposes the use of bayesian methods in drug development.

Related articles

Two Statistical Inference Paradigms

One central question in drug development is "Does the treatment work?" Two major statistical inference paradigms can address this question. Frequentist inference using *P* values and CIs has dominated medical research in the past century. A typical *P* value used in hypothesis testing quantifies how unlikely the data are if the treatment does not work. Assuming no effect simplifies the model and avoids using a prior distribution, giving a feeling of objectivity, but at the cost of changing the question of interest from "Does the treatment work?" to "Are the data unlikely if the treatment does not work?" If the *P* value is very small, the null hypothesis is rejected, suggesting that the treatment is likely to work. Thus, it provides an indirect answer to the question of interest. Similarly, CIs do not have an easy interpretation; confidence coverage is not the probability that the treatment effect is within the computed interval.

By contrast, Bayes tackles the real question of interest head-on and provides a direct answer to the question "Does the new drug or biologic work?" by computing the probability of treatment benefit. The cost of answering the real clinical question is having a prior distribution, which allows application of the Bayes theorem to combine the prior belief about effectiveness and the observed data to compute the posterior distribution representing data-informed levels of belief for all possible values of effectiveness (**Figure**).

Frequentist significance tests assume a single, fixed level of effectiveness and consider the data to be a random realization from an indefinite sequence of studies. Bayesian inference assumes the observed data are fixed and aims to quantify the evidentiary support for all possible levels of treatment effectiveness based on the data at hand. To protect against approval of ineffective treatments, frequentism emphasizes control of type I error, whereas the Bayes model uses 1 minus posterior probability of efficacy. To many, bayesian inference is more intuitive and easier to understand for both simple and complex applications. It substitutes a single transparent decision (the choice of prior) for a host of choices (eg, statistical vs clinical significance, multiplicity adjustments, noninferiority tests, analyzing sequential and adaptive trials, use of external information) required for frequentist analyses.[5,6]

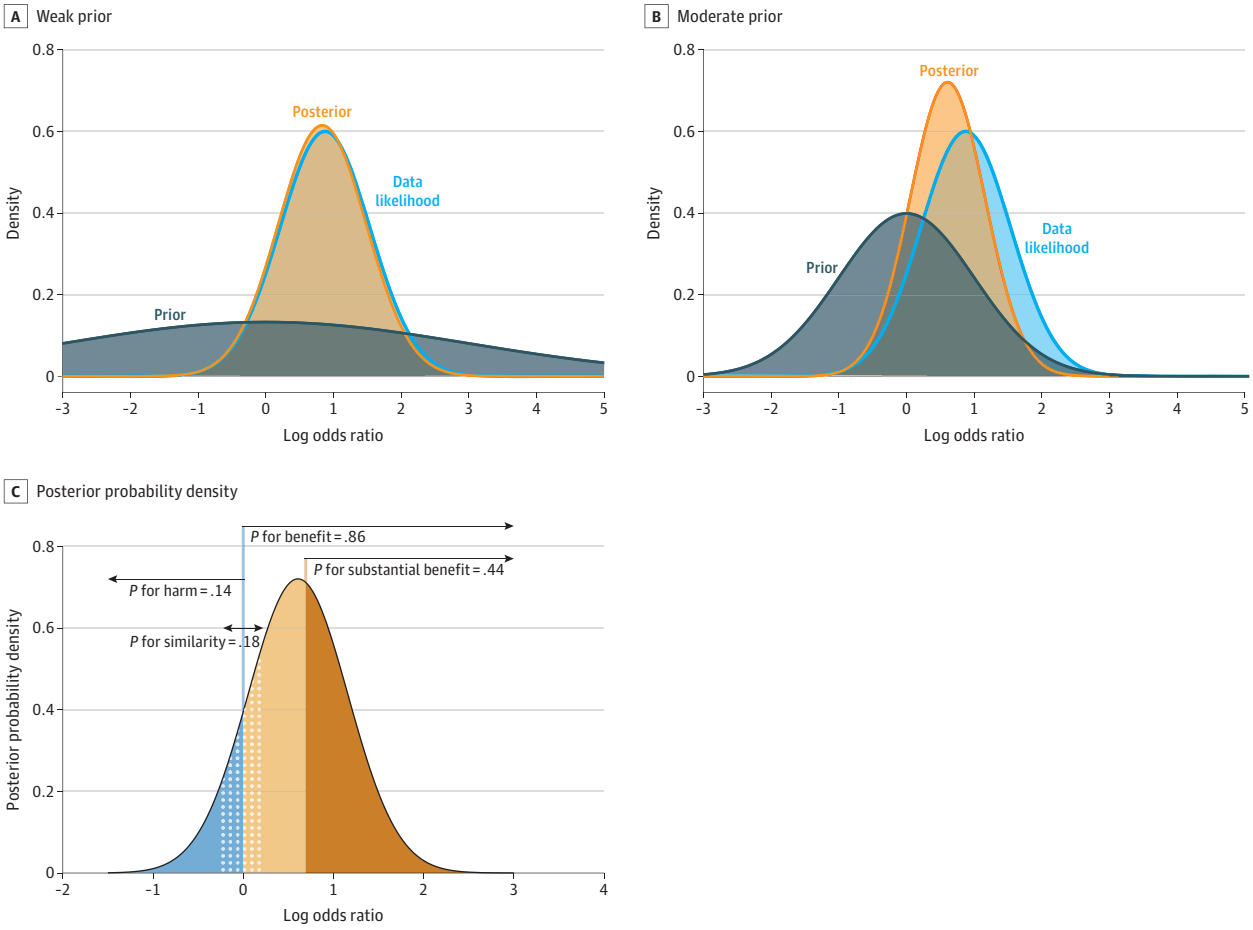
Why Does This Guidance Matter?

This draft guidance establishes bayesian methods as viable options in all contexts and offers practical solutions to their implementation in clinical trials. Exceptionally important is broadening, beyond the context of adaptive designs, the idea that the Bayes model has its own operating characteristics (the probability of correctness of decisions based on posterior probabilities) that are distinct from type I error, and that a sponsor may choose pure bayesian operating characteristics if a specific prior distribution is well justified or simulations over a range of priors demonstrate high decision reliability. The guidance illustrates the problem-solving capabilities of the Bayes model in a variety of ways.

The first is borrowing information. A newly proposed clinical trial does not start in a vacuum. Previous trials or high-quality real-world data for standard care may be available, leading to informative priors or joint modeling of old and new data and possibly lowering the sample size needed. Bayesian hierarchical models can be applied to dynamically borrow information among subgroups, eg, in basket trials to sharpen the estimation of the treatment efficacy. Occasionally, high-quality prospective comparative data are applicable to bayesian analysis, eg, adult data used to inform efficacy in children, or phase 2 data to inform phase 3.

Second is continuous learning and interim analysis. Applying Bayes theorem is simply synthesizing the information contained in the prior and the data to form the posterior. The posterior can be thought of as the new prior and, with new data, a new posterior is formed to better estimate the parameter of interest. The Bayes model is innately adaptive and no special allowance needs to be

Figure. Distribution Plots for Log Odds Ratios (ORs)



Distribution plots for log OR comparing the response rates between arm A (12 responses, 10 no responses) and arm B (5 responses, 17 no responses). A, Weak prior: prior for log OR = normal (0, 9), with data likelihood, and posterior. B, Moderate prior: prior for log OR = normal (0, 1), with data likelihood, and posterior. C, Posterior for log OR with various areas show different categories of drug efficacy ranging from similarity, harm, benefit, to substantial benefit. Similarity region: OR, 0.80 to 1.25 (log OR, −0.22 to 0.22). Substantial benefit: OR > 2 (log OR > 0.69) (95% credible interval [CrI] of OR, 0.62 to 5.43) (95% CrI of log OR, −0.48 to 1.69).

made when analyzing studies that adapt their designs as they proceed. As the trial moves along, continuous learning can guide interim toxicity and efficacy analyses. Nevertheless, to preserve study integrity, key adaptive design features and parameters need to be prespecified.

Third is the use of skeptical, optimistic, or noninformative prior distributions. A skeptical prior can be used for noncurative therapies in the absence of strong external data. Seen by many as a subjective choice, prespecification of a prior makes assumptions clear and leads to less bias in interpretation of the final result. In frequentist statistics, the step of converting probabilities about data to evidence about treatment effects is less transparent.

Fourth is obtaining operating characteristics that are fully aligned with regulatory needs. The posterior probability of efficacy given the data provides direct evidence to assess the drug for regulatory approval, given the assumptions made in the analysis are well justified, without conditioning on whether the drug works (Figure). The bayesian approach provides a rich framework to assess the totality of evidence beyond control for type I error. Bayesian methods can also better address clinical significance by computing the posterior probability of a nontrivial effect.

In oncology, we have witnessed the evolution of early-stage designs from 3 + 3 designs to continual reassessment methods, to bayesian optimal interval designs, and to posterior predictive design. Similarly, late-stage designs have evolved from Simon 2-stage designs, to bayesian optimal phase 2 designs, to multi-arm, multistage designs, and to adaptive platform designs.[7] Bayesian methods allow designs to be more adaptive, efficient, and ethical by treating more patients with better treatments based on the available information. The C3TI Demonstration Program offers useful examples, as well as opportunities for sponsors to have more interaction with FDA reviewers in developing bayesian designs.

Alignment With World's Broader Regulatory Trends

Globally, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E9 (Statistical Principles for Clinical Trials), E11A (Pediatric Extrapolation), and draft E20 (Adaptive Designs for Clinical Trials) guidelines mention the use

of bayesian approaches in advancing clinical trials. In addition, this guidance also aligns with the European Medicines Agency's 2025-2026 workplan and the development of a reflection paper on the use of bayesian methods in drug development to accelerate clinical trials.

Limitations and Challenges

More education concerning bayesian methods is needed in academia, industry, and regulatory agencies, including the need for comprehensive simulations to understand bayesian trial operating characteristics. More user-friendly bayesian software as well as more reporting standards are needed. The guidance acknowledges that the decision to use bayesian methods in drug trials needs to be carefully evaluated because the approach is not a panacea. Sometimes higher sample sizes are required to honestly reflect more sources of uncertainty or to quantify evidence for nontrivial, not just nonzero, effects. The choice of priors for either analysis or simulation purposes should be thoroughly justified and examined through sensitivity analysis.[8]

Conclusions

As in all scientific endeavors, careful planning and execution are essential for success. However, the importance of the guidance cannot be overstated. It underscores FDA's commitment to modernizing clinical research and promoting the use of bayesian methods in clinical trials.

ARTICLE INFORMATION

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