PERSPECTIVE

FDA Draft Guidance for the Use of Bayesian Methods in Clinical Trials

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The US Food and Drug Administration (FDA) released a draft guidance for industry on the use of bayesian methods in testing therapeutics.[1] As developers and users of bayesian methods in policy analysis, social science, and medical research, many features of the new guidance are heartening.

Bayesian Inference and New Success Criteria in Clinical Trials

Bayesian inference requires a data model (how the observed outcomes could arise conditional on the experimental design, the measurement process, and the true effects of experimental treatment) and a prior model (representing information coming from outside of the study, eg, on the distribution of possible treatment effects). These are then combined using Bayes' theorem to yield a posterior distribution that can be used for inferential and decision summaries.

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The prior is sometimes described as a subjective belief, but the FDA guidance frames it as prestudy information, which we think is a good framing. The formal and transparent incorporation of prior knowledge into the design and analysis of trials is the main advantage of the bayesian approach. The use of prior information, even if not in a formal bayesian framework, is not new in the context of clinical trials. For example, it is used during the planning stage of a trial using traditional frequentist methods to determine the sample size.

Bayesian methods have already been used in many FDA applications, and the guidance lists notable examples.[1] These methods are increasingly attractive to sponsors because borrowing of information allows for more efficient and flexible trials. Why, then, is there a need to issue guidance? Clear guidelines offer drugmakers predictability, which is essential to designing trials in the world in which costs of developing new medicines continue to increase. Such guidance also helps developers avoid having to interact with the FDA to vet every trial decision.

Control of type I error probability (false-positive result rate), typically under the assumption of no treatment effect, is central to frequentist hypothesis testing and is a standard requirement in clinical trials. One of the most notable features of the guidance, and a major break from the past, is that the FDA no longer insists on type I error control in the context of informative priors. The guidance still insists on type I error control when bayesian methods are used, but only when the prior is noninformative. We see the logic to this: bayesian analysis with noninformative priors is functionally similar to a traditional frequentist analysis, and in these cases there is no compelling reason to break with the current paradigm. In contrast, when substantial prior information is available, the required assumption for defining type I error of no treatment effect may already be inconsistent with that prior information to some extent, invalidating the type I error rate as a meaningful design metric.

Where informative priors are used, the guidance allows sponsors to move away from type I error rates and opt for other success criteria, which may be grounded in risk-benefit analysis. Bayesian inference with informative priors makes it easier to design trials that adapt to changing circumstances, and the resulting posterior distributions provide suitable input for downstream benefit-risk analyses.

Meta-Analysis and Partial Pooling

The FDA's draft guidance[1] sets out principles for designing informative priors based on relevant information or, as it is sometimes referred to, *borrowing strength* from external data. In clinical trials, this information can be obtained from earlier trials, historical controls, mechanistic modeling, evidence from related populations, and more. The guidance places particular focus on pediatric trials and rare diseases, which historically saw most interest in bayesian methods, but we would emphasize that bayesian methods should be applicable to all clinical trials. Pediatric trials often involve measurement challenges, and studies of rare diseases typically have small numbers of cases; it is difficult to get accurate estimates from noisy or sparse data, so priors become more relevant in such scenarios.

We would also place borrowing under the broader framework of using hierarchical (multilevel) modeling and meta-analysis.[2,3] Across trials, the effect of a treatment will depend on the patients to whom and situations in which it applied, and the basic idea of meta-analysis is to consider the effect in any particular trial as a random sample from some hypothetical population—ideally with trial-level predictors to account for systematic variation of effects.[4] The meta-analytic framework also applies to the cases of external controls, extrapolation, and subgroup analyses—all of which the draft guidance document considers. In these settings, hierarchical modeling can be used to capture different sources of variation beyond that arising from random assignment and random sampling, and bayesian inference is helpful in accounting for these different sources of uncertainty.

Challenges of Using Prior Information

The guidance creates more flexibility for trial designers by allowing them to depart from type I error rate designs. How can regulators then encourage the use of bayesian methods that lead to better, faster, and more transparent drug approval decisions without weakening evidentiary standards? In particular, there is a concern of inserting optimistic assumptions through the choice of a favorable prior.

We suggest 2 simple rules for bayesian analysis of clinical trials: (1) the prior should be clearly stated and (2) readers and reviewers should be able to assess the prior's influence on the result. The guidance already does a good job in this regard, providing clear examples of how relevant information can be used and how results should be

reported. Less concrete advice is given regarding success criteria, but that leaves room for decisions to be made on a case-by-case basis. Crucially, success criteria should be agreed on in advance.

The guidance is right to stress the importance of justifying the prior. However, we also remind readers that it is just as critical to have a prespecified and valid data model. Both the prior and the data model should be scrutinized when the data arrive, and it may be necessary to revise either. We also applaud the recommendation that computations be evaluated using simulation studies: in the bayesian framework, these would be posterior predictive checks, in silico replicated datasets simulated from the fitted model that are then compared with the observed data, with systematic discrepancies indicating problems with the model.

Bayesian Inference for the Regulator's Decisions

The draft guidance document opens by noting that bayesian methods are not only relevant to experimental design and inference, but also to decision-making.[1] While the guidance is written for trial sponsors, it is also important to ask what role bayesian methods can play in the FDA's approval decisions.

The FDA has the mission of approving safe and effective therapeutics and medical products. Consistency and transparency in these decisions are important—uncertainty about the procedures would prevent drugmakers from conducting research and lack of transparency can expose decisions to political pressure and lobbying. However, a survey of 912 FDA applications[5] found that FDA decisions did not consistently cite prior reasoning and that some approvals, after additional review, reflected new interpretations of existing evidence rather than new evidence, raising concerns about consistency across review cycles.

Some flexibility is necessary, and the FDA already allows informal clinical judgment in its decisions. The bayesian approach, which formally accounts for sources of information, has the potential to increase both transparency and consistency.

A recent high-profile example may be illustrative. In February 2026, the head of the FDA's Center for Biologics Evaluation and Research issued a refusal-to-file letter for Moderna's mRNA influenza vaccine, citing the failure to compare the vaccine against high-dose competitors in older adults[6]; however, this decision was reversed after a week.[7] The problem of comparisons among relevant subpopulations can be directly and transparently addressed using hierarchical bayesian methods. Influenza vaccines are among the best studied therapeutics in existence. Relevant information from other trials could be incorporated into the prior and data reanalyzed to conduct a risk-benefit analysis in older adults without conducting a new trial.

Conclusions

Bayesian methods are well suited to the FDA's mission and principles. The current draft guidance is a solid basis for sponsors seeking to design better trials and for better regulatory decision-making. Although often criticized as subjective, bayesian approaches, when implemented transparently, can improve on informal principles of clinical judgment that often inform the current FDA model.

ARTICLE INFORMATION

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