Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2025-D-3217

Dear Sir or Madam,

On behalf of the Pediatric Inclusion Alliance, we are pleased to submit comments on FDA's Draft Guidance for Industry "Use of Bayesian Methodology in Clinical Trials of Drug and Biological Products." We appreciate FDA providing this direction about the situations where Bayesian methods may be appropriate, especially because many of these are particularly applicable for pediatric populations.

About the Pediatric Inclusion Alliance

The Pediatric Inclusion Alliance (Alliance) is devoted to full, active collaboration among all stakeholders committed to achieving earlier inclusion of children in clinical trials across all diseases and conditions without compromising safety. For far too long, children have had to wait years for access to safe, effective therapies, often already approved for adult populations. These therapies might well have been even more effective for younger patients if administered at the best time for them.

By combining a deep understanding of the needs of pediatric patients and their families, technical expertise, and real-world experience in medical research and therapy development, knowledge of regulatory guidance and processes, public policy, regulatory knowledge, and public policy understanding, the Alliance is a united collaborative of stakeholder groups committed to ensuring that children have the earliest opportunity to access safe and effective therapies when those therapies are most likely to have maximum benefit to them.

General Considerations for Early Pediatric Inclusion

Overcoming barriers to use of Bayesian methods

The Pediatric Inclusion Alliance is very aligned with the viewpoint that Ruberg et al. put forward in their Nature Reviews Drug Discovery perspective piece "Application of Bayesian approaches in drug development: starting a virtuous cycle." The authors state that "clinical drug development, which accumulates data over time can be well suited for the use of Bayesian statistical approaches that explicitly incorporate existing data into clinical trial design, analysis and decision-making. Such approaches, if used appropriately, have the potential to substantially reduce the time and cost of bringing innovative medicines to patients, as well as to reduce the exposure of patients in clinical trials to ineffective or unsafe treatment regimens. Nevertheless, despite advances in Bayesian methodology, the availability of the necessary computational power and growing amounts of relevant existing data that could be used, Bayesian methods remain underused in the clinical development and regulatory review of new therapies."

FDA's release of this guidance is an important step forward in breaking down barriers to use of Bayesian methods in drug development and creating the "virtuous cycle" argued for in that article. We are particularly pleased that this draft guidance includes several references to pediatric drug development use cases and real-world examples, as pediatric drug development, which poses some unique challenges, does not always garner that same level of attention in regulatory guidance documents.

Advantages to pediatric patients of further use of Bayesian approaches where appropriate

For pediatric patients, there are a number of potential advantages to more common use of Bayesian methods in drug development. In addition to improvements in the time to conduct clinical trials and the cost to complete them, other advantages include:

- **Bayesian methods can ameliorate recruitment challenges.** Recruitment challenges are a well known and unfortunately common occurrence in pediatric clinical trials. Researchers estimate that around 40% of pediatric randomized trials discontinue early, and more than half of those are due to slow recruitment.[2] By utilizing Bayesian methods to incorporate prior knowledge, researchers can reduce the sample size required for clinical trials. For example, in a simulation study of pediatric patients with Type 2 diabetes, researchers found that by using Bayesian methods, the number of pediatric patients that would be required to conduct the trial could be reduced by 75-78%. In that case, the false positive rate was high; holding the false positive rate in the simulation to 10% still reduced the trial size by 30-33%.[3] A reduction in trial size could prevent some studies from discontinuing early or failing to meet recruitment goals, which would be an important advancement for pediatric drug development. From a regulatory perspective, these efficiencies can increase the likelihood that pediatric studies are completed successfully and generate interpretable evidence to support timely review decisions.

- **Bayesian approaches enable adaptive and shorter trials through earlier decisions on efficacy or futility.** Bayesian approaches offer additional advantages for pediatric rare disease trials. By incorporating Bayesian sequential monitoring into trial design, investigators can analyze accumulating data in real time, allowing emerging evidence to inform decisions and enabling earlier trial conclusion based on efficacy or futility. This approach can provide clearer and more timely insights into treatment effects than traditional fixed designs.

  In *"A Bayesian approach in design and analysis of pediatric cancer clinical trials,"* Ye et al. explore how Bayesian methods can be applied to trials of rare pediatric cancers. In these settings, trial designs are complicated by small patient numbers and limited opportunities to extrapolate efficacy data from adult indications. Bayesian methods can help overcome these barriers by enabling integration of prior data from previous pediatric trials of the same drug or from adult trials, and continuously updating evidence as new data accumulates.

  The authors demonstrate how Bayesian methods can be used to design, monitor, and analyze pediatric cancer trials, concluding that "designing a pediatric trial with both skeptical and enthusiastic priors with Bayesian sequential monitoring can be an efficient mechanism for early trial cessation for both efficacy and futility. The interpretation of efficacy using a Bayesian approach is based on posterior probability and is intuitive and interpretable for patients, parents and prescribers given limited data."[4] Similarly, Wang et al., constructed alternative designs for a published Phase III pediatric trial and reported that "designing a Bayesian adaptive pediatric trial with both skeptical and enthusiastic priors can be an efficient and robust approach for early trial stopping, thus potentially saving time and money for trial conduction."[5]

- **Bayesian hierarchical models can provide more precision in estimates of safety and efficacy**. The Staphylococcus aureus Network Adaptive Platform (SNAP) trial was designed as a "unified adult-pediatric whole-of-life clinical trial" to allow information sharing (borrowing) between trial age groups by linking intervention effects of children and adults, thereby improving inference in both groups. The authors concluded that "Bayesian hierarchical models may provide more precision for estimates of safety and efficacy of treatments in trials with heterogenous populations compared to traditional methods of analysis. They facilitate the inclusion of children in clinical trials and a shift from children deemed therapeutic orphans to the vision of no child left behind in clinical trials to ensure evidence for clinical practice exists across the life course. The SNAP trial provides an example of a Bayesian adaptive whole-of-life inclusion design that enhances trial population inclusivity and diversity overall, as well as generalizability and translation of findings into clinical practice."[6]

- **Bayesian reanalysis can help guide treatment.** Even for trials conducted using frequentist statistical methods, Bayesian reanalysis can yield important insights to guide treatment of children. For example, the THAPCA-OH (Therapeutic Hypothermia after Pediatric Cardiac Arrest Out-of-Hospital) trial compared hypothermia (33.0°C) with normothermia (36.8°C) in 295 children with out-of-hospital cardiac arrest (OHCA). In the primary frequentist analysis, the outcomes (good neurobehavioral outcome and survival

at 1 year) were higher in the hypothermia group (20 vs. 12% and 38 vs. 29%, respectively). These differences did not meet the planned statistical threshold of P<0.05. However, a Bayesian analysis, interpreting the trial in probabilistic terms using noninformative priors showed high probability (94%) that the treatment (hypothermia) provides a modest benefit in neurobehavioral outcome and survival at 1 year. The authors explained that "In contrast, when frequentist confidence intervals include zero, this merely signifies that the null hypothesis cannot be rejected, and no additional inference about treatment benefit is permitted."[7] Further, "Decisions about treatment based on these probabilities must incorporate additional considerations about the intervention, such as other risks, costs, prognosis, and patient or family preferences. By directly addressing the primary question raised by patients and clinicians — what are the probabilities of benefit and harm? — Bayesian posterior probabilities maximize the information available from trials for clinical decision-making." In this example, given that there are no other therapies to improve outcomes of pediatric OHCA beyond supportive care, this offers an important opportunity for clinicians and parents to make treatment decisions.

Specific Considerations for Guidance

The Pediatric Inclusion Alliance offers the following comments on specific sections of the guidance.

III. Situations where Bayesian methods have been used

A. Borrowing from previous clinical trials (page 3, lines 82-93)

This section provides a single example of forming an informative prior for a clinical trial based on previous clinical trial results from the same drug. Given that the number of pediatric clinical trials is so limited, it is likely infrequent that a trial is proposed where the same drug has been tested before in a pediatric population. We encourage FDA to clarify in the final guidance that, in appropriate circumstances, informative priors may be derived not only from prior trials of the same drug, but also from drugs with shared mechanisms of action or well characterized biological similarity—particularly in pediatric contexts where direct evidence is limited.

Augmenting a randomized concurrent control using an external control or nonconcurrent control data (page 3, lines 95-109). We are pleased that FDA has included an example in this section of a clinical trial in pediatric patients with multiple sclerosis that was proposed through the Complex Innovative Trial Designs program. Given that many pediatric diseases, as discussed above, affect small patient populations, making trial recruitment inherently challenging, we appreciate FDA's explicit mention of ways to reduce the size of the control group needed by utilizing Bayesian methods.

B. Pediatric extrapolation (page 3, lines 111-130)

We are extremely pleased that pediatric extrapolation is explicitly addressed in this guidance and agree with FDA's view that when pediatric extrapolation is justified, Bayesian methods can be considered as an appropriate method to improve the analysis. In the type 2 diabetes

example provided, FDA notes that the pathophysiology is similar in adults and children, so the information is relevant and borrowing is justified.

In many other situations, the similarity between adult and pediatric presentation and pathophysiology of the same disease may be less well understood, making the case for extrapolation less clear. We encourage sponsors to consider when borrowing is appropriate, and note some limitations such as ongoing growth or metabolic differences for children that may pose challenges. In addition, there is great heterogeneity among children such that borrowing may be easier and more appropriate when comparing adolescents to adults than for example, borrowing when the children are infants or toddlers

The Pediatric Inclusion Alliance is advocating for, and trying to help develop, better pre-clinical data to enable pediatric studies. We urge FDA to consider this preclinical data in making the determination that a sponsor's plan to extrapolate adult data to pediatric populations can be appropriate, even in circumstances where less is known about the similarities between adult and pediatric presentations of the same disease.

C. Borrowing information across similar diseases or disease subtypes (page 3, lines 132-146)

As noted throughout our comments, many pediatric diseases are rare, with different subtypes in any specific condition sometimes caused by specific genetic mutations. Therefore, the concept of borrowing across similar diseases or disease subtypes is quite applicable in pediatric clinical trials, especially those using innovative designs. For example, basket trials using Bayesian hierarchical borrowing may allow evaluation across several cancer types simultaneously and small pediatric subgroups to gain precision from related tumor types [8].

V. Prior Distributions

D. Informative priors to borrow external information (page 11, line 443)

In this section, FDA notes that areas where informative priors have been most often proposed include pediatrics and rare disease and that additional areas can be considered on a case-by-cases basis. The Alliance agrees with FDA's articulation of the elements that should be part of the justification for borrowing external information in these case-by-case fit-for-purpose scenarios.

3. Prior Construction (page 13, lines 531-624)

We recommend that the guidance recognize the value of an iterative approach to updating priors in pediatric development. A structured process for integrating evidence from previous pediatric Bayesian trials would allow priors to be refined as the collective experience grows. This approach can strengthen estimates in areas with limited data while ensuring that any borrowing of external information is appropriately governed by clinical and statistical relevance. An evolving prior framework would help ensure that priors used in new pediatric studies remain clinically credible, transparent, and increasingly informative as the pediatric evidence base expands.

Conclusion

Thank you for the opportunity to comment on this draft guidance. We welcome continued dialogue with FDA on the application of Bayesian approaches in pediatric drug development and would be pleased to engage further as the Agency refines this guidance and considers future pediatric focused examples.

References

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