

Panel session Bayes in Rare Disease

Panelists: Lucinda Billingham, University of Birmingham, UK

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Moderator: Arnaud Monseur

Topic 1: Borrowing and Priors

Rare disease clinical trials are often challenged by extremely small, heterogeneous patient populations and the ethical imperative to minimize placebo exposure. In such scenarios, Bayesian approaches provide an attractive framework by allowing the incorporation of external trial data, natural history studies, or real-world evidence. However, a key concern among regulatory bodies and clinicians remains *how much borrowing of information is appropriate* and *how robustly the priors should be specified*.

Aysun, from your perspective, what guiding principles should trial statisticians and sponsors use when determining the degree and structure of prior information to be incorporated into a Bayesian rare disease trial? Could you illustrate, perhaps with past examples, how one navigates the balance between making efficient use of scarce data and avoiding undue influence of potentially misaligned external sources?"

Topic 2: Adaptive designs in small populations

One of the major promises of Bayesian methods in rare disease trials is their compatibility with adaptive design elements — such as response-adaptive randomization, early stopping for futility, or seamless phase II/III transition. Yet, while methodologically appealing, these designs can introduce operational complexities, and regulators sometimes express concern about trial interpretability and credibility of results.

Cindy, In your opinion, what are the best practices for implementing Bayesian adaptive designs specifically in rare diseases, where patient populations are fragmented and trial timelines are often prolonged? Further, how do you envision the use of modern computational methods — for example hierarchical or dynamic borrowing models — to enhance the flexibility and acceptability of adaptive Bayesian designs in this unique setting?"

Topic 3: Regulatory/ communication Challenges

One of the most important discussions in the field of Bayesian statistics for rare diseases centers not only on the technical modeling aspects, but also on the regulatory and communication challenges. Regulators and clinicians often express uncertainty about the transparency of Bayesian methods, particularly around prior elicitation, posterior interpretation, and the translation of Bayesian probabilities into actionable evidence for approval or clinical guidelines.

Peter, Given your experience advising both regulators and clinical investigators, what strategies do you see as most effective for bridging the gap between methodological sophistication and regulator or clinician trust in Bayesian analyses? And relatedly, do you believe the field is progressing toward a paradigm where Bayesian trial results will not only supplement but in some cases *replace* conventional frequentist evidence in rare disease contexts?"

Topic 4: How do you see the future ?

"Given the diversity of your expertise — from statistical methodology to adaptive trial innovation and regulatory translation — where do you see the biggest opportunities for consensus and progress in integrating Bayesian methods into rare disease trials in the *next five years*? Conversely, where do you anticipate the greatest resistance, and what role should statisticians play in educating stakeholders on these issues?"