



Case Study

Bayesian Extrapolation

Bayesian Extrapolation to Evaluate Efficacy in Pediatric Subjects using Adult Data.



KerusCloud.

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KerusCloud is a ground-breaking new clinical study design and analytics software platform which can generate and evaluate the performance and outcomes of clinical development scenarios. In this case study, KerusCloud was used to evaluate the efficacy of a new drug in pediatric subjects.

As part of a Pediatric Investigation Plan (PIP) commitment to the European Medicines Agency (EMA), a large pharmaceutical company wished to conduct a clinical trial to investigate the efficacy of a drug in pediatric patients previously approved in adults.

The Challenge

A clinical trial was commenced but recruited slowly and was terminated early, with only 68% of the planned number of subjects recruited. Therefore, the Pediatric Committee (PDCO) of the EMA recommended that an extrapolation study be conducted to evaluate the efficacy of the drug in the recruited pediatric sample. To do this, a Bayesian extrapolation approach was employed, where data from previous adult studies was leveraged to increase precision for the final efficacy endpoint in the pediatric population. The PDCO stipulated a tight timeline for completion of the analysis.

The Approach

Adult studies for the drug, which looked at similar endpoints, were identified in the literature. The pediatric data was first analysed using frequentist techniques which had been previously employed within the adult studies and the results were compared to ensure consistency, increasing confidence in the appropriateness of implementing an extrapolation approach.

A primary Bayesian extrapolation analysis was conducted, initially using data from a single adult study, and then using the results of a meta-analysis from multiple adult studies was used as a sensitivity analysis. Initially, a weak and informative prior distribution for the primary endpoint were defined:

• The informative prior was specified using the mean and standard error of the adult data

 The weak prior was specified by a unit-information normal distribution with mean zero and variance scaled to represent information equivalent to one subject

A Bayesian 'dynamic borrowing' approach was then employed, where the informative prior was combined with the weak prior, resulting in a robust weighted mixture prior distribution, allowing the analysis to learn how much of the adult information to borrow, based upon the consistency observed between the pediatric data and the adult prior.



Figure 1: Informative and weak priors



Figure 2: Robust Mixture priors



Exploristics Ltd. 24 Linenhall Street Belfast, Northern Ireland BT2 8BG find out more T +44 (0) 28 9600 1996 info@exploristics.com

The Results

Plotting w^* against w consistently shows the posterior weight to be larger than the prior weight (i.e. $w^* > w$), meaning that the pediatric data is sufficiently consistent with the adult prior information, increasing the confidence in the extrapolation strategy. The sensitivity analysis gave similar conclusions.

Testimonial

Exploristics has provided excellent service on the Bayesian extrapolation of efficacy in pediatric patients. This is a highly technical expertise that several preferred vendors could not provide when we sought bids from them for this project. I can't say enough it was an absolute pleasure to work with the team at Exploristics!

Project Statistician and Statistical Manager Large Pharmaceutical Company UK



Figure 3: Prior Versus Posterior Weight on Adult Component of Robust Mixture Prior

The Impact

KerusCloud showed that:

The results support extrapolation of drug efficacy in adults to pediatric subjects.

- The available efficacy data within the pediatric population appears consistent with that within the larger adult population, as there were no observed differences in treatment effect across the adult and pediatric populations.
- A significant increase in the primary endpoint in pediatric subjects was supported through the extrapolation analysis with only a relatively small (25%) prior confidence in the pediatric treatment effect being similar to the adult treatment effect.

Full documentation (analysis plans), statistical reports, code and log files were provided to the client within the required timeframes allowing them to meet their key regulatory commitments.



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