

## Case Study

### Bayesian Extrapolation

# Bayesian extrapolation to evaluate efficacy in pediatric subjects using adult data

KerusCloud® is a revolutionary simulation-guided study design tool that ensures clinical trials are designed effectively to collect the right data, in the right patients, in the right way. Its use supports evidence-based design decisions to extensively de-risk real clinical studies, reducing development time, costs and patient burden.



## The Software

KerusCloud® allows multiple study uncertainties to be explored simultaneously, in minutes, within a virtual environment. Study outcomes are visualized with an interactive heatmap where detailed results help identify the pros and cons of different design options. This allows the key drivers of study success to be pinpointed rapidly so that the best design and analysis approach can be selected, first time.

Diverse information and data types inform the simulations with sources including the scientific literature, disease registries, historical trials and real-world data. These data are captured in the platform as synthetic data sets, avoiding privacy constraints, and used to build virtual patient populations to answer 'what if' study scenarios questions.

KerusCloud's synthetic data driven simulations are uniquely informative. They best represent the complexity found in real studies by accurately mimicking the quirks found in real patient-level data, like missingness. Therefore, KerusCloud® provides exceptional advanced analytical insights able to deliver the smarter studies needed to address today's complex clinical research challenges.

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## The Challenge

A clinical trial was commenced by a large pharmaceutical company but recruited slowly and was terminated early, with only 68% of the planned number of pediatric subjects recruited. Following their review, 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 required, where data from previous adult studies was leveraged to increase precision for the final efficacy endpoint in the pediatric population. A tight timeline was stipulated for completion of the analysis.

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## The Approach

The recommended analysis would involve multiple stages requiring specific expertise deployed intensively to meet the overall timeline with no guarantee of success. Prior to committing to the work KerusCloud® was used to rapidly evaluate the feasibility and probability of success of the recommended approach, taking into account the volume of data available and anticipated effect sizes and variability. This allowed confirmation that the approach had a good chance of providing robust evidence of efficacy of the new drug in pediatric subjects.

The analysis could then proceed with greater confidence through the following steps:

- + Adult studies for the drug, which looked at similar endpoints, were identified in the literature.
- + The pediatric data was first analyzed 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 as a sensitivity analysis.
- + Initially, a weak and informative prior distribution for the primary endpoint were defined (Figure 1). The informative prior was specified using the mean and standard error of the adult data.
- + 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 (Figure 2), 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.

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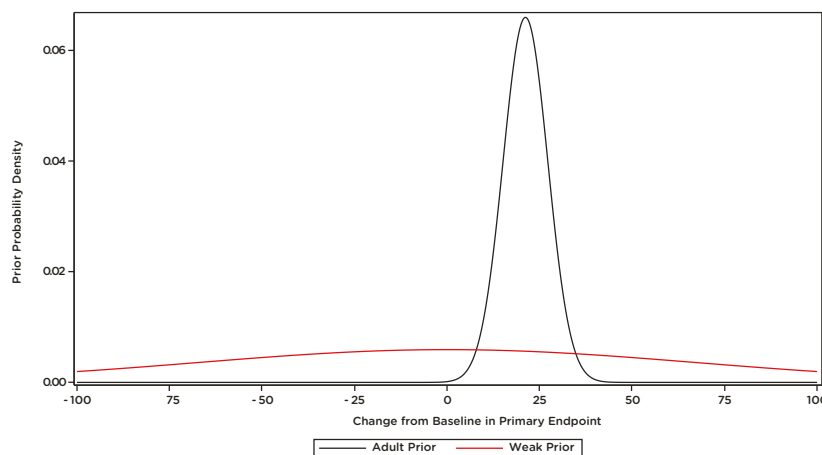
## The Results

**KerusCloud® showed that the Bayesian dynamic borrowing approach was feasible and had a good probability of success before any work was undertaken.**

**The subsequent analysis went on to show:**

**The available efficacy data for the pediatric population appeared consistent with that for 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 could be 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.**



**Figure 1.** Informative and weak priors

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## The Impact

With KerusCloud®:

Extrapolation of drug efficacy in adults to pediatric subjects could be supported in this case as part of a robust evidence package for Regulators.

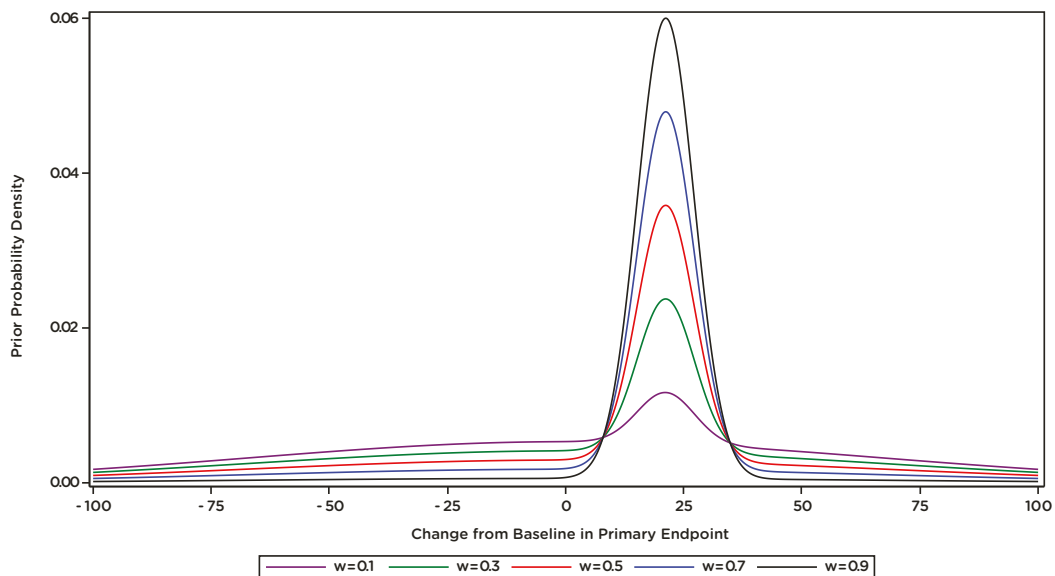


Figure 2. Robust Mixture priors

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“MMS 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 MMS!”

**Project Statistician and Statistical Manager,  
Large Pharmaceutical Company**

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## Why MMS?

### Expertise In Early Development

The development of investigational drugs is a complex and expensive process with many risks. For over ten years our teams have been supporting and de-risking clinical development with their in-depth statistics and modelling expertise. Our study planning, statistical analysis and programming services add value to early stage development programs by ensuring they deliver the robust evidence needed for incisive, informed decision-making.

With many of our development solutions built around our unique KerusCloud® platform, we can provide exceptional, bespoke, end-to-end biostatistics support from strategic decision-making and protocol development to analysis, reporting and stakeholder engagement.

### Robust Evidence Packages

The unique offering of our comprehensive biostatistics services in combination with KerusCloud® ensures that MMS can help to generate strong evidence packages to support regulatory engagement or investment, accelerating development timelines and increasing the value of pipelines.

### Let's talk!

If you'd like to discuss this case study further or learn more on how our technology enabled services can support your development project, please visit our website: [mmsholdings.com](http://mmsholdings.com)

## MMS. The Difference Is In The Data