An Open-Source R-Shiny Application Designed to Perform Frequentist and Bayesian Mixed Model Repeated Measures (MMRM)

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CONCLUSIONS

The developed R-Shiny application successfully bridges the gap in Mixed Model Repeated Measures (MMRM) analyses by providing a standardized, user-friendly, and secure Frequentist and Bayesian modeling platform. It allows researchers to easily perform complex mixed models while ensuring reproducibility and transparency. Future updates will include additional correlation structures and support for non-linear models. Enhanced visualizations will allow for deeper exploration of model diagnostics and treatment effects. Integration with Clinical Data Interchange Standards Consortium (CDISC) standards will facilitate regulatory compliance and data sharing.

INTRODUCTION

- MMRM is widely used for assessing longitudinal clinical trial data, where multiple correlated measurements are taken from the same subject over time. MMRM considers within-subject correlations, missing data, and flexible correlation structures [1]
- In the Frequentist framework, MMRM typically employs maximum likelihood estimation, including methods such as restricted maximum likelihood (REML), and utilizes advanced inference techniques like the Satterthwaite approximation for hypothesis testing[1]
- The Bayesian MMRM approach integrates prior information and provides a probabilistic interpretation of model parameters, making it particularly valuable in scenarios with limited sample sizes or when quantifying uncertainty is essential[2]
- By supporting both Frequentist and Bayesian paradigms, MMRM enables a robust, comprehensive analysis of longitudinal data in clinical trials, ultimately aiding in better assessment of treatment effects over time [2]
- While several R packages are available to implement MMRM, there is currently no standardized, streamlined solution tailored for end-users, highlighting the need for a unified and accessible platform

OBJECTIVE

To develop an open-source, user-friendly, and standardized R Shiny application that enables non-programmers to perform robust Frequentist and Bayesian MMRM analyses without extensive coding expertise.

METHODS

- The application incorporates two key R packages - **nlme** for Frequentist and **brms.mmrm** for Bayesian MMRM modeling to support robust statistical analyses of repeated measures data (R Version 4.4.1)
- The application offers flexible modeling capabilities, allowing users to specify fixed and random effects, include interaction terms, toggle between Frequentist and Bayesian frameworks, and customize Bayesian settings such as the number of chains and iterations
- In the Frequentist framework, the tool supports multiple correlation structures to model the correlation between repeated measures. Some of these include:
  a. **General Symmetry - Unstructured correlation:** no assumptions about the pattern of correlation over time
  b. **Autoregressive (AR1) - Repeated measures over time** assumes correlations decrease as the time gap increases
  c. **Compound Symmetry (CS) - Equal correlation between all measurements** assumes equal correlation between all time points

METHODS (CONT'D)

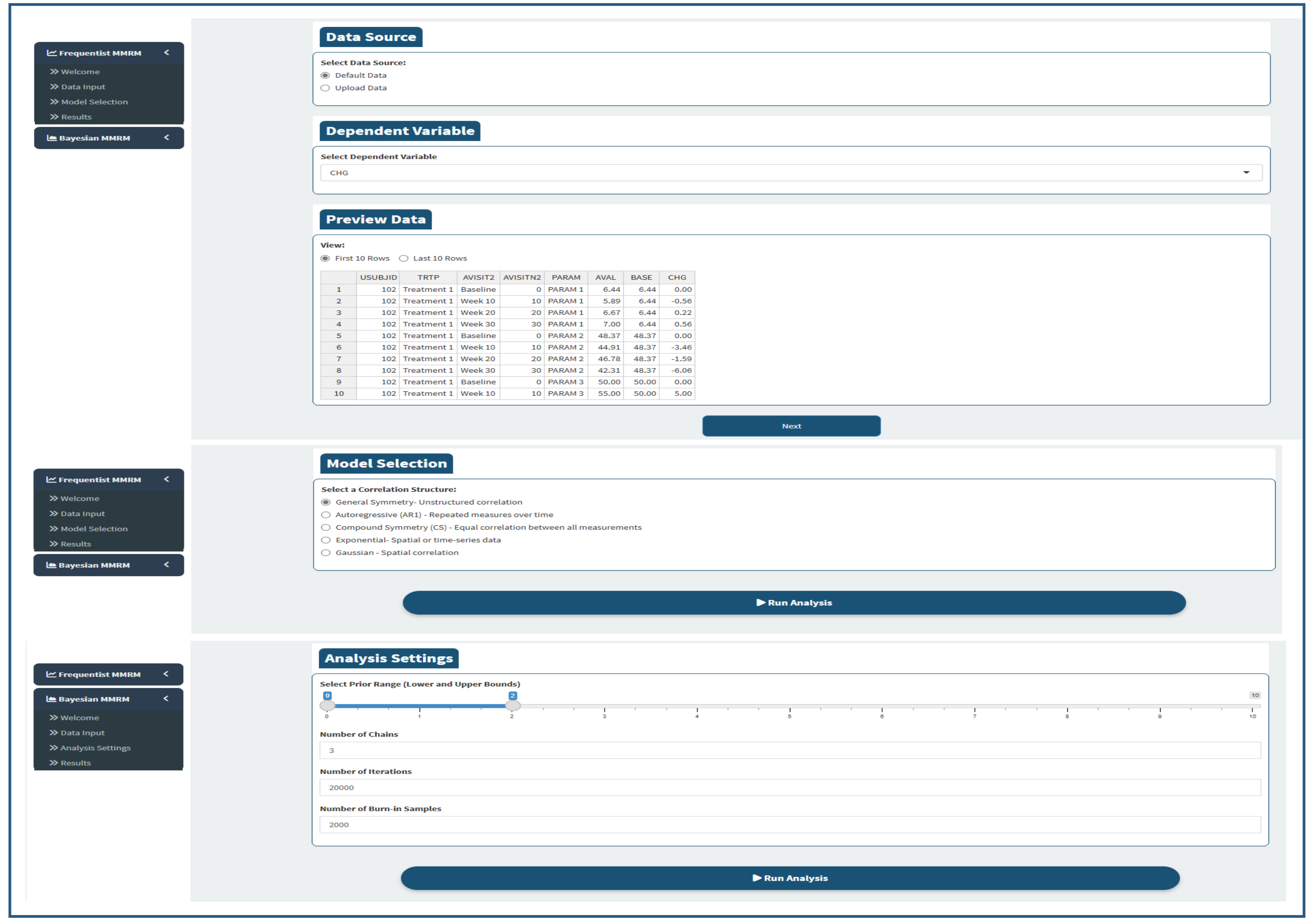
  a. **Exponential - Spatial or time-series data:** Correlation decreases exponentially with distance (spatial/time)
  b. **Gaussian - Spatial correlation:** models spatial correlation using a Gaussian function, where correlation decreases with the square of the distance

- Users can visually compare how different correlation structures impact model fit and estimates, promoting a deeper understanding of model assumptions
- The tool visualizes the results using error bars representing least-squares means (LSM) with 95% confidence interval (CI) for all the parameters included in the analysis, allows for easy comparison of adjusted means across groups, accounting for covariates included in the model
- It supports dynamic data input and real-time model updates, allowing users to iteratively refine model specifications and immediately view updated results
- The tool was deployed on Amazon Web Services (AWS) with Auth0 authentication to ensure secure user access. All uploaded data were processed locally in-session and deleted after each session to maintain data privacy
- This tool allows the export of results, including tables and diagnostics, in multiple formats (Excel, PDF) for convenient reporting and documentation

RESULTS

- The interactive tool includes an option for users to upload their data, enabling customized analysis, as shown in **Figure 1**

Figure 1: Input Data Interface, Model Selection, and Analysis Settings



Data Source

Select Data Source:
● Default Data
○ Upload Data

Dependent Variable

Select Dependent Variable: CHG

Preview Data

View: ● First 10 Rows ○ Last 10 Rows

	USUBJID	TRTP	AVISIT2	AVISITN2	PARAM	AVAL	BASE	CHG
1	102	Treatment 1	Baseline	0	PARAM 1	6.44	6.44	0.00
2	102	Treatment 1	Week 10	10	PARAM 1	5.89	6.44	-0.56
3	102	Treatment 1	Week 20	20	PARAM 1	6.67	6.44	0.22
4	102	Treatment 1	Week 30	30	PARAM 1	7.00	6.44	0.56
5	102	Treatment 1	Baseline	0	PARAM 2	48.37	48.37	0.00
6	102	Treatment 1	Week 10	10	PARAM 2	44.91	48.37	-3.46
7	102	Treatment 1	Week 20	20	PARAM 2	46.78	48.37	-1.59
8	102	Treatment 1	Week 30	30	PARAM 2	42.31	48.37	-6.06
9	102	Treatment 1	Baseline	0	PARAM 3	50.00	50.00	0.00
10	102	Treatment 1	Week 10	10	PARAM 3	55.00	50.00	5.00

Model Selection

Select a Correlation Structure:
● General Symmetry- Unstructured correlation
○ Autoregressive (AR1) - Repeated measures over time
○ Compound Symmetry (CS) - Equal correlation between all measurements
○ Exponential- Spatial or time-series data
○ Gaussian - Spatial correlation

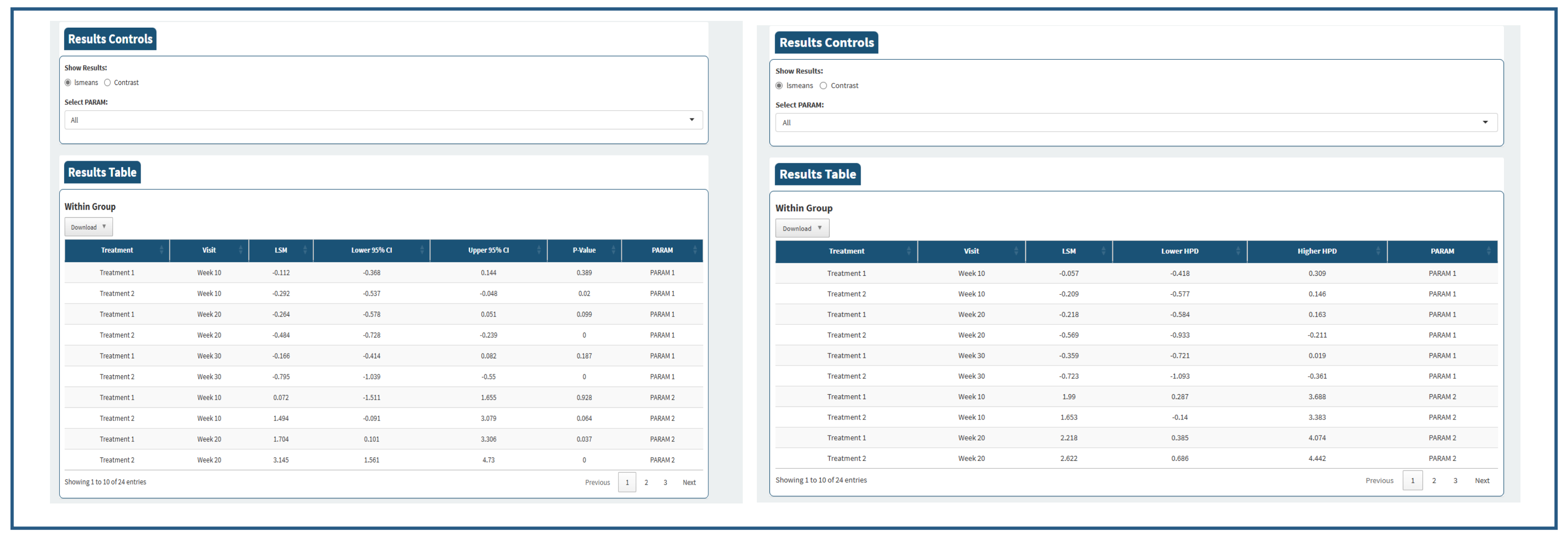
Analysis Settings

Select Prior Range (Lower and Upper Bounds): 0 – 2
Number of Chains: 3
Number of Iterations: 20000
Number of Burn-in Samples: 2000

RESULTS (CONT'D)

- In the Frequentist approach, users can choose from various correlation structures, including unstructured, autoregressive, and spatial correlations, among others
- The Bayesian interface (**Figure 1**) enables flexible model customization by allowing users to define prior ranges, chains, iterations, and burn-in samples
- **Figure 2** shows Frequentist results as LSM with 95% CI and contrast-based results with p-values

Figure 2: Frequentist and Bayesian MMRM Results



Show Results: ● lsmeans ○ Contrast
Select PARAM: All

Within Group

Treatment	Visit	LSM	Lower 95% CI	Upper 95% CI	P-Value	PARAM
Treatment 1	Week 10	-0.112	-0.368	0.144	0.389	PARAM 1
Treatment 2	Week 10	-0.292	-0.537	-0.048	0.02	PARAM 1
Treatment 1	Week 20	-0.264	-0.578	0.051	0.099	PARAM 1
Treatment 2	Week 20	-0.484	-0.728	-0.239	0	PARAM 1
Treatment 1	Week 30	-0.166	-0.414	0.082	0.187	PARAM 1
Treatment 2	Week 30	-0.795	-1.039	-0.55	0	PARAM 1
Treatment 1	Week 10	0.072	-1.511	1.655	0.928	PARAM 2
Treatment 2	Week 10	1.494	-0.091	3.079	0.064	PARAM 2
Treatment 1	Week 20	1.704	0.101	3.306	0.037	PARAM 2
Treatment 2	Week 20	3.145	1.561	4.73	0	PARAM 2

Showing 1 to 10 of 24 entries

Show Results: ● lsmeans ○ Contrast
Select PARAM: All

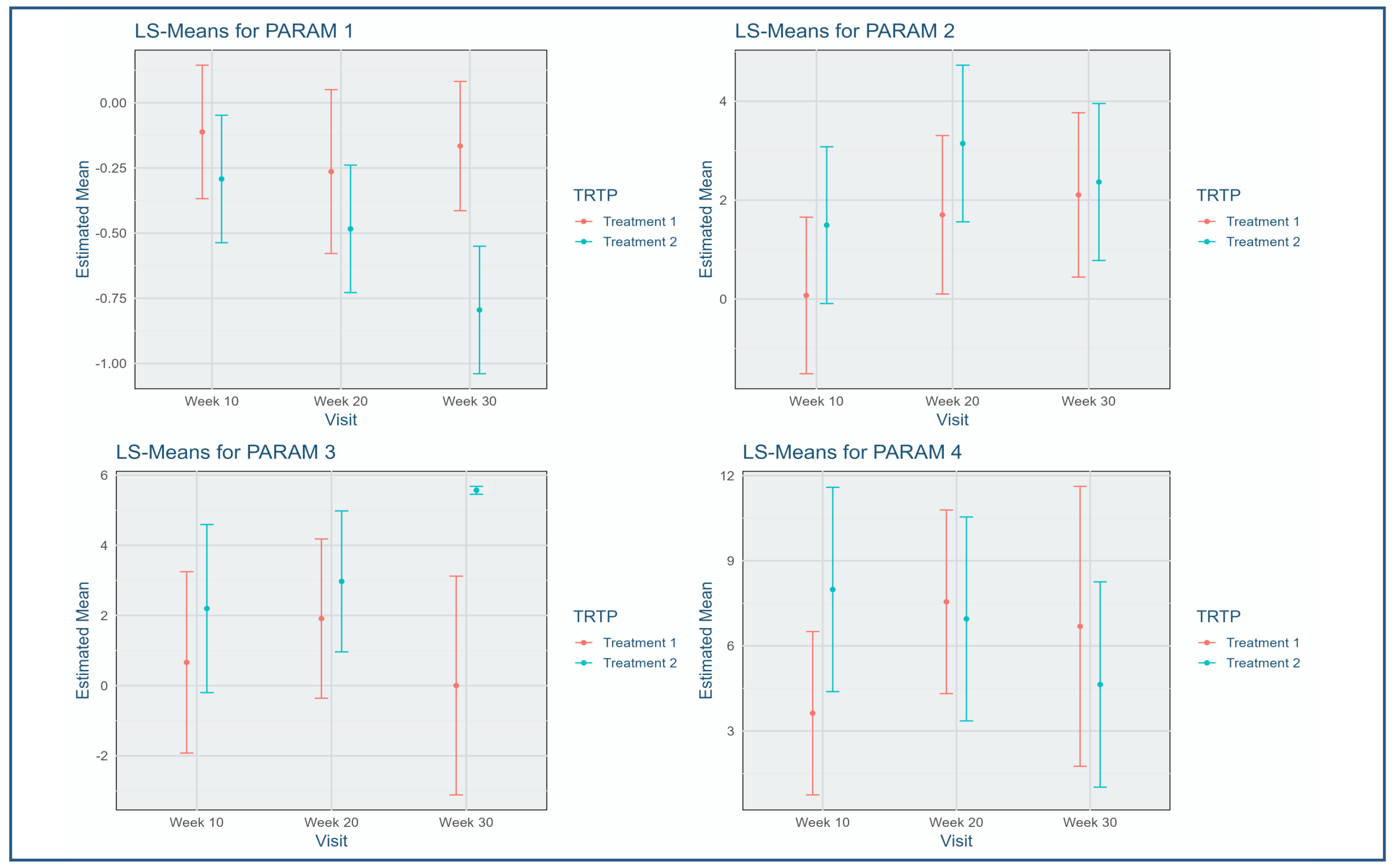
Within Group

Treatment	Visit	LSM	Lower HPD	Higher HPD	PARAM
Treatment 1	Week 10	-0.057	-0.418	0.309	PARAM 1
Treatment 2	Week 10	-0.209	-0.577	0.146	PARAM 1
Treatment 1	Week 20	-0.218	-0.584	0.163	PARAM 1
Treatment 2	Week 20	-0.569	-0.933	-0.211	PARAM 1
Treatment 1	Week 30	-0.359	-0.721	0.019	PARAM 1
Treatment 2	Week 30	-0.723	-1.093	-0.361	PARAM 1
Treatment 1	Week 10	1.99	0.287	3.688	PARAM 2
Treatment 2	Week 10	1.653	-0.14	3.383	PARAM 2
Treatment 1	Week 20	2.218	0.385	4.074	PARAM 2
Treatment 2	Week 20	2.622	0.686	4.442	PARAM 2

Showing 1 to 10 of 24 entries

- The Bayesian approach reports the Highest Posterior Density (HPD) interval, representing the most credible parameter values. This method adapts to skewed posterior distributions, providing a more accurate reflection of uncertainty by narrowing intervals in regions of lower probability density
- The tool provides interactive visualizations of LS-Means across visits for multiple parameters, enabling clear comparisons between treatment groups

Figure 3: Combined plot for LS-Means



References

1. Mixed Model Repeated Measures (MMRM) – Lex Jansen
2. MMRM Model Repeated Measures (MMRM) Analysis Package in R

Sponsorship

This research is conducted solely by the authors without any collaboration from other institutes or pharmaceutical/biotech companies

Disclosures

SK, RR, AS, and SP, the authors, declare that they have no conflict of interest

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