R SHINY Application for CUI Dose Optimization Approach for Multiple-Dose, Multiple-Outcome Randomized Trial Designs (CUI-MET)

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CUI-MET Shiny App Overview

- **Purpose**

The CUI-MET shiny app is designed as a user-friendly tool for dose optimization in multiple-dose randomized trial designs, combining multiple binary endpoints into a composite score – the Clinical Utility Index (CUI). It incorporates the CUI with graphical dose comparisons to identify the Optimal Biological Dose (OBD).

- **Key features**
  - Interactive platform with dynamic visuals and tables
  - Integrates toxicity, efficacy and more binary endpoints (tolerability, PD biomarkers, ...)
  - Calculates utility mean and utility weighted mean for the Clinical Utility Index (CUI)
  - Identifies the OBD with the highest CUI
  - Generates bootstrap confidence intervals and probabilities of OBD selections.
  - Doses can be compared and ranked.

CUI-MET Metrics Definition

Suppose there are N patients. Let Y_{ijk} be the binary outcome value of k^{th} endpoint EP_k for the i^{th} patient with dose level j. To achieve consistency across all K endpoints, where EP_k =1 indicates patient improvement, we need to adjust the toxicity value to 1-toxicity before proceeding with the utility calculation. This adjustment aligns the toxicity endpoint with others, maintaining uniform interpretation of the data.

We adopt a weighting scheme similar to that used by Winzenborg et al. The weights for each endpoint, w_1, w_2,…, w_K, range from 0 to 5 and can be set within this interval, with higher values denoting greater importance. These weights are then normalized to ensure their sum equals one

$$\widetilde{w_k} = \frac{w_k}{\sum_{l=1}^{K} w_l},\ k = 1, 2, \dots, K$$

- Utility mean (UM) for dose level j:

$$UM_j = \frac{1}{K}\sum_{k=1}^{K} P(EP_k = 1|dose\ j)$$

- Utility weighted mean (UWM) for dose level j given normalized weights $\widetilde{w_k}$:

$$UWM_j = \sum_{k=1}^{K} \widetilde{w_k} P(EP_k = 1|dose\ j)$$

- UWM is equivalent to UM when all endpoints are weighted equally.

CUI-MET Methods

The CUI-MET framework supports both empirical and modeling methods for estimating the marginal probability $P(EP_k = 1|dose\ j)$. The four parametric modeling methods include: linear and quadratic regression models on the logit scale, the Emax model, and the exponential model. Each endpoint is modeled independently, assuming monotonic increase with dose for toxicity. Non-monotonic associations are permitted for other endpoints when using a logit model. By definition, the Emax and exponential model inherently assume monotonic relationships due to their mathematical structure.

- Empirical Method

$$P(EP_k = 1|dose\ j) = \frac{1}{N}\sum_{i=1}^{N} Y_{ijk}$$

- Logit Linear Model

$$\text{logit}\big(P(EP_k = 1)\big) = \beta_{0k} + \beta_{1k} * dose$$

- Logit Quadratic Model

$$\text{logit}\big(P(EP_k = 1)\big) = \beta_{0k} + \beta_{1k} * dose + \beta_{2k} * dose^2$$

CUI-MET Methods – cont'd

- Emax Model

$$\text{logit}(\hat{p}) = E_0 + E_{max} * \frac{dose}{ED_{50} + dose}$$

In this model, $\hat{p}$ is the predicted probability of a positive response from the first-stage GLM fitting, E_0 is the baseline effect, E_{max} represents the maximum achievable effect above the baseline, and ED_{50} is the dose at which half of the maximum effect is achieved. The Emax model is particularly valued for its ability to describe saturation effects as dose increases.

- Exponential Model

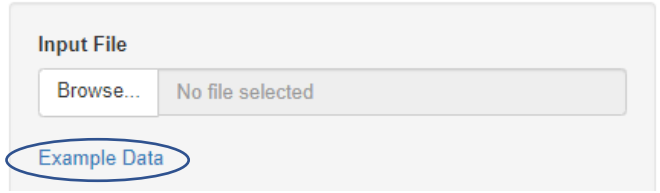
$$\text{logit}(\hat{p}) = E_0 + E_{max}(\exp(dose/\sigma) - 1)$$

Here, σ is a scale parameter that controls therate at which the effect approaches the maximum as dose increases, shaping the convexity of the dose-response curve.

The Emax and exponential models are fitted using two-stage modeling approach in the R package DoseFinding.

Input Requirement

Input data should be a data frame saved in a .csv format file. For reference, you can access an example data set by clicking on the “Example Data” hyperlink. This example dataset will give you a clear understanding of the desired data structure.



ID	Dose	Toxicity	Efficacy	Tolerability
1	1	0	0	0
2	1	0	1	1
3	1	0	0	0
4	1	1	0	1
5	1	0	1	1
6	1	0	0	0
7	1	0	0	0
8	1	0	0	1
9	1	0	0	0
10	1	0	0	0
11	1	0	0	0
12	1	0	0	0

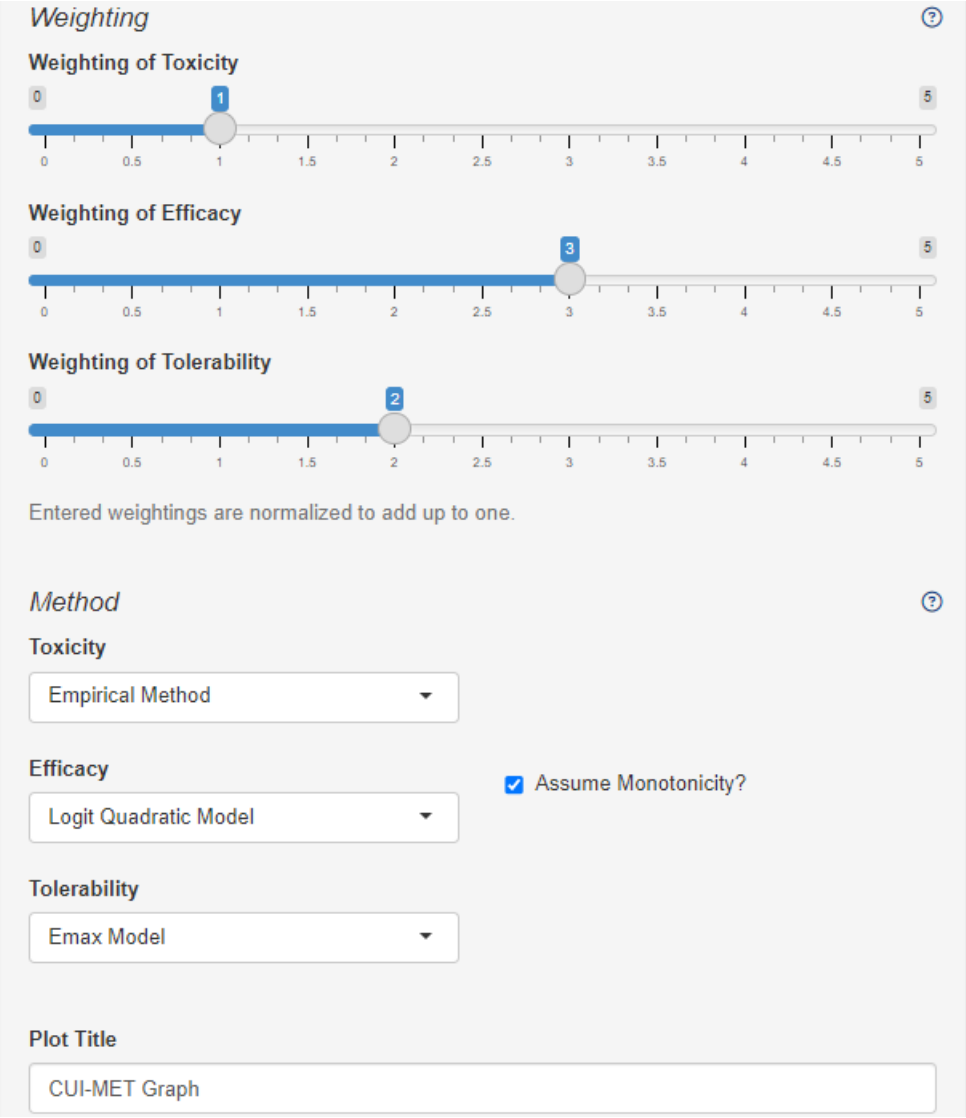
- **ID**: Patient ID number
- **Dose**: Numerical values ranging from 1 to the highest dose level used in the study, indicating the dosage administered to each patient.
- **Toxicity**: Binary values (0 or 1), with 1 representing patients who experienced toxicity, and 0 representing patients who did not experience toxicity during the study.
- **Efficacy**: Binary values (0 or 1), where 1 denotes patients with positive efficacy outcomes, while 0 denotes patients without positive efficacy outcomes during the study.
- Other binary endpoints if needed. All these binary endpoints (except toxicity) should follow the same direction with 1 indicating the patient doing better.

Please note that the variable names “ID”, “Dose”, “Toxicity” and “Efficacy” are essential for the functionality of the shiny app. Additional binary outcomes can be imported, and the app will automatically extract and display the corresponding user-specified variable names in the weighting parameter labels.

Although the app allows for missing values in the endpoint data, a minimum of 10 observations per dose level is required for each endpoint. Additionally, marginal probabilities for each endpoint may not be estimated well if there is a large portion of missing values.

If the input data fails to meet the necessary criteria, a warning message will be displayed.

Input Parameter



After uploading the input data file, the weighting input parameter for each endpoint becomes available. For example, if the data file includes three endpoints, such as Toxicity, Efficacy, and Tolerability, three sliders will appear. These sliders have a range from 0 to 5 with a default value of 1. Users can adjust the weighting in increments of 0.1, with higher values indicating greater importance for a particular endpoint. The flexible weighting scheme allows users to customize the relative significance of each endpoint according to their preferences and analytical needs.

As an example, if input weightings are defined as 1, 3, and 2 for toxicity, efficacy and tolerability, the corresponding normalized weightings will be 17%, 50% and 33%, respectively.

Method selections for each endpoint are available via dropdown menus, with options to specify monotonicity assumptions for endpoints analyzed using logit models.

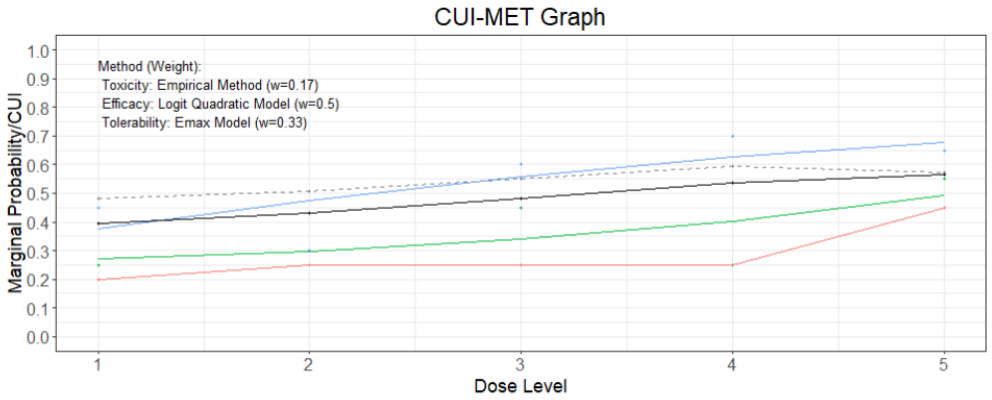
The Plot Title option allows users to specify the title of the CUI-MET graph as needed.

Output Overview

Output panel contains the input data summary, results and visualizations based on the input parameters. It functions as a reactive output panel, automatically updating when changes are made to the input weightings.

Input Summary

In the study, 20 subjects are assigned to 5 dose levels. There are 3 endpoints: Toxicity, Efficacy and Tolerability. The weights given to these endpoints are 0.17, 0.5 and 0.33, respectively. The utilities are calculated using the Empirical Method for Toxicity, Logit Quadratic Model for Efficacy and Emax Model for Tolerability with a monotonic assumption for Efficacy.



Please note that we use the flipped toxicity (1-toxicity) when calculating utility mean and weighted mean.

☐ Show 95% confidence intervals on the graph

Utility Summary

Dose	Toxicity	1-Toxicity	Efficacy	Tolerability	UtilityMean	UtilityWeightedMean
1	0.20	0.80	0.27	0.38	0.48	0.39
2	0.25	0.75	0.30	0.48	0.51	0.43

- Input Summary
- CUI Graph
- Utility Summary Table

Output – Input Summary

The input summary provides an overview of the study's specifics including the sample size, dose levels, endpoints, normalized weightings and method/modeling selection.

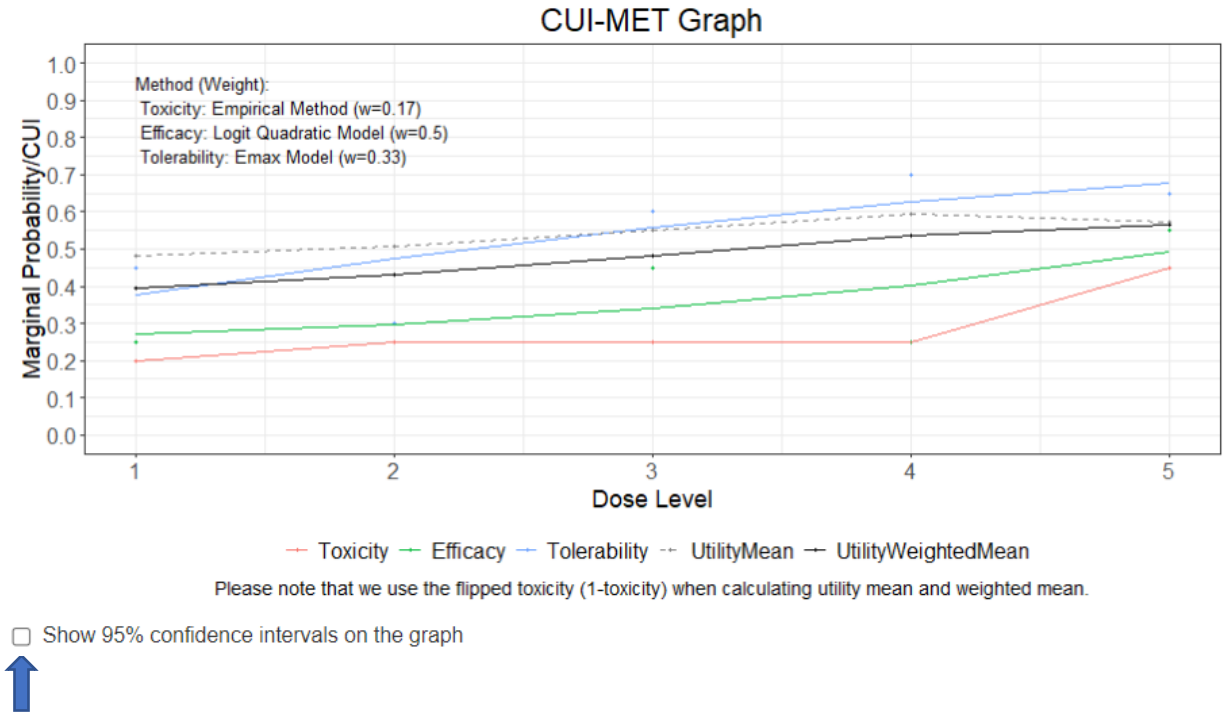
- The sample size and the number of dose levels are determined by the number of unique IDs and unique doses.
- The endpoints are the column names extracted from the input data excluding the “ID” and “Dose”.
- The weights are the normalized weightings that sum up to 1.

Input Summary

In the study, 20 subjects are assigned to 5 dose levels. There are 3 endpoints: Toxicity, Efficacy and Tolerability. The weights given to these endpoints are 0.17, 0.5 and 0.33, respectively. The utilities are calculated using the Empirical Method for Toxicity, Logit Quadratic Model for Efficacy and Emax Model for Tolerability with a monotonic assumption for Efficacy.

Output – CUI Graph

The output metrics are visualized in a single plot. Consider a scenario with input weightings 1, 3, and 2 for toxicity, efficacy and tolerability.

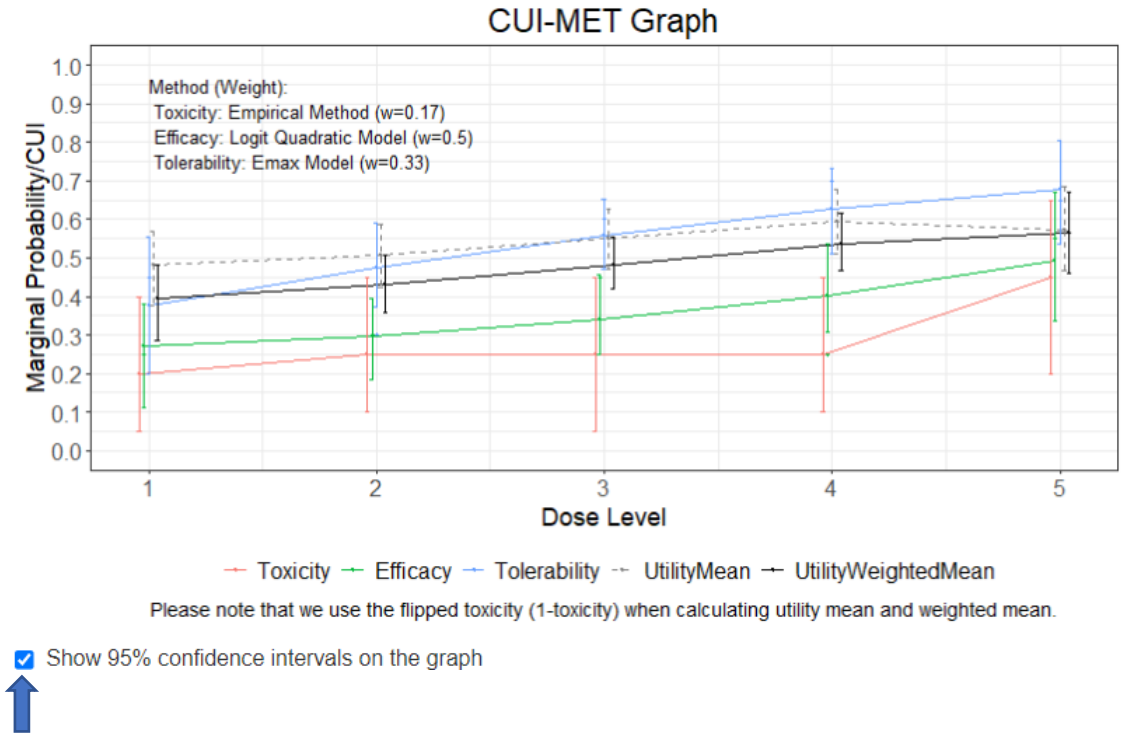


For user's interest, an option is provided below the graph allows users to show the 95% confidence intervals (CI).

- This is a graph showing Marginal Probability vs Dose Level for the three endpoints and their combined metrics - CUI.
- The x-axis represents the Dose Level, numbered from 1 to 5.
- The y-axis represents the Marginal Probability/CUI scale, ranging from 0 to 1.
- There are five lines on the graph: Toxicity (in red), Efficacy (in green), Tolerability (in blue), UtilityMean (in dashed gray), UtilityWeightedMean (in solid black).
- The footnote clarifies that the flipped value of toxicity (1-toxicity) is used for utility calculation.

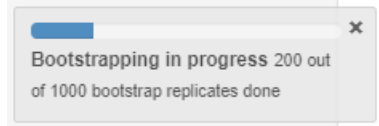
Output – CUI Graph with 95% bootstrap CIs

Add 95% CIs into the plot.



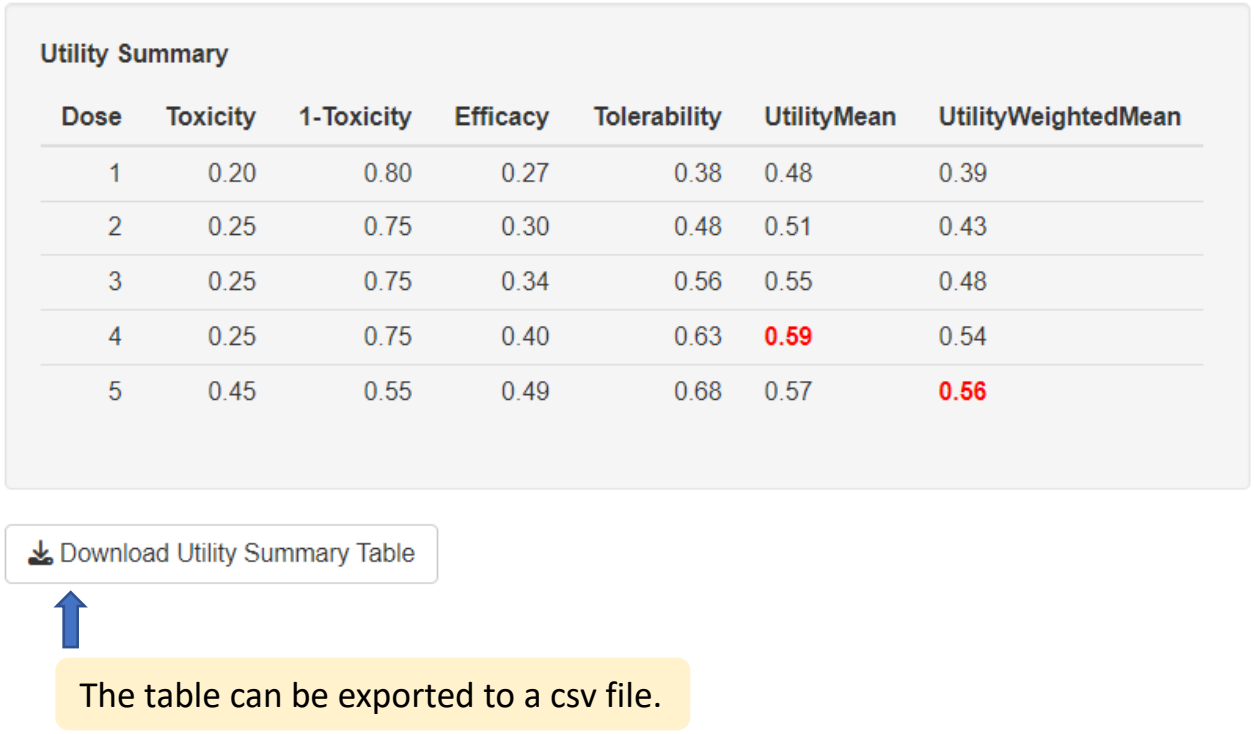
For user's interest, an option is provided below the graph allows users to show the 95% confidence intervals (CI).

- 1000 bootstrap replicates are generated via the ordinary nonparametric bootstrap resampling stratified by dose level.
- Given α=0.05, the two-sided (1-α)*100% confidence intervals are calculated using the percentile bootstrap method. The lower and upper bounds are the 100*(α/2) and 100*(1-α/2) percentiles of the 1000 bootstrap parameter estimates.
- R package boot is used for stratified bootstrap resampling.
- A progress bar is provided to track how many bootstrapping replicates have been completed.



Output – Utility Summary

The app also provides the summary data along with the graph.



Utility Summary

Dose	Toxicity	1-Toxicity	Efficacy	Tolerability	UtilityMean	UtilityWeightedMean
1	0.20	0.80	0.27	0.38	0.48	0.39
2	0.25	0.75	0.30	0.48	0.51	0.43
3	0.25	0.75	0.34	0.56	0.55	0.48
4	0.25	0.75	0.40	0.63	**0.59**	0.54
5	0.45	0.55	0.49	0.68	0.57	**0.56**

- This is a table summarizing the utility values for each dose level across the endpoints. The dose with the largest CUI is the most desirable, therefore the dose with the largest CUI can be identified as the “optimal” dose.
- In this example, the two metrics result in different optimal dose selections – dose 3 with highest utility mean of 0.59 (in red) and dose 5 with highest utility weighted mean 0.56 (in red) across 5 dose levels.

Output – Utility Summary from Bootstrapping

An additional table will be generated to display the estimates derived from bootstrapping when including the CIs on the graph. Beyond the marginal probabilities and CUI, this table introduces two extra columns that indicate the probability of a particular dose being chosen as optimal based on two metrics: the utility mean and the utility weighted mean. For example, out of 1,000 bootstrapped samples, dose 4 is selected as the optimal choice 57.8% of the time when using the utility mean metric, while dose 5 is identified as optimal with a frequency of 64.9% when assessed by the utility weighted mean.

Utility Summary from Bootstrapping

Dose	Toxicity	1-Toxicity	Efficacy	Tolerability	UM	UWM	%OBD(UM)	%OBD(UWM)
1	0.20 (0.05-0.40)	0.80 (0.60-0.95)	0.25 (0.11-0.38)	0.38 (0.20-0.55)	0.47 (0.38-0.57)	0.38 (0.28-0.48)	1.3%	0.2%
2	0.25 (0.10-0.45)	0.75 (0.55-0.90)	0.29 (0.19-0.40)	0.48 (0.37-0.59)	0.51 (0.43-0.59)	0.43 (0.36-0.51)	2.4%	0.2%
3	0.26 (0.05-0.45)	0.74 (0.55-0.95)	0.35 (0.25-0.46)	0.56 (0.47-0.65)	0.55 (0.47-0.63)	0.49 (0.42-0.55)	11.3%	1.9%
4	0.25 (0.10-0.45)	0.75 (0.55-0.90)	0.42 (0.31-0.54)	0.62 (0.51-0.73)	0.60 (0.51-0.68)	0.54 (0.47-0.62)	57.8%	32.8%
5	0.45 (0.20-0.65)	0.55 (0.35-0.80)	0.49 (0.34-0.67)	0.67 (0.54-0.80)	0.57 (0.47-0.68)	0.56 (0.46-0.67)	27.2%	64.9%

OBD: Optimal biologic dose. UM: Utility mean. UWM: Utility weighted mean.

References

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2. Winzenborg, I., A. M. Soliman and M. Shebley (2021). "A Personalized Medicine Approach Using Clinical Utility Index and Exposure-Response Modeling Informed by Patient Preferences Data." CPT Pharmacometrics Syst Pharmacol 10(1): 40-47.
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7. R package Boot. https://cran.r-project.org/web/packages/boot/.

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