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Forest plot checklist and best practices

To facilitate a clear and informed communication of covariate effects from pharmacometric models.

1. Best practices for the creator of forest plots
2. Checklist for interpreting forest plots
3. Checklist for the creator of forest plots
4. Information to include in a forest plot caption

Reference ACoP12 (Nov 2023), Poster M-122L
Checklists and best practices to support the informed use of Forest plots to illustrate the impact of covariates in pharmacometric models.

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1. Best practices for the creator of forest plots



Consider forest plots in the analysis planning stage to align methodologies and intended inferences.

Provide an overview of the data and analysis limitations and suggest suitable inferences from the provided forest plots.

Ensure covariates are independent or employ a method that handles correlated covariates.

Do not mix objective and subjective covariate values in the same forest plot.

Do not visualize between subject variability with forest plots to avoid misunderstandings.

Visualize all covariates included in the analysis or explain why some are omitted from the forest plot.

Explain the methodologies and assumptions impacting the forest plot to aid a technical review.

Use the checklist to give viewers all essential details for understanding the plot.*

*Checklist for the creator of forest plots

2. Checklist for interpreting forest plots



1. Is the study design informative enough for the intended analysis?
2. Is the study population relevant for the intended inference?
3. Are all relevant covariates available for the analysis?
4. Are all covariates collected with the appropriate level of exactness and completeness?
5. Are the covariates in the model independent (low correlation)?
6. Are there available covariates that were not included in the analysis?
7. Are there potential biases introduced by non-random patient dropouts?
8. Were the covariates included based on a Full model approach or based on statistical significance (e.g. SCM)?
9. Are there parameters that were omitted from the covariate analysis?
10. Will the covariate model parameterization impact the forest plot interpretation?
11. Will the handling of missing covariates impact the forest plot interpretation?
12. How was the uncertainty assessed?
13. Is the width of the confidence interval clear?
14. Are there covariates that were part of the analysis that are not shown in the forest plots? Why?
15. How were the covariate values to visualise chosen?
16. How was the reference line computed?
17. Is there an objective rationale for the width of the reference interval?

3. Checklist for the creator of forest plots



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1. Specify the covariate modelling method.

 2. Specify how correlated covariates were handled during the analysis.

 3. Specify which covariates that were included in the covariate analysis, and which were left out.

 4. Specify how much missing covariate information there was and how it was handled in the modelling.

 5. Specify which parameters that were subject to covariate modelling even if only one or a subset of them are visualized.

 6. Specify the covariate model parameterization.

 7. Specify how the uncertainty in the parameter estimates was derived.

 8. Specify any limitations due to study design and conduct.

4. Information to include in a forest plot caption

An example on how the caption to a forest plot can be organized.

Information listed	As described in figure text
The parameter that is visualised	<i>"Forest plot illustrating the effects of covariates on CL..."</i>
The model which was used to generate the predictions	<i>"... based on the final model. "</i>
If the covariate effects are univariable or multivariable and/or the covariate modelling method used	<i>"The covariate effects are derived from an SCM analysis, ..."</i>
The conditioning used when predicting the parameter values	<i>"... and the predictions are conditioned on a typical reference subject. "</i>
If all covariates considered for the analysis is included in the plot or only a subset	<i>"Only the covariates that impact CL are shown. "</i>
How the covariate values for illustration were selected	<i>"The covariate values on the y-axis were used to generate the predicted parameter values and were obtained from the observed data as either the unique values of the categorical covariates or as the 10th and 90th percentile of the continuous covariates. "</i>
If the predicted parameter values are shown on an absolute or relative scale	<i>"Closed dots represent the median of the predicted relative change from the reference subject;"</i>
The width of the confidence interval and if they include the uncertainty in the reference subject	<i>"the 90% CI associated with the medians are visualized by the error bars and includes the uncertainty in the predictions for the reference subject. "</i>
How the uncertainty was obtained	<i>"The specific values of the medians and 90% CIs are shown in the Statistics box on the right-hand side of the parameter; these values are calculated based on 175 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. "</i>
What the reference line represents	<i>"The parameter values for a reference subject (for whom covariate characteristics are provided below the plot) are shown by the dotted vertical line;"</i>
The rationale for the choice of reference interval width	<i>"... the shaded area indicate the 80%-125% margins relative to the reference subject and are based on the standard bioequivalence limits."</i>

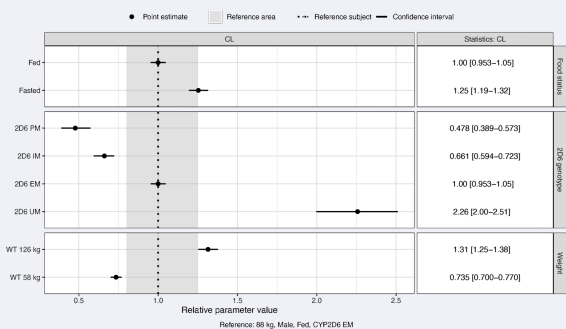


Figure 7. Forest plot illustrating the effects of covariates on CL based on the final model. The covariate effects are derived from an SCM analysis, and the predictions are conditioned on a typical reference subject. Only the covariates that impact CL are shown. The covariate values on the y-axis were used to generate the predicted parameter values and were obtained from the observed data as either the unique values of the categorical covariates or as the 10th and 90th percentile of the continuous covariates. Closed dots represent the median of the predicted relative change from the reference subject; the 90% CI associated with the medians are visualized by the error bars and includes the uncertainty in the predictions for the reference subject. The specific values of the medians and 90% CIs are shown in the Statistics box on the right-hand side of the parameter; these values are calculated based on 175 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. The parameter values for a reference subject (for whom covariate characteristics are provided below the plot) are shown by the dotted vertical line; the shaded area indicate the 80%-125% margins relative to the reference subject and are based on the standard bioequivalence limits.

Forest plots can be created using our open-source R package **PMXForest**

Read more at github.com/pharmetheus/PMXForest



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