T-017

Visualization of Complex Trial Data in Non-Linear Mixed-Effect Analyses With Covariates

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INTRODUCTION

When models/data are trellised by covariate value, apparent sparsity of data increases (**Figures 1** and **2**). This may raise concerns about model quality for those less familiar with modeling. To provide a more intuitive presentation of the model, we created a novel approach to visualizing model-based analyses with multiple covariates. This allowed the team to provide critical input to the model and to use it for decision support.

The method scales the effects of covariates out of data (and associated confidence intervals) to obtain an easily interpreted single plot.

OBJECTIVE

- To create an intuitive presentation of modeling results when there are limited data and multiple covariate effects

METHODS

1. Model

- Analysis dataset constructed from published trial data
- Non-linear mixed-effects model gives human incidence rate as function of pharmacodynamic (PD) biomarker values (developed in R, v3.4.2)
- The model is sigmoidal in nature and is characterized by an IC_{50} (concentration of PD biomarker linked to 50% inhibition):

$$IR = IR_{max} \cdot e^{\log(\frac{IR_{min}}{IR_{max}}) \cdot suppr} \quad \text{where} \quad suppr = \frac{log(B)^{\gamma}}{log(B)^{\gamma} + log(IC_{50})^{\gamma}}$$

and where:

IR = incidence rate
IR_{max} = maximum IR
IR_{min} = minimum IR
suppr = inhibition depending on PD biomarker value
B = PD biomarker value
IC_{50} = PD biomarker value at which 50% inhibition is achieved
γ = parameter giving the maximum slope of the sigmoidal curve

- Model accounts for
  - Between-trial variability (BTV)
  - Covariate effects: population, disease severity, and formulation
- Data were plotted on semilogarithmic axes to better visualize proportional differences, especially at low incidence rates

2. Transforming data and model curves

- To visualize all data and model curves in one plot, the raw data and prediction curves were transformed by
  1. Removing the effect of BTV to typical trial responses
  2. Shifting the PD biomarker values reflecting formulation and population differences to a common IC_{50}
  3. Scaling incidence rates across levels of disease severity and population to the scale appropriate for the target product profile (population B, disease severity level 2)

3. Confidence intervals

- Data were plotted using a log y axis with associated 95% confidence intervals
- After the transformation steps in (2), we needed to provide fair comparisons of the uncertainty of each raw data point in these plots
- Thus confidence intervals for each data point were scaled so that the plotted interval size would remain the same (the length of the line indicating the confidence interval in the semilogarithmic plot was preserved)
- The method presents residuals in a manner visually consistent with residuals in the original plots and is related to the prediction–correction method[1]

Table 1. Number of Published Data Points Available From 17 Clinical Trials By Population, Disease Severity Level, and Formulation of the Compound

Each data point represents an aggregated incidence rate of one arm of a clinical trial. The number of arms is the number of points used to build the model, and is the number of points plotted in each of **Figures 1-7**.

	Population A		Population B		Population C		All Populations		
	Formulation 1	Formulation 2	Formulation 1	Formulation 2	Formulation 1	Formulation 2	Formulation 1	Formulation 2	Total
Severity 1	5	1	2	1	13	1	20	3	23
Severity 2	0	0	8	2	6	1	14	3	17
Severity 3	0	0	4	0	9	1	13	1	14
All severity levels	5	1	14	3	28	3	47	7	54
Total	6		17		31		54		

Figure 1. Raw Data for Incidence Rate in Humans Vs PD biomarker Value, Population, and Disease Severity

Data point weights are determined using trial size.

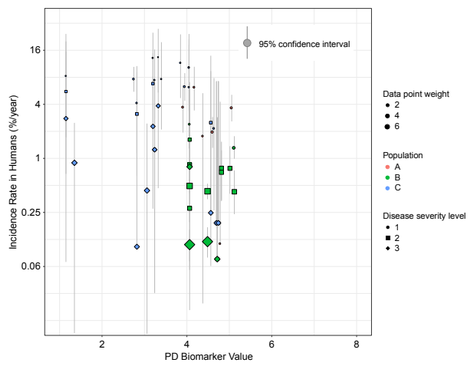


Figure 2. Raw Data for Incidence Rate in Humans Vs PD biomarker Value Trellised by Population and Disease Severity Level

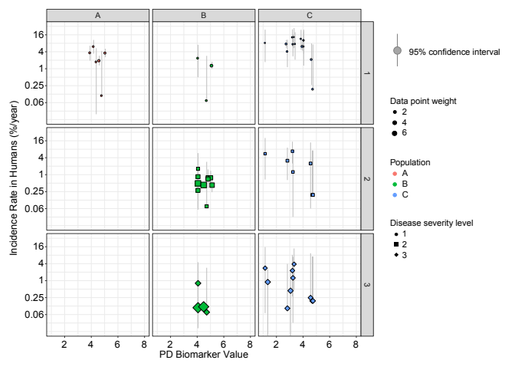


Figure 3. Data From Figure 1 Adjusted for Between-Trial Variability

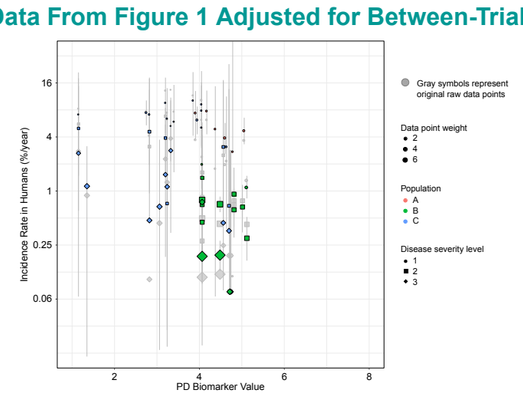


Figure 4. Data From Figure 3 Adjusted for Covariates Affecting Potency of the Drug

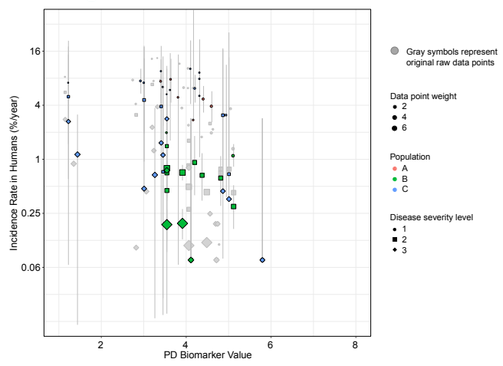


Figure 5. Data From Figure 4 Scaled to Population B and Disease Severity Level 2

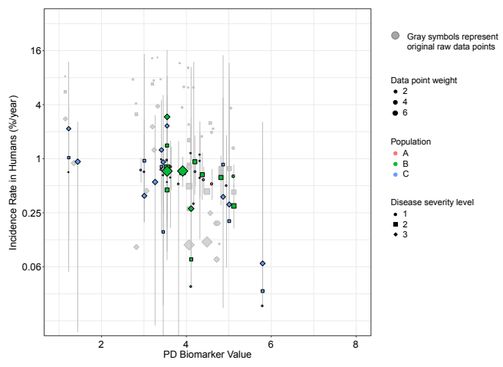
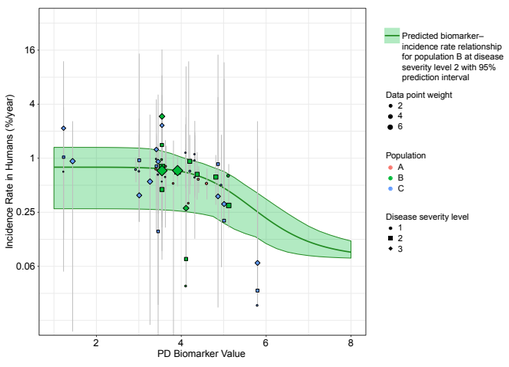


Figure 6. Data From Figure 5 Including the Model Prediction for Population B at Disease Level 2



RESULTS

- **Table 1** lists an overview of the used summary level raw trial arm data
- **Figure 1** shows all summary level raw trial data with original confidence intervals
- Model covariates included in the model were disease severity level, population, and drug formulation:
  $IR_{max,new} = IR_{max} \cdot (1 + covariate_{IRmax,disease\text{-}severity}) \cdot (1 + covariate_{IRmax,population})$
  $IC_{50,new} = IC_{50} \cdot (1 + covariate_{IC50,population}) \cdot (1 + covariate_{IC50,formulation})$
  where $IR_{max,new}$ *and* $IC_{50,new}$ include correction for covariate effects
- The summary raw data were transformed in several steps:

1. Raw data were corrected by the modeled BTV (**Figure 3**)

   IR(btv-corrected) = IR – IR(ipred) + IR(pred)
   where: *IR is the original IR*
   IR(ipred) is the individual trial prediction
   IR(pred) is the typical trial prediction

2. Covariate effects impacting the estimated IC_{50} (shift of the model curves along the PD biomarker axis) were used to shift the raw data to a common IC_{50} (**Figure 4**)

   $B(covariate\text{-}adjusted) = B / (1 + covariate_{IC50,population}) / (1 + covariate_{IC50,formulation})$
   where: *B is the original PD biomarker value*

3. Incidence rates as viewed on a log axis were scaled for both population effects and disease severity. Results were scaled to the target product population and disease level (**Figure 5**)

   IR(scaled) = IR(btv-corrected) · IR(model, ref) / IR(model, disease severity, population)

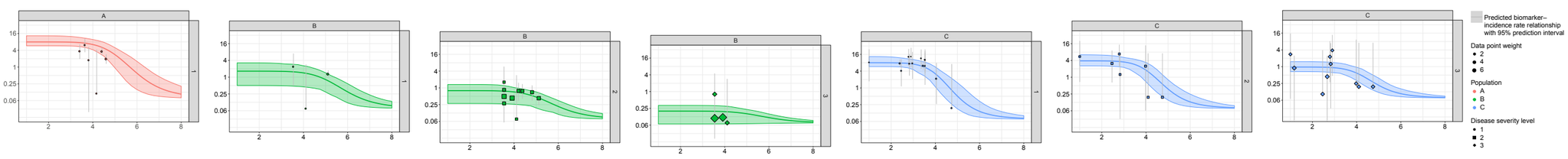
   where: *IR(model, ref) is the typical model prediction in the reference situation*
   IR(model, disease severity, population) is the typical model prediction for a particular disease severity level and population

- This resulted in a single plot (**Figure 6**) visualizing the modeled PD biomarker–incidence rate relationship for the target population B and disease severity level 2 with associated transformed raw data and confidence intervals. The 90% model prediction interval for population B, severity level 2 has been added to visualize the precision of model predictions.

CONCLUSIONS

Visualization of modeling results is critical to engage a development team in model evaluation and obtain feedback for further model development. The single plot created (**Figure 6**) enabled the team to understand how data were integrated into a coherent model. The plot could then be back-transformed and trellised by covariates to discuss impact of covariate effects and use of the model (**Figure 7**).

Figure 7. Data From Figure 6 Trellised by Population and Disease Severity Level, Together With Their Respective Model Predictions



References

1. Bergstrand M, et al. *AAPS J*. 2011;13(2):143-151.

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