Time-Varying Coefficient Model with Linear Smoothing Function for Longitudinal Data in Clinical Trial

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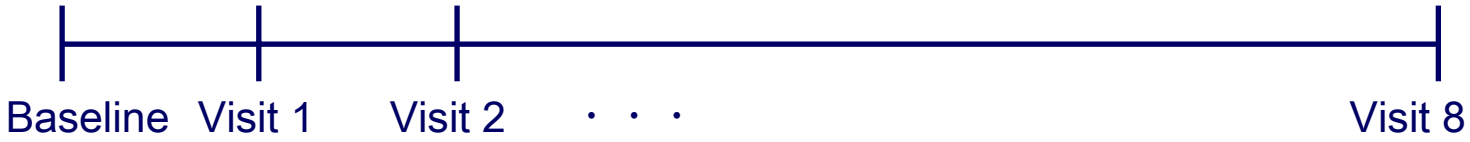
Introduction

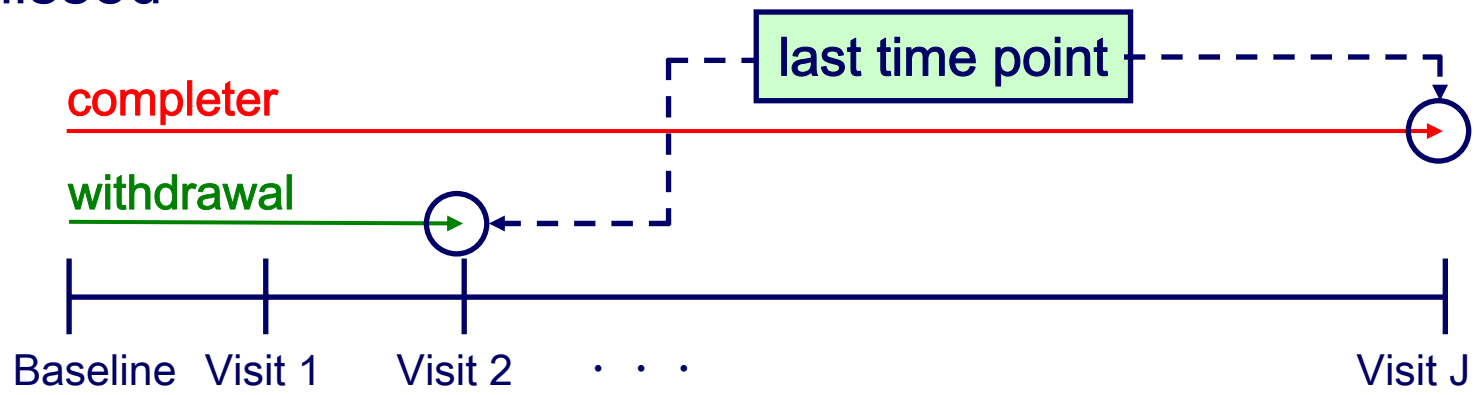
In clinical trials, the treatment period and the number of scheduled visits for efficacy evaluation are predetermined by design.



[Ex.] each patient would be treated for eight weeks (baseline and at the end of each week)

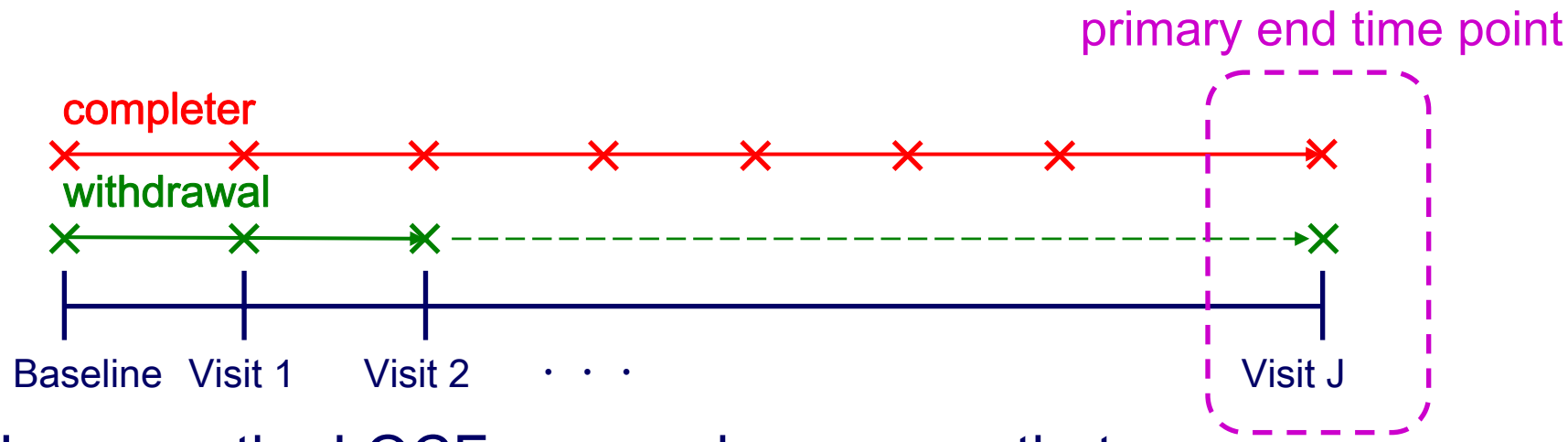
Introduction

- Patients are evaluated at a number of time points
- "primary end time point" at which efficacy of test drug would be evaluated
- The primary end time point is taken as the last time point of the predetermined treatment period
- If a patient withdrew from the trial before completion, some observations posterior to the discontinuation would be missed



Last Observation Carried Forward: LOCF

Missing data is often stored into carrying the last observation forward (LOCF).



However, the LOCF approach assumes that

1) ***missing data are MCAR (missing completely at random),***
2) ***subject's responses are constant from the last observed value to the endpoint of the trial.***

Both of the assumptions are often unrealistic in clinical trials, so these conditions are seldom seen (Verbeke and Molenberghs, 2000).

LOCF ANCOVA (analysis of covariance) Model

For subjects $i = 1,..., I$ and repeated observations per visit $j = 1,..., J_i$ (end of study visit), LOCF ANCOVA model is

$$Y_{iJ_i} = \beta_0 + \beta_1 Y_{i0} + \beta_2 x_i + \varepsilon_{ij}$$

Y_{ij} : change from baseline (Y_{i0}) of outcome measurement at the *j* th time point for the *i* th subject

β_0 : intercept

β_1 : effect of baseline measurement (Y_{i0})

β_2 : effect size at time *J*

x_i : dummy coded covariate for subject *i*
(ex. $x_i = 0$ for placebo group and $x_i = 1$ for treatment group)

ε_{ij} : assumed to be independently distributed from a univariate normal distribution

* If Y_{iJ} is missing, then $Y_{iJ} = Y_{ij}$ (where *j* =1,…, *J* -1)

Mixed-effects Model Repeated Measures: MMRM

Several authors propose likelihood-based mixed effects models to analyze incomplete data from longitudinal clinical trials.

same meaning as
Missing At Random (MAR)

In general, when dropouts are ignorable, the parameters of dropout and outcome processes are assumed to be distinct, and hence likelihood-based methods can be used on the marginal distribution of the observed data for statistical inferences.

Mixed-effects Model Repeated Measures approach

MMRM analysis

For subjects $i = 1,..., I$ and repeated observations per visit $j = 1,..., J_i$, MMRM model can be described as

$$\mathbf{Y}_i = X_i\boldsymbol{\beta} + Z_i\mathbf{b}_i + \boldsymbol{\varepsilon}_i$$

$\mathbf{Y}_i$: J_i dimensional vector of outcome measurement for the ith subject

$\boldsymbol{\beta}$: p dimensional vector containing the fixed effects (e. g. baseline, treatment effect and time)

X_i, Z_i: $(J_i \times p)$ and $(J_i \times q)$ dimensional design matrices of known covariates

$\mathbf{b}_i$: q dimensional vector containing the random effects $(\mathbf{b}_i \sim \mathrm{N}(0, D))$

$\boldsymbol{\varepsilon}_i$: J_i dimensional vector of residual components $(\boldsymbol{\varepsilon}_i \sim \mathrm{N}(0, \sum_i))$

D : general $(q \times q)$ covariance matrix with (i, j) element $d_{ij} = d_{ji}$

$\sum_i$: $(J_i \times J_i)$ covariance matrix which depends on i only through its dimension J_i

Issues

MMRM is quite flexible and powerful parametric model approach for a longitudinal data in clinical trials.

As is well known, parametric approaches are often too restrictive and unrealistic for the clinical trials data.

While parametric approaches are useful, questions will always arise about the adequacy of the model assumptions and the potential impact of model misspecifications on the analysis

Hoover *et al.*, 1998

Time-Varying Coefficient Model: TVCM

The useful model for studying the association between the covariates and response for the longitudinal data in clinical trial is the time-varying coefficient model,

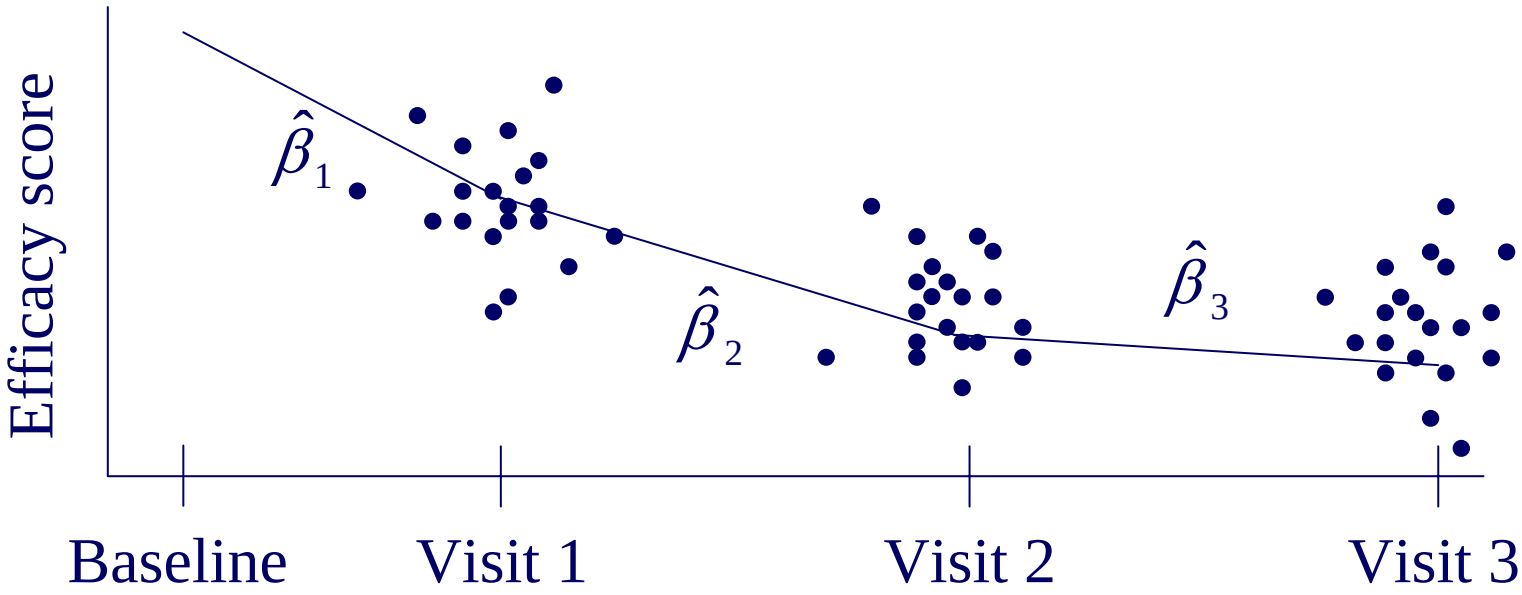
$$Y_{ij} = X_{ij}^{\mathrm{T}} \boldsymbol{\beta}(t_{ij}) + \boldsymbol{\varepsilon}_i(t_{ij})$$

where $\boldsymbol{\beta}(t) = (\beta_0(t),..., \beta_p(t))'$ are smooth function of t and $\boldsymbol{\varepsilon}_i(t)$ is zero mean stochastic process.

Estimation of $\boldsymbol{\beta}(t)$

- smoothing spline method (***Hastie and Tibshirani, 1993***)
- locally weighted polynomial (***Hoover et al., 1998***)
- investigated the cross validation criteria for selecting smoothing parameters

How to select the regression models and Knots



We focus on the analysis for the clinical trial data of ***chronic condition***. In general, the subjects visit the hospital according to the scheduled time for a chronic disease study, therefore subjects data are concentrated visit by visit.

Linear smoothing spline function **with visits as knots is enough to express the longitudinal variation of treatment effects**

Linear smoothing spline function

Time-varying coefficient model allows the intercept and slope coefficients to be arbitrary smooth functions of t_{ij}. The penalized linear spline version of this model is

$$Y_{ij} = \alpha_0 + \alpha_1 t_{ij} + \sum_{k=1}^{K} b_k^{\alpha} (t_{ij} - \kappa_k)_+ + \left(\beta_0 + \beta_1 t_{ij} + \sum_{k=1}^{K} b_k^{\beta} (t_{ij} - \kappa_k)_+ \right) x_i + \varepsilon_{ij},$$

$\kappa_1, \ldots, \kappa_J$	: knots (visits) over the range of the t_{ij} values
K	: the number of the knots
α_0, α_1	: parameters of the intercept
$b_k^{\alpha} (k = 1, \ldots, K)$	: random effects of the intercept
β_0, β_1	: parameters of the slope coefficients
$b_k^{\beta} (k = 1, \ldots, K)$	: random effects of the slope coefficients
$(t_{ij} - \kappa_k)_+$	: positive part of the function $t_{ij} - \kappa_k$ (It is zero for those values of t_{ij} where $t_{ij} - \kappa_k$ is negative)

Representation of Mixed-Effect Model

From the equation of MMRM and Linear spline function, the mixed-effects model representation is written as

$$\mathbf{Y}_i = X_i\boldsymbol{\beta} + Z_i\mathbf{b} + \boldsymbol{\varepsilon}_i \quad .$$

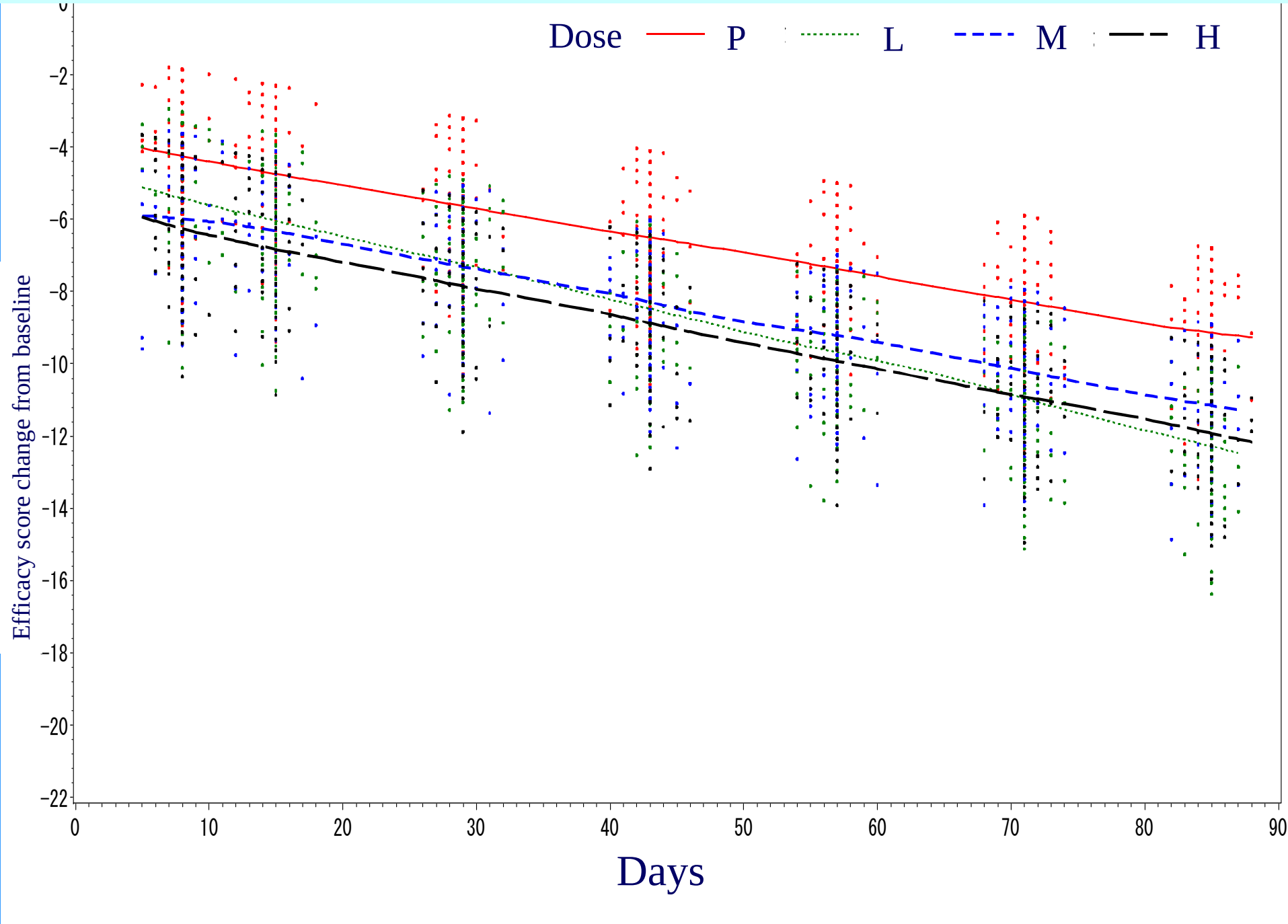
It is obtained by setting

$$\begin{aligned}
&\mathbf{X} = [1 \quad t_{ij} \quad x_i \quad t_{ij}x_i]_{1\le j\le J_i},\\
&\boldsymbol{\beta} = [\alpha_0 \quad \alpha_1 \quad \beta_0 \quad \beta_1]^{\mathrm{T}},\\
&\mathbf{Z}_i = [(t_{ij} - \kappa_k)_+ \quad x_i(t_{ij} - \kappa_k)_+]_{1\le j\le J_i},\\
&\qquad\quad {\scriptstyle 1\le k\le K} \qquad\qquad {\scriptstyle 1\le k\le K}\\
&\mathbf{b} = [b_1^{\alpha},\ldots, b_K^{\alpha}, b_1^{\beta},\ldots, b_K^{\beta}],\\
&\mathrm{Cov}\,(\mathbf{b}) = \mathrm{diag}\,\{\sigma_{\alpha}^2\mathbf{1}_{K\times 1}, \sigma_{\beta}^2\mathbf{1}_{K\times 1}\}.
\end{aligned}$$

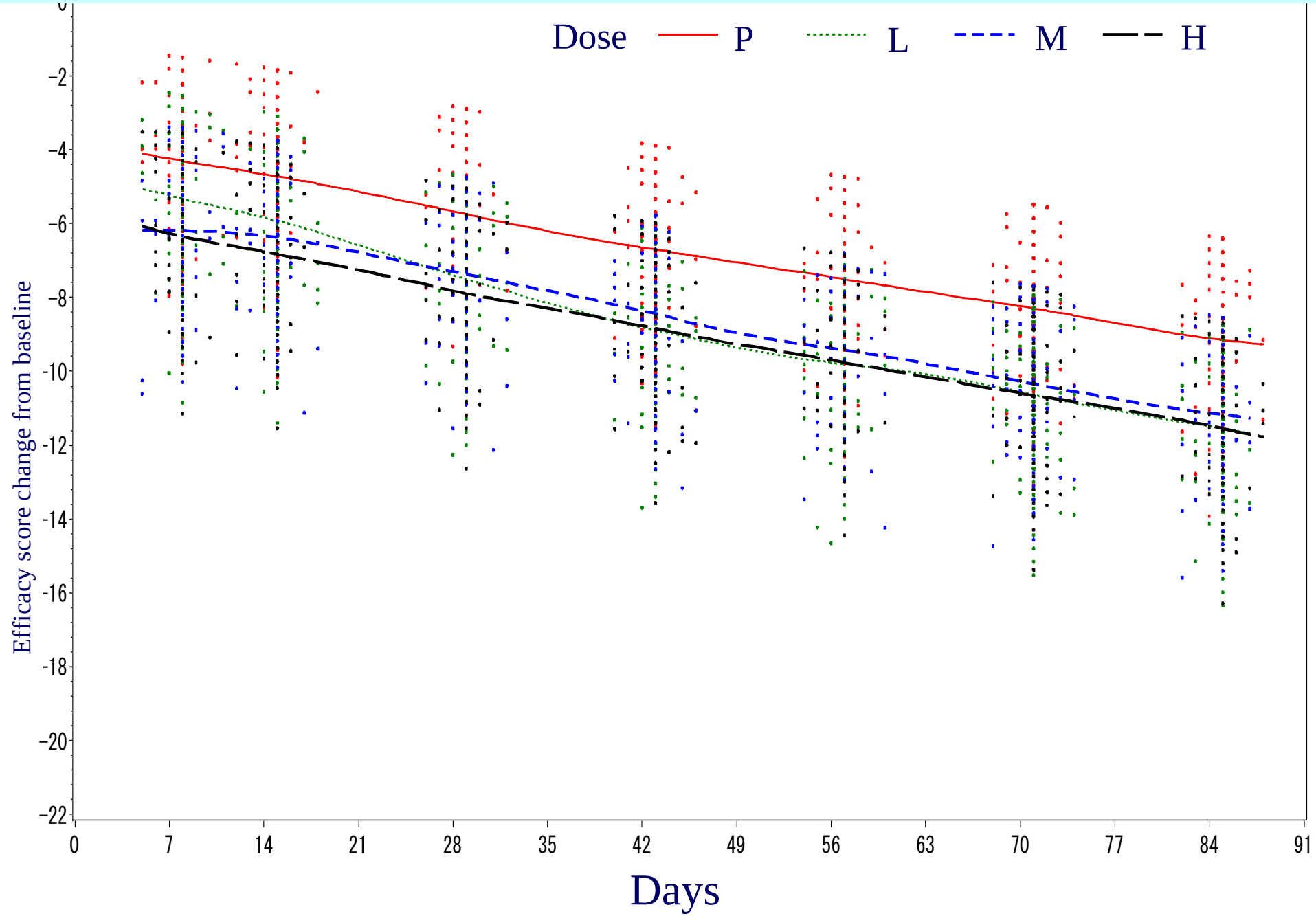
Example: Sample Study Data

Design	Randomized, double blinded parallel dose finding study
Dose	Placebo, Low dose, Middle dose and High dose
Duration	12 weeks
Primary variable	Efficacy QOL (Quality Of Life) score change from baseline (*negative direction means improvement*)
Assumable disease area	Chronic disease (ex. CNS=Central Nerve System disease)
Sample size	100 patients per dose group

Mean response prediction of MMRM (linear model)



Mean response prediction of time-varying coefficient model (linear smoothing function)

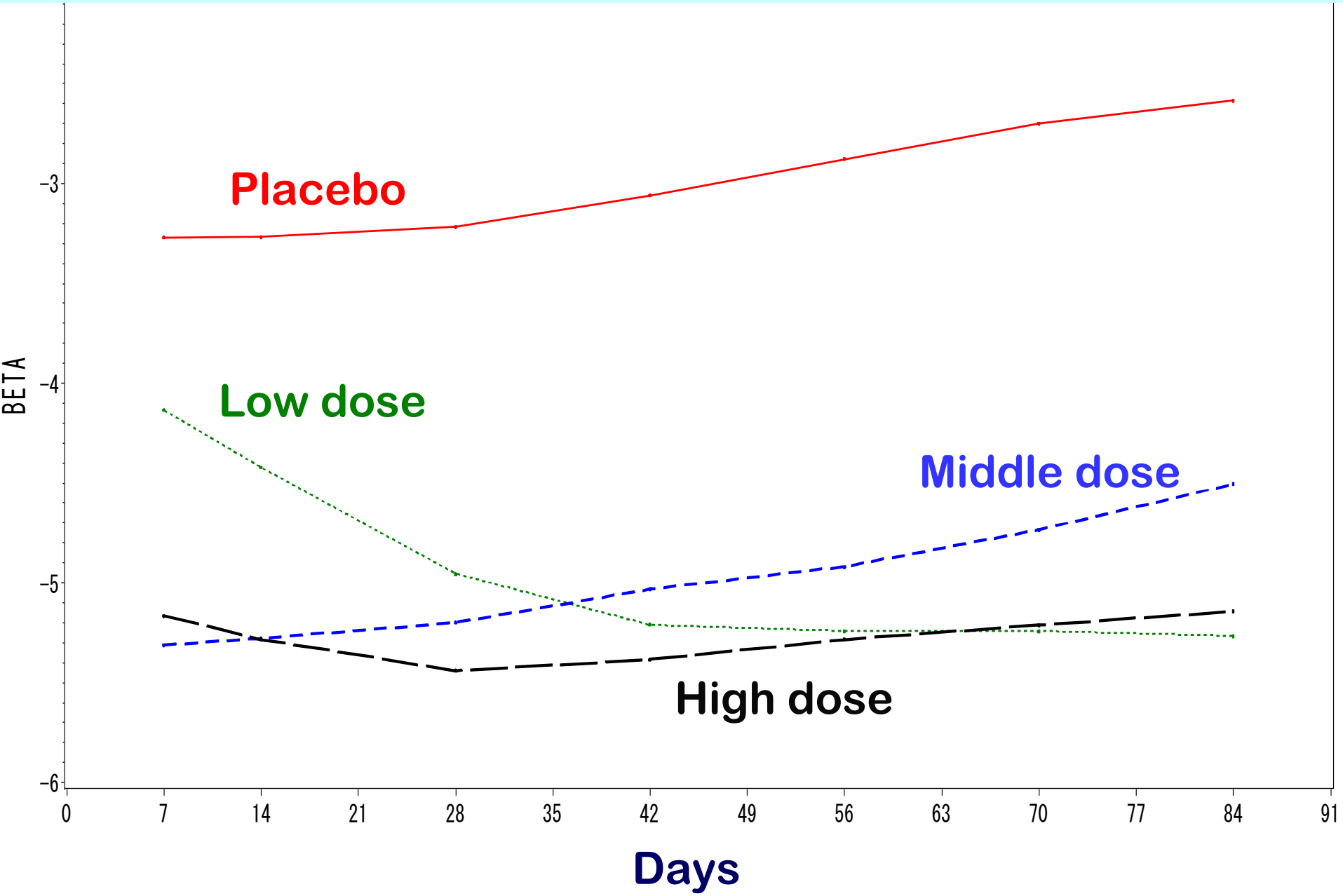


Results

Least square means for efficacy score change from baseline difference between placebo and each treatment group (p-values are adjusted by Dunnett test)

	Low dose	Middle dose	High dose
LOCF ANCOVA	-2.17 P=0.0738	-1.42 P=0.3411	-2.44 P=0.0413
MMRM (first order time effect)	-2.04 P=0.0147	-1.93 P=0.0236	-2.33 P=0.0049
MMRM (second order time effect)	-2.31 P=0.0161	-1.92 P=0.0246	-2.31 P=0.0054
Time-Varying Coefficient	-1.01 P=0.269	-1.94 P=0.0078	-2.07 P=0.0044

Plots of the predictions for the time-varying coefficient



Consideration

-The superiority of high dose to placebo was confirmed by all approaches.
-MMRM and TVCM also showed the superiority of middle dose to placebo.
-As for the results of the least square means, only TVCM showed the clear monotone increase as a dose-response.
-For the first several weeks in the clinical trial, it seemed that the low dose was not effective in Fig 1. and Fig 2.
-Fig. 3. shows the results of the estimated time-varying coefficients at each time. Clearly, the trend of the coefficients for low dose was different from other doses in early days.

With regard to this case study, we concluded that TVCM is superior to LOCF ANCOVA and MMRM approaches in terms of evaluating the treatment effect coupled with time variation in the early phase of the treatment in particular.

Reference

- Davidian, M. and Giltinan, D. M. (1995): *Nonlinear Models for Repeated Measurement Data*. London: Chapman and Hall.
- Diggle, P. J. (1988): An Approach to the Analysis of Repeated Measurements. *Biometrics*, 44, 959-971.
Hastie, T. and Tibshirani, R. (1993): Varying-Coefficient Models. *Journal of the Royal Statistical Society. Series, B* 55(4), 757-796.
- Hoover, D. R., Rice, J. A., Wu, C. O. and Yang, L. P. (1998): Nonparametric Smoothing Estimates of Time-Varying Coefficient Models with Longitudinal Data. *Biometrika*, 85, 809-822.
- Laird, N. M. and Ware, J. H. (1982): Random Effects Models for Longitudinal Data. *Biometrics*, 38, 963-974.
- Liang, K. and Zeger, S. L. (1986): Longitudinal Data Analysis using Generalized Linear Models. *Biometrika*, 73, 13-22.
- Mallinckrodt, C. H., Clark, W. S. and David, S. R. (2001): Accounting for Dropout Bias using Mixed-Effects Models. *Journal of Biopharmaceutical Statistics*, 11, 9-21.
- Mallinckrodt, C. H., Kaiser, C. J., Watkin, J. G., Molenberghs, G., Carroll, R. J. (2004): The Effect of Correlation Structure on Treatment Contrasts Estimated from Incomplete Clinical Trial Data with Likelihood-based Repeated Measures Compared with Last Observation Carried Forward ANOVA. *Clinical Trials*, 1(6), 477-489.
- Ruppert, D., Wand, M. P. and Carroll, R. J. (2003): *Semiparametric Regression*. Cambridge.
- Siddiqui, O., Hung, H. M. and O'Neill, R. (2009): MMRM vs. LOCF: A Comprehensive Comparison Based on Simulation Study and 25 NDA Datasets. *Journal of Biopharmaceutical Statistics*, 19, 227-246.
- Verbeke, G. and Molenberghs (2000): *Linear Mixed Models for Longitudinal Data*. New York: Springer-Verlag.