Simulation for BEST-ITP model under multiple scenarios and application of BEST-ITP model to longitudinal summary level data

302381

OakPil Han[1], Hyori Yun[1], Seungjae Baek[1]
[1]Hanmi Pharm. Co., Ltd, Seoul, South Korea

ABSTRACT

The BEST-ITP model, developed by Ding et al, has the advantage of being able to estimate the treatment effect at a specific time-point of our interest, allowing all summary level data measured at different time-points for different studies. As a results, the model is being used in many meta analyses for mixed treatment effects across different longitudinal studies where observation values decrease over time by drug efficacy such as HbA1c or body weight. But when applying BEST-ITP model to the real data, various considerations need to be taken due to the diversity of the study.

Our study shows that the precision and accuracy of estimated parameter by BEST-ITP model under multiple scenarios. We generated summary level data at each assumed study to have different sample size and number of time-points. In another scenario, short term studies were assumed in order to see the effect of study duration on the accuracy of extrapolation using the BEST-ITP model. Precision and accuracy were evaluated by Mean Square Error (MSE) and Bias, Standard Deviation through 1000 simulation runs.

We found that the precision of the estimation is affected by the size of the studies which can be defined by both (1) having a large sample size at each time-point and (2) having a large number of time points to be used as a form of summary level data. We also found that unbalanced size of studies doesn't affect the estimation of treatment effect and applied BEST-ITP methods to the actual clinical trial results.

BACKGROUND

Ding[1] proposed BEST-ITP model to compare the longitudinal profiles of different treatment arms from different studies. BEST-ITP model only uses summary level information, $(\bar{Y}_{ikl}, S_{ijk}, n_{ijk})$. Each values are mean treatment response, corresponding standard deviation and the sample size observed at study i, treatment k at time l. d represents treatment duration. t_{ijk} represents specific time-point. The fixed effects BEST-ITP model format :

$$
\begin{cases}
\bar{Y}_{ikl} \sim N(\mu_{ikl}, \sigma^2_{ikl}) \\
\frac{S^2_{ikl}(n_{ikl}-1)}{\sigma^2}\left(\frac{1-e^{p_k d}}{1-e^{p_k t_{ijl}}}\right)^2 \sim \Gamma\{(n_{ikl}-1)/2, 2\} \\
\mu_{ijl} = (\phi_i + \theta_k)\left(\frac{1-e^{p_k t_{ijl}}}{1-e^{p_k d}}\right), \theta_1 = 0 \\
\sigma^2_{ikl} = \frac{\sigma^2}{n_{ikl}}\left(\frac{1-e^{p_k t_{ijl}}}{1-e^{p_k d}}\right)^2 \\
\bar{Y}_{ikl} = \left(\phi_i + \theta_k + \frac{\epsilon_{ikl}}{\sqrt{n_{ikl}}}\right)\frac{1-e^{p_k t_{ijl}}}{1-e^{p_k d}} \\
Var(\epsilon_{ikl}) = \sigma^2
\end{cases}
$$

- $Non-informative\ priors$
- $\theta_k \propto 1\ (Vague\ normal)$
- $P_k \propto 1$
- $\phi_i \sim N(\mu_\phi, \tau^2_\phi)$
- $\mu_\phi \propto 1$
- $\log(\tau^2_\phi) \propto 1$
- $\epsilon_{ikl} \sim \mathrm{N}(0, \sigma^2)$
- $\log(\sigma^2) \propto 1$

In this model, we assume the treatment response (Y_{ikl}) are time-dependent and additive by multiplying $1-e^{p_k t_{ijl}}/1-e^{p_k d}$ which is ranged 0 to 1. ϕ_i means study effect. θ_k which represents treatment effect at d and p_k determines the degree to which treatment response decreases steeply over time. With the fixed d, we can interpret the estimated treatment effect θ_k as an treatment effect at d. Further, extrapolation can be simply done by expending d with the assumptions of that we will have the same nonlinear profile.

METHODS

- (Simulation 1,2) To compare the effect of study variability on estimation of treatment effect, we generated summary data based on the assumption of parameters described in table 1. In each scenarios, the sample size and number of time-points of studies were differently set. The MCMC sampling method was used to fit the BEST-ITP model to each 1000 data sets.
- (Simulation 3) To investigate the accuracy of extrapolation, 1000 datasets which has only under week 8 & week 12 were generated. The duration(d) for extrapolation was set to week 24.

Table 1. True parameter values and study information for simulation setting

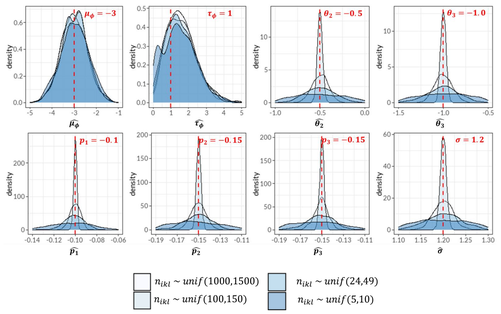
Parameter	Study information, Time-point
$\mu_\phi = -3$	• Study 1 : Treatment 1 vs Treatment 2 - Week 4, 8, 12, 24
$\tau_\phi = 1$	• Study 2 : Treatment 1 vs Treatment 3 - Week 4, 12, 24
$\theta_k = (0, -0.5, -1.0)$	• Study 3 : Treatment 2 vs Treatment 3 - Week 4, 8, 12
$p_k = (-0.1, -0.15, -0.15)$	
$\sigma = 1.2$	

RESULTS

Simulation 1. Sample Size / Time-Point

Figure 1. density plot of estimated parameter values from 1000 simulation run For each run of simulation, the estimated parameter values is the mean of 1000 posterior samples.

(a) Different Number of sample size

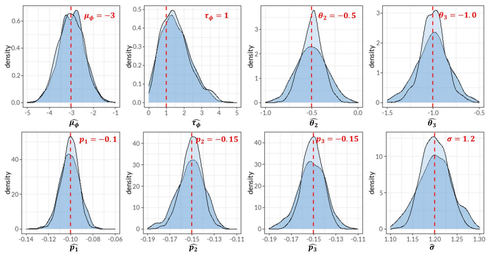


$n_{ikl} \sim unif(1000,1500)$ $n_{ikl} \sim unif(24,49)$
$n_{ikl} \sim unif(100,150)$ $n_{ikl} \sim unif(5,10)$

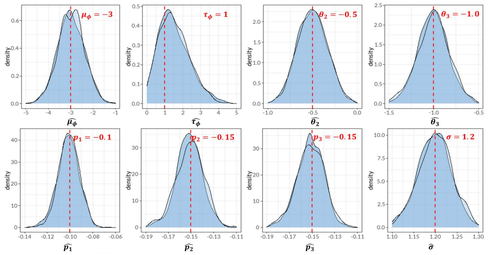
➢ From Simulation 1, the precision of the estimation (measured by MSE, Bias, SD) was shown to be affected by the size of the study. The size of the study means both (1) having a large sample size at each time-point and (2) a lot of time-points to be used as a form of summary data.

(b) Different Number of time-point

$Study1 = 7$ $Study2 = 6$ $Study3 = 6$ | $Study1 = 4$ $Study2 = 3$ $Study3 = 3$



(c) Different Sample Size & Number of time-point



$Study1 = 8, Study2 = 6, Study3 = 6,\ n_{ikl} \sim unif(24,49)$
$Study1 = 4, Study2 = 3, Study3 = 3,\ n_{ikl} \sim unif(12,25)$

Simulation 2. Unbalanced data

(d) Unbalanced sample size between studies

Table 2. Parameter estimations from 1000 runs of simulation

	μ_ϕ			τ_ϕ			θ_2 at week 24			θ_3 at week 24		
n_{ikl}	Bias	SD	MSE	Bias	SD	MSE	Bias	SD	MSE	Bias	SD	MSE
Balanced	0.022	0.576	0.332	0.535	0.846	1.001	-0.002	0.168	0.028	-0.005	0.183	0.034
Unbalanced	0.004	0.590	0.348	0.489	0.847	0.955	-0.004	0.110	0.012	0.013	0.361	0.130
	p_1			p_2			p_3			σ		
	Bias	SD	MSE	Bias	SD	MSE	Bias	SD	MSE	Bias	SD	MSE
Balanced	-0.001	0.009	0.000	-0.002	0.013	0.000	-0.002	0.013	0.000	0.001	0.041	0.002
Unbalanced	-0.001	0.007	0.000	-0.001	0.009	0.000	-0.017	0.132	0.018	-0.002	0.033	0.001

Balanced sample size between study : $n_{1kl} \sim unif(24,49), n_{2kl} \sim unif(24,49), n_{3kl} \sim unif(24,49)$
Unbalanced sample size between study : $n_{1kl} \sim unif(100,150), n_{2kl} \sim unif(5,10), n_{3kl} \sim unif(5,10)$

➢ Bias increased only in treatment effect of 3 (θ_3), which was reduced in sample size by scenario setting. The impact of imbalanced sample size between studies on accuracy of parameter estimation was not observed.

Simulation 3. Duration of Study

(e) Maximum duration of the study

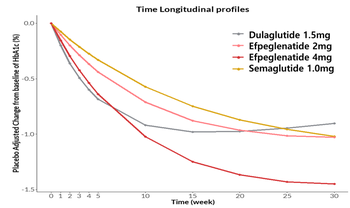
Parameter estimations from 1000 runs of simulation												
	μ_ϕ			τ_ϕ			θ_2 at week 24			θ_3 at week 24		
Max Duration	Bias	SD	MSE	Bias	SD	MSE	Bias	SD	MSE	Bias	SD	MSE
24	0.022	0.576	0.332	0.535	0.846	1.001	-0.002	0.168	0.028	-0.005	0.183	0.034
12	-0.014	0.607	0.369	0.535	0.822	0.962	-0.004	0.202	0.041	-0.004	0.223	0.050
8	-0.039	0.602	0.363	0.561	0.846	1.030	0.017	0.233	0.054	0.004	0.26	0.068
	p_1			p_2			p_3			σ		
	Bias	SD	MSE	Bias	SD	MSE	Bias	SD	MSE	Bias	SD	MSE
24	-0.001	0.009	0.000	-0.002	0.013	0.000	-0.002	0.013	0.000	0.001	0.041	0.002
12	-0.001	0.013	0.000	-0.002	0.016	0.000	-0.002	0.015	0.000	0.002	0.056	0.003
8	0.000	0.016	0.000	-0.003	0.021	0.000	-0.002	0.023	0.001	0.010	0.093	0.009

$Duration\ of\ Study\ 1 = 24, Study\ 2 = 24, Study\ 3 = 12$
$Duration\ of\ Study\ 1 = 12, Study\ 2 = 12, Study\ 3 = 12$
$Duration\ of\ Study\ 1 = 8, Study\ 2 = 8, Study\ 3 = 8$

➢ The shorter the duration of the study, the lower the accuracy of extrapolation.

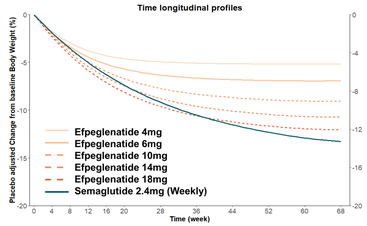
APPLICATION

(1) HbA1C[2,3,4,5,6,7,8,9,10,11,12]



➢ Efpeglenatide 4mg lowered change from baseline hba1c levels about 1.5%.

(2) Body Weight[13,14]



➢ Efpeglenatide 18mg showed approximately 12kg body weight reductions in patients with obesity at week 68.

CONCLUSION & CONSIDERATION

- **As demonstrate in this simulation, fixed effect models put more weight on large studies. Since the fixed effects model assumes treatment effects to be the same for all trials, when there is large study variability, random effect model (θ_i to θ_{ik}) can be considered as an alternative.**
- **In application of BEST-ITP for weight loss prediction by Efpeglenatide compared with other marketed GLP-1 receptor agonists, we modeled the relationship between the observed Efpeglenatide doses and the weight loss from a phase 2 study with 21 week treatment and predicted the weight loss by higher doses at 52 week. It presented promising response by Efpeglenatide 18 mg/QW in the Figure (2) and needs to be investigated further by a clinical trial.**

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