

Baseline as a covariate or dependent variable in analysis of change from baseline in clinical trials

Mohammad Ehsanul Karim

Department of Statistics
University of British Columbia

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Outline

- ▶ Problem Setup
- ▶ Methods under Consideration
- ▶ Generalization of the Methods
- ▶ Illustration with an Example Data
- ▶ Summary

Problem Setup > Basic Terminology

- ▶ Randomized Clinical Trial
- ▶ Pre-post Designs
- ▶ Baseline Measurements
- ▶ Repeated measurements
 - ▶ Simple case, $t = 0, 1$
 - ▶ Several Time points, $t = 0, 1, \dots, T$
- ▶ Treatment Arms
 - ▶ Placebo
 - ▶ Standard Treatment
 - ▶ New treatment

Problem Setup > Basic Terminology

- ▶ Data Settings
 - ▶ Wide Format
 - ▶ Long Format
- ▶ Randomization in practice

Problem Setup > Problem of Interest

To assess the treatment effect based on the mean change from baseline at the last time point T .

Problem Setup > Issue of Modelling

While setting up a model to assess the treatment effect, a frequently asked question is - whether to add baseline as a covariate or as a dependent variable?

Methods under Consideration > Methods

1. Change Score
2. ANCOVA
3. cLDA (Constrained Longitudinal Data Analysis)

Methods under Consideration > Change Score

For $i = 0, 1, \dots, n$;

$t = 0, 1$

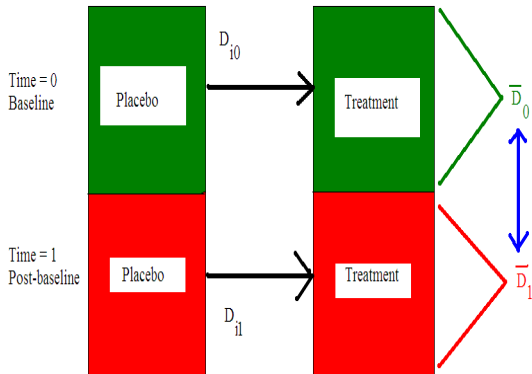
$n = n_{Tr} + n_P$

$j = \text{Placebo (} P \text{) and New Treatment (} Tr \text{):}$

$$\begin{aligned} D_i = (Y_{1i} - Y_{0i}) &= \mu_0 + \beta_1 I_i(\text{treatment} = j) + \varepsilon_i & (1) \\ \Rightarrow Y_{1i} &= \mu_0 + \beta_1 I_i(\text{treatment} = j) + Y_{0i} + \varepsilon_i, \end{aligned}$$

Methods under Consideration > Change Score

Figure: Change Score Method



Methods under Consideration > Change Score

$$t = \frac{\bar{D}_1 - \bar{D}_0}{\hat{\sigma} \sqrt{\left(\frac{1}{n_{Tr}} + \frac{1}{n_P}\right)}}$$

$$\hat{\sigma}^2 = \frac{\sum_{j=P}^{Tr} \sum_{i=1}^{n_j} (D_{ij} - D_{i.})^2}{n_{Tr} + n_P - 2}$$

Methods under Consideration > Change Score

Let \bar{y}_{jt} is the mean of j -th treatment (placebo = 0 and new treatment = 1) at time t .

Treatment Effect

= difference in treatment groups at (time = 1) - difference in treatment groups at (time = 0)

$$= (\bar{y}_{11} - \bar{y}_{01}) - (\bar{y}_{10} - \bar{y}_{00})$$

$$= (\bar{y}_{.Tr1} - \bar{y}_{.P1}) - (\bar{y}_{.Tr0} - \bar{y}_{.P0})$$

Methods under Consideration > ANCOVA

ANCOVA Model:

$$Y_{1i} = \mu_0 + \beta_1 I_i(\text{treatment} = j) + \alpha_1 Y_{0i} + \varepsilon_i \quad (2)$$

Alternative Formulation:

$$D_i = \mu_0 + \beta_1 I_i(\text{treatment} = j) + \alpha'_1 Y_{0i} + \varepsilon_i \quad (3)$$

- ▶ Liang, Zeger (2000) mentioned that the estimates of μ_0 and β_1 in equation (3) are unbiased only if α'_1 equals to zero.
- ▶ Liu et al. (2009) mentioned wider variance of treatment effect obtained from ANCOVA.

Methods under Consideration > ANCOVA

$$\text{Treatment effect} = \hat{\theta}_1 = (\bar{y}_{.Tr1} - \bar{y}_{.P1}) - \hat{\alpha}_1(\bar{y}_{.Tr0} - \bar{y}_{.P0})$$

$$\hat{var}_{ANCOVA}(\hat{\theta}_1 | \underline{Y}_0) = \left(\frac{n_{Tr} + n_P}{n_{Tr} n_P} + \frac{(\bar{y}_{.Tr0} - \bar{y}_{.P0})^2}{\sum_{j=P}^{Tr} \sum_{i=1}^{n_j} (y_{ij0} - \bar{y}_{.j0})^2} \right) \hat{\sigma}^2 \quad (4)$$

$$\hat{\sigma}^2 = \frac{\left(\sum_{j=P}^{Tr} \sum_{i=1}^{n_j} (y_{ij1} - \bar{y}_{.j1})^2 - \frac{(\sum_{j=P}^{Tr} \sum_{i=1}^{n_j} (y_{ij1} - \bar{y}_{.j1})(y_{ij0} - \bar{y}_{.j0}))^2}{\sum_{j=P}^{Tr} \sum_{i=1}^{n_j} (y_{ij0} - \bar{y}_{.j0})^2} \right)}{n_{Tr} + n_P} \quad (5)$$

$$\hat{\alpha}_1 = \frac{\sum_{j=P}^{Tr} \sum_{i=1}^{n_j} (y_{ij1} - \bar{y}_{.j1})(y_{ij0} - \bar{y}_{.j0})}{\sum_{j=P}^{Tr} \sum_{i=1}^{n_j} (y_{ij0} - \bar{y}_{.j0})^2} \quad (6)$$

Methods under Consideration > cLDA

With two observations per subject (Y_{i0}, Y_{i1}), a simple linear regression model for each subject is (Stage 1):

$$Y_{it} = \gamma_{0i} + \gamma_{1i} I_i(\text{time} = t) + \epsilon_{it}, \quad t = 0, 1, \quad (7)$$

Stage 2 or population level models then describe subject specific parameters:

$$\gamma_{0i} = \gamma_{00} + \gamma_{01} I_i(\text{tr} = j) + \xi_{0i}, \quad i = 0, 1, \dots, n, \quad (8)$$

and

$$\gamma_{1i} = \gamma_{10} + \gamma_{11} I_i(\text{tr} = j) + \xi_{1i}, \quad i = 0, 1, \dots, n, \quad (9)$$

Methods under Consideration > cLDA

The underlying assumptions are:

$$\epsilon_{it} \sim N(0, \sigma^2)$$

$$\begin{pmatrix} \xi_{0i} \\ \xi_{1i} \end{pmatrix} \sim N_2 \left[\mu = \begin{pmatrix} 0 \\ 0 \end{pmatrix}, \Sigma = \begin{pmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{12} & \Sigma_{22} \end{pmatrix} \right]$$

Methods under Consideration > cLDA

$$Y_{it} = \gamma_{00} + \gamma_{01} I_i(tr = j) + \gamma_{10} I_i(time = t) + \gamma_{11} I_i(tr = j) I_i(time = t) + \epsilon_{it}^* \quad (10)$$

with

$$E(\epsilon_{it}^*) = 0$$

$$V(\epsilon_{it}^*) = \sigma^2 + \Sigma_{11} + [I_i(time = t)]^2 \Sigma_{22} + 2 I_i(time = t) \Sigma_{12}$$

$$cov(\epsilon_{it}^*, \epsilon_{it'}^*) = \Sigma_{11} + [I_i(time = t)]^2 \Sigma_{22} + 2 I_i(time = t) \Sigma_{12}$$

Methods under Consideration > cLDA

The likelihood function is complex, because there are several parameters to consider: the parameter space is $\Omega = (\gamma_0, \gamma_1, \Theta)$:

- ▶ $\gamma_0 = (\gamma_{00}, \gamma_{01})$,
- ▶ $\gamma_1 = (\gamma_{10}, \gamma_{11})$ and
- ▶ Covariance parameters, $\Theta = (\sigma, \Sigma_{11}, \Sigma_{12}, \Sigma_{22})$.

Therefore, we assume $\Sigma_{22} = \text{var}(\xi_{1i}) = 0$ and equal baseline at each treatment arms ($\gamma_{01} = 0$).

Methods under Consideration > cLDA

This will give us the MLE of γ_{11}

$$\begin{aligned}\hat{\gamma}_{11} &= \frac{1}{n_1} \sum_{i=1}^n d_i I_i(tr = j) - \frac{1}{n_0} \left(\sum_{i=1}^n d_i (1 - I_i(tr = j)) \right) \\ &= (\bar{y}_{.Tr1} - \bar{y}_{.Tr0}) - (\bar{y}_{.P1} - \bar{y}_{.P0}) \\ &= (\bar{y}_{.Tr1} - \bar{y}_{.P1}) - (\bar{y}_{.Tr0} - \bar{y}_{.P0}),\end{aligned}$$

which is equal to change score estimate of treatment effect for the complete data case.

Generalization of the Methods > ANCOVA

For $T > 1$ repeated measures, the generalization to model (3) (for $t = 1, 2, \dots, T$) is as follows in a without intercept form, conditional on baseline:

$$E(Y_{ijt} | Y_{ij0}) = \alpha_t Y_{ij0} + \beta_{jt} I(tr = j) I(time = t)$$

$$E(Y_{ijt} - Y_{ij0} | Y_{ij0}) = (\alpha_t - 1) Y_{ij0} + \beta_{jt} I(tr = j) I(time = t)$$

Treatment / time	1	t
Treatment (Tr)	$\alpha_1 Y_{iTr_0} + \beta_{Tr_1}$	$\alpha_t Y_{iTr_0} + \beta_{Tr_t}$
Placebo (P)	$\alpha_1 Y_{iP_0} + \beta_{P_1}$	$\alpha_t Y_{iP_0} + \beta_{P_t}$

At time t , the treatment effect on the mean change from baseline is $\theta_t = \beta_{Tr_t} - \beta_{P_t}$.

Generalization of the Methods > cLDA

The extension of the model (10) for more than one post-randomized time point measurements ($t = 0, 1, 2, \dots, T$) is as follows:

$$E(ijt) = \gamma_0 + \gamma_{jt} I(tr = j)I(time = t).$$

Treatment / time	0	1	t
Treatment (Tr)	γ_0	$\gamma_0 + \gamma_{Tr_1}$	$\gamma_0 + \gamma_{Tr_t}$
Placebo (P)	γ_0	$\gamma_0 + \gamma_{P_1}$	$\gamma_0 + \gamma_{P_t}$

The treatment effect on the mean change from baseline estimated for the treatment group at time t is then $\gamma_t = \gamma_{Tr_t} - \gamma_{P_t}$.

Generalization of the Methods > Comparison

Change score is essentially a special case for cLDA model for $t = 0, 1$. From the unconditional covariance matrix,

$$\Sigma = \begin{pmatrix} \sigma_{00} & \cdots & \sigma_{0t} & \cdots & \sigma_{0T} \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ \sigma_{0t} & \cdots & \sigma_{tt} & \cdots & \sigma_{tT} \\ \vdots & \ddots & \vdots & \ddots & \vdots \\ \sigma_{0T} & \cdots & \sigma_{tT} & \cdots & \sigma_{TT} \end{pmatrix},$$

we have the treatment effects equal from both methods:

$$\theta_t = \beta_{Tr_t} - \beta_{P_t} = (\gamma_0 + \gamma_{Tr_t}) - \frac{\sigma_{0t}}{\sigma_{00}} \gamma_0 - (\gamma_0 + \gamma_{P_t}) + \frac{\sigma_{0t}}{\sigma_{00}} \gamma_0 = \gamma_{Tr_t} - \gamma_{P_t} = \gamma_t. \text{ but,}$$

$$\hat{\sigma}^2 \left(\left(\frac{1}{n_{Tr}} + \frac{1}{n_P} \right) + \frac{v\hat{a}r_{ANCOVA}(\hat{\theta}_t | \underline{Y}_0) \leq v\hat{a}r_{cLDA}(\hat{\gamma}_t)}{\sum_{j=P}^{Tr} \sum_{i=1}^{n_j} (Y_{ij0} - \bar{y}_{.j0})^2} \right) \leq \hat{\sigma}^2 \left(\frac{1}{n_{Tr}} + \frac{1}{n_P} \right)$$

Illustration with a data $>$ Treatment arms

517 patients were randomized into six treatment arms:

- ▶ Placebo
- ▶ Haloperidol (20 mg), a standard treatment
- ▶ Risperidone
 - ▶ 2 mg
 - ▶ 6 mg
 - ▶ 10 mg
 - ▶ 16 mg

A standard measure of the severity of schizophrenia is PANSS (Positive and Negative Score Scale). Higher value of PANSS indicates more severe condition of schizophrenia. A negative or downward trend in PANSS score would mean that the treatment is effective.

Illustration with a data $>$ Repeated Measures

This is recorded as a response from one week prior to baseline measuring (this measurement is omitted in this paper), one at baseline (week 0) and five measures after randomization (at week 1, 2, 4, 6, 8).

Illustration with a data > Boxplots

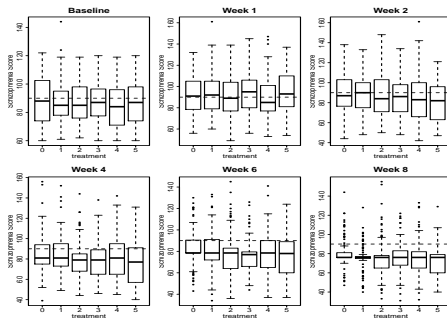


Illustration with a data > Boxplots

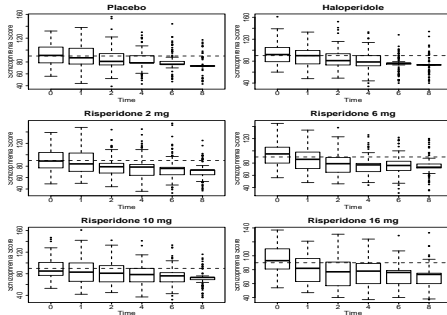


Illustration with a data > Smoothed Lines

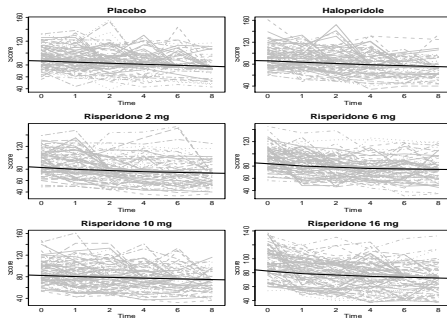


Illustration with a data \succ Spaghetti plot

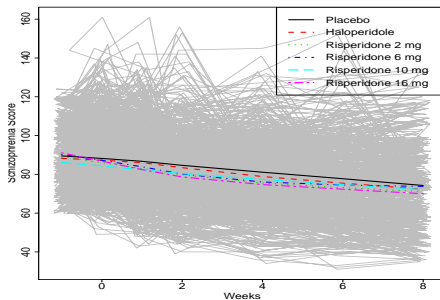


Illustration with a data \succ Spaghetti plot

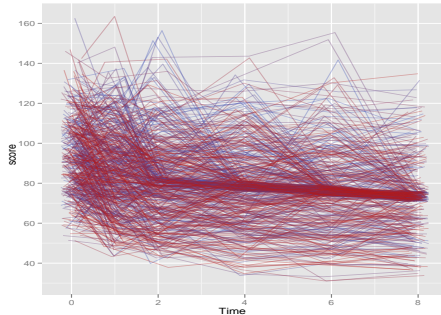


Illustration with a data \succ For simple case

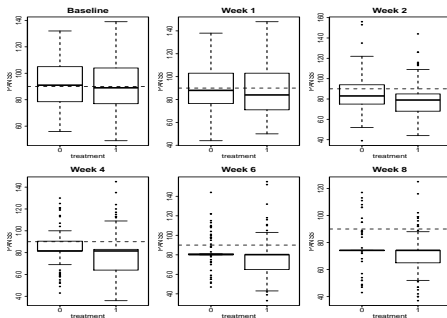


Illustration with a data \succ For simple case

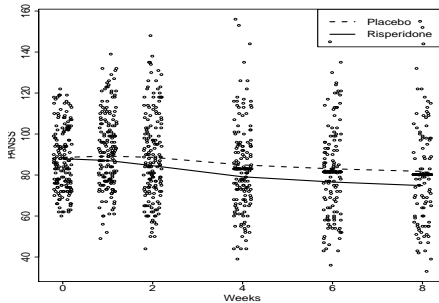


Illustration with a data > For simple case

Table: Treatment effects at specified time points estimated from the three approaches under consideration (complete data case)

Method	$t = 1$	$t = 2$	$t = 4$	$t = 6$	$t = 8$
Change Score	-2.119	-6.312	-4.086	-5.385	-2.671
cLDA	-2.119	-6.312	-4.086	-5.385	-2.671
ANCOVA (1) (without baseline)	-2.119 (2.230)	-6.312 (2.691)	-4.086 (2.906)	-5.385 (2.980)	-2.671 (3.053)
ANCOVA (2) (with baseline)	-2.243 (2.196)	-6.615 (2.492)	-4.489 (2.566)	-5.821 (2.589)	-3.306 (2.153)

Illustration with a data > For simple case

Table: Treatment effects at specified time points estimated from the three approaches under consideration (results after missing values are omitted, which made the data imbalanced)

Method	$t = 1$	$t = 2$	$t = 4$	$t = 6$	$t = 8$
Change Score	-2.179	-7.994	-6.393	-10.602	-7.470
cLDA	-2.536	-7.500	-7.362	-13.356	-10.351
ANCOVA (1) (without baseline)	-2.470 (2.223)	-7.548 (2.931)	-6.769 (3.467)	-11.061 (4.229)	-7.658 (5.079)
ANCOVA (2) (with baseline)	-2.619 (2.192)	-7.815 (2.871)	-6.861 (3.417)	-11.130 (4.187)	-7.9667 (4.674)

Summary

- ▶ Change Score is very basic, very easy to explain, only applicable for complete cases
- ▶ ANCOVA model is unbiased when baseline assumed equal in the model, but variance is still not the smallest. Not applicable in missing value cases.
- ▶ A generalized framework, easily extendable. Since this unified the above methods for complete case in terms of treatment effect estimates, it is interpretable easily. Smallest variance. Assumes baselines as random and Multivariate assumption for baseline and post-baseline measurements.

Thank You!