Evaluating Statistical Interaction between Various Therapy in Clinical Trials

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INTRODUCTION

●The Interaction between the mono and combination therapy

The feature of pre-marketing clinical trial for the antihypertensive drug is that not only monotherapy trials (comparative study concerning using testing antihypertensive) but combination therapy trials (comparative study concerning co-administration with other antihypertensive) is often done. It can be a practical concern to know how different the degree of efficacy or safety is between the two therapies, that is, to investigate the interaction between the two factors, the status of mono or combined and the treatment.

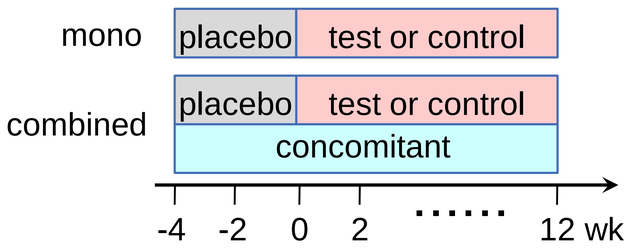


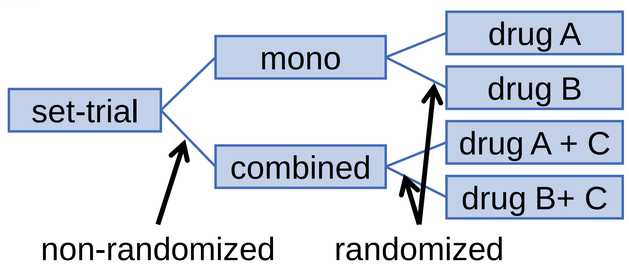
Figure 1 : Administration schedule

●Trial registration is not randomized

It should be noted that the registration in each trial (mono or combined) may be not randomized and be selective (Figure 2). The factor of selectivity may be

- ✓ background
- ✓ laboratory test values
- ✓ previous disease or contraindication disease for concomitant drug

Doctors may register the subject out of consideration of these factor. In fact, patient with experience of diuretic before trials tend to entry into combination therapy trials. If interest is on safety and efficacy difference between mono- and combined, that is interaction, the unbalance could yield bias, and that's why it should be analyzed in consideration for this unbalance.



test : drug A (ex : CCB)
control : drug B (ex : β)
concomitant : drug C (ex : diuretic)

Figure 2 : Trial registration and allocation

OBJECTIVES

We aim to evaluate the interaction between the two factors above (i.e. the status of mono or combined and the treatment) by adjusting for patients' covariates which may affect the registration in the each trial. In this poster, outcome is odds ratio about worsening of the neuropsychiatric symptoms as against before administration, included newly symptoms.

METHODS

Notation

i : patient ID ($i = 1, \dots, n$)
S : indicator variable about the trials (0: mono, 1: combined)
T : indicator variable about drug group (0: control, 1: test)
$Y^{(st)}$: potential outcome
$\boldsymbol{\beta} = (\beta_{00}\ \beta_{01}\ \beta_{10}\ \beta_{11})^T$: expectation of potential outcome, $\beta_{st} = \mathrm{E}[Y_{st}]$
$\boldsymbol{X}$: observed covariate vector
$e_1(\boldsymbol{X}) = \Pr(S = 1 \mid \boldsymbol{X})$: propensity score about the registration into the combi- trial
$e_2(S) = \Pr(T = 1 \mid S)$: probability about the allocation into the test group
$m_{st}(\boldsymbol{X}) = \mathrm{E}[Y^{(st)} \mid S = s, T = t, \boldsymbol{X}]$: regression of the outcome on $\boldsymbol{X}$ in each trial and group

$e_1(\boldsymbol{X})$, $e_2(S)$ and $m_{st}(\boldsymbol{X})$ are estimated from observed data by assuming that parametric model $e_1(\boldsymbol{X};\alpha_1)$, $e_2(S;\alpha_2)$ and $m_{st}(\boldsymbol{X};\alpha_3)$. Additionally, estimated these statistics $\hat{e}_{1,i} = e_1(\boldsymbol{X}_i;\hat{\alpha}_1)$, $\hat{e}_{2,i} = e_2(S_i;\hat{\alpha}_2)$ and $\hat{m}_{st,i} = m_{st}(\boldsymbol{X}_i;\hat{\alpha}_3)$ for all i.

Average Causal Effect and Their Interaction

average causal effect about mono and combined, and their interaction

- average causal effect $\mu_s = \mathrm{logit}(\beta_{s1}) - \mathrm{logit}(\beta_{s0})$
- interaction $\Delta = \mu_1 - \mu_0$

Strongly Ignorable Treatment Assignment [SITA]

$(Y^{(00)}, Y^{(01)}, Y^{(10)}, Y^{(11)}) \perp\!\!\!\perp S \mid \boldsymbol{X}$ ・・・・・・ assumption about trial registration

$(Y^{(00)}, Y^{(01)}, Y^{(10)}, Y^{(11)}, \boldsymbol{X}) \perp\!\!\!\perp T \mid S$ ・・・ assumption about treatment allocation

Estimator of the Average Causal Effect

■ Horovitz-Thompson form estimator [HT]

$$\hat{\beta}_{00} = \frac{1}{n}\sum_i \frac{(1-S_i)(1-T_i)Y_i^{(00)}}{(1-\hat{e}_{1,i})(1-\hat{e}_{2,i})}, \quad \hat{\beta}_{01} = \frac{1}{n}\sum_i \frac{(1-S_i)T_iY_i^{(01)}}{(1-\hat{e}_{1,i})\hat{e}_{2,i}},$$
$$\hat{\beta}_{10} = \frac{1}{n}\sum_i \frac{S_i(1-T_i)Y_i^{(10)}}{\hat{e}_{1,i}(1-\hat{e}_{2,i})}, \quad \hat{\beta}_{11} = \frac{1}{n}\sum_i \frac{S_iT_iY_i^{(11)}}{\hat{e}_{1,i}\hat{e}_{2,i}}$$

Other Type of Estimators

■ Standardized estimator [STD]

$$\hat{\beta}_{11} = \left(\sum_i \frac{S_iT_i}{\hat{e}_{1,i}\hat{e}_{2,i}}\right)^{-1} \sum_i \frac{S_iT_iY_i^{(11)}}{\hat{e}_{1,i}\hat{e}_{2,i}}$$

■ Doubly robust estimator [DR]

$$\hat{\beta}_{11} = \frac{1}{n}\sum_i \left(\frac{S_iT_iY_i^{(11)}}{\hat{e}_{1,i}\hat{e}_{2,i}} - \frac{S_iT_i - \hat{e}_{1i}\hat{e}_{2i}}{\hat{e}_{1i}\hat{e}_{2i}}\hat{m}_{11,i}\right)$$

$\hat{\beta}_{00}, \hat{\beta}_{01}, \hat{\beta}_{10}$ are derived in a similar way

CASE EXAMPLE

■ Phase III clinical trial(drugs are in Figure 2)
■ Sample size: 383 (mono is 199, combined is 184)
■ Event: worsening of the neuropsychiatric symptoms (binary data); against before administration included newly symptoms
■ Covariate: drug experience about diuretic before trials, abnormality of total cholesterol, complication of renal dysfunction
■ Compare with estimate simply from 2 × 2 table(crude analysis)

Table I: 2 by 2 table [count *(row proportion)*]

trial	group	outcome: event		outcome: non-event		sum
mono	test	14	*(0.13)*	90	*(0.87)*	104
	control	18	*(0.19)*	77	*(0.81)*	95
	sum	32	*(0.16)*	167	*(0.84)*	199
comb	test	9	*(0.10)*	85	*(0.90)*	94
	control	15	*(0.17)*	75	*(0.83)*	90
	sum	24	*(0.13)*	160	*(0.87)*	184

Table II: Estimate of Average Causal Effects [translation to odds ratios]

trial	methods	odds ratios(95% CL)
mono	crude	0.67 (0.31, 1.43)
	adj : HT	0.98 (0.37, 2.64)
	adj : STD	0.98 (0.37, 2.60)
	adj : DR	1.02 (0.41, 2.53)
comb	crude	0.53 (0.22, 1.28)
	adj : HT	0.49 (0.17, 1.39)
	adj : STD	0.44 (0.16, 1.27)
	adj : DR	0.44 (0.16, 1.20)

The adjustment for mono-therapy is large, so much so that interaction is adjusted widely. However, because the population for adjustment analysis is different from one of crude analysis, we cannot simply compare adjustment with crude about average causal effects. The estimates of three adjustment methods show a similar trend.

Table III: Estimate of Interaction [translation to odds ratios]

methods	odds ratios(95% CL)
crude	※0.80 (0.25, 2.55)
adj : HT	0.50 (0.12, 2.08)
adj : STD	0.45 (0.11, 1.89)
adj : DR	0.43 (0.11, 1.66)

※ comb / mono = 0.53／0.67 = 0.80

CONCLUSION and FUTURE WORK

As the usual method of propensity score weighting, our method is useful in that it allows for the interaction between the two factors above and the patients' covariates, and avoids modeling the association between the outcome and the patients' covariates. The propensity score in our problem is a little more complicated, but it can be easily estimated due to the hierarchical structure of registration and treatment allocation. Our future works are below.

■ Sensitive analysis : If unmeasured confounding factor is exist, estimators are …
■ Non-randomized trial : If treatment allocation is non-randomized, SITA is …
■ Restricted population : If interested population is restricted, estimators are …

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