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.

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 concomitant disease for concomitant drug

Doctors may register the subject out of consideration of these factors. 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.

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 (\( i = 1, \ldots, n \))
\( S \) : indicator variable about the trials (0: mono, 1: combined)
\( T \) : indicator variable about drug group (0: control, 1: test)

\( \beta \) : potential outcome
\( \beta_0, \beta_1, \beta_0 \beta_1 \) : expectation of potential outcome, \( \beta_0 = E(Y_{0a}) \)
\( X \) : observed covariate vector
\( \phi_1(X) = Pr(S = 1 | X) \): propensity score about the registration into the combi- trial
\( \phi_2(S) = Pr(T = 1 | S) \): probability about the allocation into the test group
\( m_{0a}(X) = E(Y_{0a}|S = s, T = 1, X) \): regression of the outcome on \( X \) in each trial and group

\( \phi_1(X), \phi_2(S) \) and \( m_{0a}(X) \) are estimated from observed data by assuming that parametric model \( \phi_1(X; \alpha_1), \phi_2(S; \alpha_2) \) and \( m_{0a}(X; \alpha_3) \). Additionally, estimated these statistics \( \hat{\beta}_1 = \phi_1(X; \hat{\alpha}_1), \hat{\phi}_2 = \phi_2(S; \hat{\alpha}_2) \) and \( m_{0a}(X; \hat{\alpha}_3) \) for all \( i \).

Average Causal Effect and Their Interaction

\( \hat{\beta}_0 = \frac{1}{n} \sum_{i} \frac{(1 - S_i)(1 - T_i) Y_{00}^{(i)}}{(1 - \hat{\phi}_2)(1 - \hat{\phi}_1)}, \quad \hat{\beta}_1 = \frac{1}{n} \sum_{i} \frac{(1 - S_i) T_i Y_{10}^{(i)}}{(1 - \hat{\phi}_2)(1 - \hat{\phi}_1)} \)
\( \hat{\beta}_0 = \frac{1}{n} \sum_{i} \frac{S_i(1 - T_i) Y_{01}^{(i)}}{\hat{\phi}_2(1 - \hat{\phi}_1)}, \quad \hat{\beta}_1 = \frac{1}{n} \sum_{i} \frac{S_i T_i Y_{11}^{(i)}}{\hat{\phi}_2(1 - \hat{\phi}_1)} \)

\( \hat{\beta}_{00}, \hat{\beta}_{10}, \hat{\beta}_{01}, \hat{\beta}_{11} \) are derived in a similar way.

OTHER TYPE OF ESTIMATORS

- 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)
- Covariate: drug experience before trials
- Abnormality of total cholesterol, complication of renal dysfunction
- Compare with estimate simply from 2×2 table(crude analysis)

CASE EXAMPLE

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

<table>
<thead>
<tr>
<th>Trial group</th>
<th>Outcome</th>
<th>Event</th>
<th>Non-event</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>14 (0.13)</td>
<td>90 (0.87)</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Mono control</td>
<td>18 (0.19)</td>
<td>77 (0.81)</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td>32 (0.16)</td>
<td>167 (0.84)</td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>9 (0.10)</td>
<td>85 (0.90)</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Comb control</td>
<td>15 (0.17)</td>
<td>75 (0.83)</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Sum</td>
<td>24 (0.13)</td>
<td>160 (0.87)</td>
<td>184</td>
<td></td>
</tr>
</tbody>
</table>

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.

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 ...

REFERENCE