Recurrent event estimands: With or without competing terminal event

Dr. Jiawei Wei.
Different estimand?

Does it mean Cox, WLW, and PWP estimate different estimand (target value)? If so, please let us know what are two (or more) estimand?

<table>
<thead>
<tr>
<th>Estimand 1</th>
<th>Estimand value</th>
<th>Method</th>
<th>Estimate</th>
<th>Estimate/Estimand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-poly</td>
<td>0.685</td>
<td>Cox</td>
<td>0.694</td>
<td>1.013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NB</td>
<td>0.682</td>
<td>0.996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LWYY</td>
<td>0.684</td>
<td>0.999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WLW</td>
<td>0.611</td>
<td>0.892</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PWP</td>
<td>0.707</td>
<td>1.032</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimand 2</th>
<th>Estimand value</th>
<th>Method</th>
<th>Estimate</th>
<th>Estimate/Estimand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothetical</td>
<td>0.65</td>
<td>Cox</td>
<td>0.665</td>
<td>1.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NB</td>
<td>0.647</td>
<td>0.995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LWYY</td>
<td>0.647</td>
<td>0.995</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WLW</td>
<td>0.576</td>
<td>0.886</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PWP</td>
<td>0.671</td>
<td>1.032</td>
</tr>
</tbody>
</table>

- The numerical value for the treatment policy estimand is closer to 1 than the hypothetical estimand because the effect is diluted under treatment policy.
- NB and LWYY give consistent mean effects for both estimands.
- Cox, WLW and PWP models are not appropriate since their target values are different from the estimand values.

*WLW: Wei-Lin-Wei model; PWP: Prentice-Williams-Peterson model*
Estimands, Sensitivity Analysis and Missing Data
Dr. Lipkovich
Sensitivity estimand

DISCUSSION: SENSITIVITY ANALYSIS OR A “SENSITIVITY ESTIMAND”?

Historically “sensitivity analysis” was used for almost any variation on the “primary analysis”.

Following the NRC 2010 report on missing data, sensitivity analysis was framed as analysis under varying untestable assumptions, e.g. governing missingness mechanism. A sensitivity analysis involves sensitivity parameter(s), not estimable from data alone.

Typically we would think of a set of sensitivity analyses addressing the same estimand under varying assumptions.

While different hypothetical estimands may be legitimate targets, as considered in this presentation, it is important to understand that in absence of data required by the estimand, the analysis has to necessarily follow a path of sensitivity analysis.

An important consideration is that one should not just plug-in the sensitivity assumptions in the estimand, obtain a new estimand (under "sensitivity assumption") and proceed to its estimation.

- In our example this led to replacing the original estimand with a “sensitivity estimand” that had a form of a shrinkage estimand whose value was known to be 0 with certainty if all patients on the experimental treatment arm would discontinue treatment.
- This led to a reduced variance estimator that ignored the sampling variability that would be inherent in any estimator of the original estimand.
Sensitivity estimand?

Is this sensitivity estimand? If so, what is the primary estimand for your trial?
A.5.2.1. Role of Sensitivity Analysis

- One or more analyses, focused on the same estimand, should then be pre-specified to investigate these assumptions with the objective of verifying that the estimate derived from the main estimator is robust to departures from its assumptions. Distinct from this sensitivity analysis, each other analysis that is planned, presented or requested in order to more fully investigate and understand the trial data can be termed supplementary analysis. Each supplementary analysis may refer to a different estimand, or a different estimator to the same estimand.

Will "sensitivity estimand" be estimated for
(i) primary analysis,
(ii) sensitivity analysis of the primary analysis, or
(iii) supplementary analysis?
Some estimating method

estimand

$$E(\delta) = [\pi \cdot \mu_{(1)|S=1} + (1 - \pi) \cdot \mu_{(1,-1)|S=0}] - \mu_{(0)}$$

Hypothetical-I: if not meeting rescue condition, continue randomized treatment, if meeting rescue condition, discontinue treatment and remain untreated

$$\mu_{(1,-1)|S=0}$$ (unidentifiable)

\[ E(\hat{\mu}_{(1,-1)|S=0}) = \mu_{(1,-1)|S=0} \]
Based on my understanding,

estimand

\[ E(\delta) = \left[ \pi \cdot \mu(1) | S=0 \right] \]

*Hypothetical-I*: if not meeting rescue condition, continue randomized treatment, if meeting rescue condition, discontinue treatment and remain untreated

\[ \mu(1,-1) | S=0 \text{ (unidentifiable)} \]

\[ \mu(1,-1) | S=0 = E(\hat{\mu}(0)) = \mu(0) \]

\[ \mu(1,-1) | S=0 = E(\hat{\mu}(0) + \tau) = \mu(0) + \tau \]

```
proc mi data=m.armd13 seed=486048 simple out=m.armd13as1
   nimpute=10 round=0.1;
   title 'Shift multiple imputation';
   class treat;
   var lesion diff4 diff12 diff24 diff52;
   fcs reg;
   mnar adjust (diff12 / shift=10 adjustobs=(treat='2'));
   mnar adjust (diff24 / shift=15 adjustobs=(treat='2'));
   mnar adjust (diff52 / shift=20 adjustobs=(treat='2'));
   by treat;
run;
```
Can we use LB-MLP as a primary analysis?

I am surprised at this result! You explained that mechanism of this phenomenon. Do you have any investigation about type I error? I am interested in whether the type I error is kept for LB-MLP.
What is an Appropriate Estimand When There are Incomplete Data?
Some Case Studies
Dr. Masataka Taguri
reproducibility

On hypothetical strategy

• The effect of interest is referred to as the efficacy of the treatment
• The biological or causal effect of the treatment is more likely to be reproducible outside the trial settings
• It may not be a realistic effect if the intercurrent event is, for example, strong adverse event

Efficacy is not affected by some trial conditions. I dare ask... Are there any situations where ITT has to be chosen as a primary analysis even if some defectives are known? Cont’
Is it acceptable to change the variable of the study?

Some clinical setting, physician may want to know numerical outcome even if there are some difficulties. In this situation, do you have any justification for changing variable from numerical to dichotomous? Or is it not worth to use composite strategy for this setting? How about to use ITT as a primary analysis with numerical outcome.

**Summary**

- ITT effect is estimable as long as outcomes are observed but it *won’t be equal to neither efficacy nor effectiveness*
- Efficacy can be sometimes estimated by reasonable assumptions (*but usually not*)
- Composite estimands might be a *good compromise* between two approaches
  - Can estimate relatively weaker assumptions
  - Estimate some aspects of efficacy
Estimands, Missing Data, and Sensitivity Analysis

Dr. Geert Molenberghs

I understand your talk should not be included in the discussion because you gave a keynote lecture.
Intensity of sensitivity analysis

• How much sensitivity analysis should be done?

Shift
(sensitivity parameter)

Sample size

Relationship between shift and sample size when p value is just 0.05.
P value or estimate

• Do we need to take account “shift” for sample size calculation at the designing stage of the trial to keep small p-value less than 0.05 for sensitivity analysis?
  • If so, we have to prespecify sufficient tipping point in the planning stage. Is it possible?

-> for keep small p-value

• Is it enough to check whether estimate change markedly by sensitivity analysis without considering the shift at the designing stage of the trial?
-> only investigate robustness of estimate
Three different models

- Pattern-mixtures, selection model, shared-parameter model
- PMM is used for some trials as a sensitivity analysis, because of easiness of understanding for non-stat.
- Are there any excellent point for SM or SPM when we conduct a sensitivity analysis?