Assessment of Tipping Point Analysis for Handling Various Types of Missing Data

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Introduction

In clinical trials, statistical analyses frequently assume missing data are missing at random (MAR), even though in many clinical settings, the outcome may be more likely, or less likely to be missing in the most severely ill patients, indicating data are missing not at random (MNAR). Regulatory authorities typically require an assessment of the impact on results of the post-discontinuation data being MNAR in patients who discontinue randomised treatment early.

Traditionally, intermittent (i.e. pre-discontinuation) missing data have been assumed to be MAR in tipping point analyses. However, in some trials there may be considerable missing data of this type, in which case treating these data as MAR may not be sensible.

Aims

To compare the relationship between penalisation and p-value for various tipping point analysis methods on data with different levels of intermittent and monotone missingness.

Methods

Data were simulated based on the results of a real longitudinal clinical trial with assessments of on-going therapeutic benefit measured by success/failure at each visit. Various missing data quantities of intermittent missing (IM) and monotone missing (MM) were considered. Data were analysed by repeated measures logistic regression. Two tipping point analyses were conducted: traditional (Figure 1); novel (Figure 2). The penalty applied was between 0 and 3: 0 corresponds to imputation under the MAR assumption; 3 corresponds to almost certain probability of imputing a missing value as a non-responder.

Figure 1: Traditional tipping point analysis

Figure 2: Novel tipping point analysis

Same process flow as in Figure 1, but with the following changes:

- Intermittent missing data is additionally considered to be MNAR to some degree δ.
- Missing data in both the experimental treatment and control arms are penalised under the MNAR assumption.

Table 1: Simulated data characteristics

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Experimental Treatment</th>
<th>Control Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>2969</td>
<td>2968</td>
</tr>
<tr>
<td>Responder</td>
<td>2114 (71.2%)</td>
<td>2185 (73.6%)</td>
</tr>
<tr>
<td>Non-responder</td>
<td>855 (28.8%)</td>
<td>783 (26.4%)</td>
</tr>
<tr>
<td>Missing</td>
<td>2031</td>
<td>2032</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1576 (77.6%)</td>
<td>1616 (79.5%)</td>
</tr>
<tr>
<td>Monotone</td>
<td>455 (22.4%)</td>
<td>416 (20.5%)</td>
</tr>
</tbody>
</table>

Table 2: Results from simulated data

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental vs. Control</td>
<td>1.13 (1.01, 1.27)</td>
<td>0.0313</td>
</tr>
</tbody>
</table>

Results

Figure 2: Tipping point approaches: 2-sided p-value vs. δ

Figure 3: A closer look

Traditional tipping point is more sensitive to increasing δ compared to the novel tipping point.

Traditional tipping point:
- For all scenarios, significant treatment effect is lost with low penalisation.
- For the high MM scenario, as δ increases beyond 1 the p-value becomes continually more significant as the treatment effect is in favour of the control arm.

Novel tipping point:
- The p-value increases slowly with increasing penalisation.

Discussion

For both tipping point methods, the different scenarios of missing data had little effect on the penalty required to meet the tipping point, but the relationship between p-value and penalty varied considerably. However the tipping point was reached with much lower penalty in the traditional tipping point analysis compared to the novel tipping point analysis.

The traditional tipping point method is a conservative approach. It assumes the IM from both treatments and the MM from the control arm is MAR, and assumes MM in the experimental arm is MNAR, which may not be realistic assumptions. For this method, the tipping point delta was closer to 0 (MAR imputation) than 3 (non-responder imputation in experimental arm) for all levels of missing data, but difficult to interpret.

Results may be affected by imbalance of missing data quantity between two arms.

Conclusion

- Findings will contribute to better understanding of sensitivity of results to various proportions of IM and MM.
- Additional sensitivity analyses which penalise both arms would increase understanding about the potential impact of missing data on results.
- Interpretation of delta (δ) as a quantity needs further investigation.

Further work

- Examine the impact of missing data on results when there are different proportions of success or an imbalance of missing data across treatment arms.
- Examine other methods to investigate the impact of missing data on results, such as including information on the reason for missingness.

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References

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