Estimand in AD: a closer look at the hypothetical strategy

Paul Delmar, 3 Nov 2020
Disclaimer

• My own personal views

• Do not represent the views of Roche

• Do not represent the views of the AD Estimand SWG
AD Specific Estimand Resources

Intercurrent Events

Start of symptomatic treatment in early AD trial

COVID-19 related treatment skipped doses

Discussion on the Hypothetical Strategy
EMA AD Guideline

• In general, «treatment policy» strategy for IE of non-adherence to study treatment (alternative should be duly justified)

• Hypothetical Strategy for IE of start of symptomatic treatment (‘if symptomatic medications had not been introduced’) could be appropriate

Guideline on the clinical investigation of medicines for the treatment of Alzheimer’s disease

<table>
<thead>
<tr>
<th>Draft agreed by CNSWP</th>
<th>December 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adopted by CHMP for release for consultation</td>
<td>28 January 2016</td>
</tr>
<tr>
<td>Start of public consultation</td>
<td>01 February 2016</td>
</tr>
<tr>
<td>End of consultation (deadline for comments)</td>
<td>31 July 2016</td>
</tr>
<tr>
<td>Agreed by CNSWP</td>
<td>December 2017</td>
</tr>
<tr>
<td>Adopted by CHMP</td>
<td>22 February 2018</td>
</tr>
<tr>
<td>Date of coming into effect</td>
<td>1 September 2018</td>
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</table>

This guideline replaces ‘Guideline on medicinal products for the treatment of Alzheimer’s disease and other dementias’ (CPMP/EWP/553/95 Rev. 1).

Keywords: Alzheimer disease, clinical diagnostic criteria, Alzheimer biomarkers, preclinical Alzheimer disease
Estimand Subsection / ASA - AD Scientific Working Group

- Estimand simulation work presentation at the Regulatory/Industry Statistics Workshop (September, 2019)
- DIA Webinar Series on Estimands (September, 2018)
- Statistical Workshop on Estimands at Alzheimer’s Association International Conference (July, 2018)
- Presentation on Estimands at PSI Annual Meeting (June, 2018)
- Invited Session/Panel on ADSWG at DIA/FDA Statistical Forum (April, 2018)
- Educational Workshop on Estimands at Clinical Trials for Alzheimer’s Disease (November, 2017)
- Roundtable Discussion on ADSWG at the Regulatory/Industry Statistics Workshop (September, 2017)
- Invited Session on ADSWG at CEN-ISBS Conference (September, 2017)
- Roundtable Discussion on ADSWG at the Regulatory/Industry Statistics Workshop (September, 2016)

- **White Paper / Manuscript in preparation**
Intercurrent Events in early AD
### Intercurrent Events: Treatment Policy or Hypothetical?

<table>
<thead>
<tr>
<th>Intercurrent Event</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawal from Study Treatment</td>
<td>Depends on reason for withdrawal</td>
</tr>
<tr>
<td></td>
<td><strong>Trt Policy</strong> ← AE, LoE...</td>
</tr>
<tr>
<td></td>
<td><strong>Hypothetical</strong> ← administrative, COVID-19, ...</td>
</tr>
<tr>
<td>Start of other AD medication</td>
<td><strong>Hypothetical</strong> ← EMA guidelines</td>
</tr>
<tr>
<td>COVID-19 related treatment interruption</td>
<td><strong>Hypothetical</strong> ← Effect in a world without COVID-19 pandemics</td>
</tr>
<tr>
<td>Death</td>
<td><strong>Hypothetical</strong> Treatment Policy</td>
</tr>
</tbody>
</table>
Start of Symptomatic Treatment
Treatment policy concern with Start of other AD medication

Therefore we might assume: $E[\text{Treatment policy effect}] < E[\text{Hypothetical effect | no symptomatic meds}]$

Is this assumption supported by available data?

Donohue M, ASA Biopharma 2019
Data from ADNI


Initial theoretical assumptions don’t necessarily match a data driven approach or clinician’s observations.
ADNI data suggests $E[\text{Treatment policy effect}] > E[\text{Hypothetical effect} \mid \text{no symptomatic meds}]$.

The selection bias induced by requiring rescue is stronger than the benefit of symptomatic treatment.
COVID-19 related treatment interruption
Treatment Policy Concern with COVID related treatment interruption

1. Estimand
   a. Target of estimation: treatment effect in a world without pandemics
   b. → Hypothetical strategy

2. Estimator
   a. Treatment interruption → reduce treatment effect → loss of power ?
   b. Remove data after treatment interruption and impute using MAR
Treatment policy concern revisited

- **rho**: between visits correlation
- **IE Effect**: Proportion of “preserved” treatment effect after IE [0% -100%]

Whether or not MAR imputation improves power over using post-IE data depends on
1. Proportion of preserved treatment effect after IE
2. The correlation between visits
Discussion
Discussion

• What if censoring + MAR imputation is not an adequate estimator for an Hypothetical IE?
• Maybe “use observed data” appears as a reasonable option instead?
• Then we have the same estimator/estimate for Hyp and Trt Policy ...
• What does this imply?
  • Is this OK?
  • Should we change the IE strategy to Trt Policy?
  • Maybe the “thing” actually does not qualify as IE?
• **Could we think of other hypothetical estimator instead of simple censoring+MAR imputation?**
Conclusion

- Estimand framework is set to have a profound positive impact on analysis and reporting of clinical studies in AD
- The hypothetical strategy is crucially important and may be appropriate for several types of intercurrent events
- For estimation in an hypothetical strategy, it could be important to critically assess the censoring+MAR imputation approach and consider alternatives

“A wide variety of hypothetical scenarios can be envisaged [...] it should be made clear what hypothetical scenario is envisaged”

ICH E9 r1

“For some studies with significant pandemic-related treatment interruptions, the minimal duration of interruption expected to dilute the treatment effect could be defined. Different strategies can be used for interruptions exceeding this duration as opposed to shorter interruptions.”

Doing now what patients need next