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

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 February 2018
CPMP/EWP/553/95 Rev.2
Committee for Medicinal Products for Human Use (CHMP)

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

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

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)

- Delmar, P. et al. (2018) 'Estimand in Early Alzheimer's Disease: Progress Update from the International Alzheimer's Disease Scientific Working Group (Ad Swg) Substream', Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 14(7), p. P1437. doi: 10.1016/j.jalz.2018.06.2416.
- Donohue, M. C. et al. (2020) 'Initiation of symptomatic medication in Alzheimer's disease clinical trials: Hypothetical versus treatment policy approach', Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 16(5), pp. 797–803.

- **White Paper / Manuscript in preparation**

Biogen Lilly Eisai USC University of Southern California

Boehringer Ingelheim NOVARTIS Roche

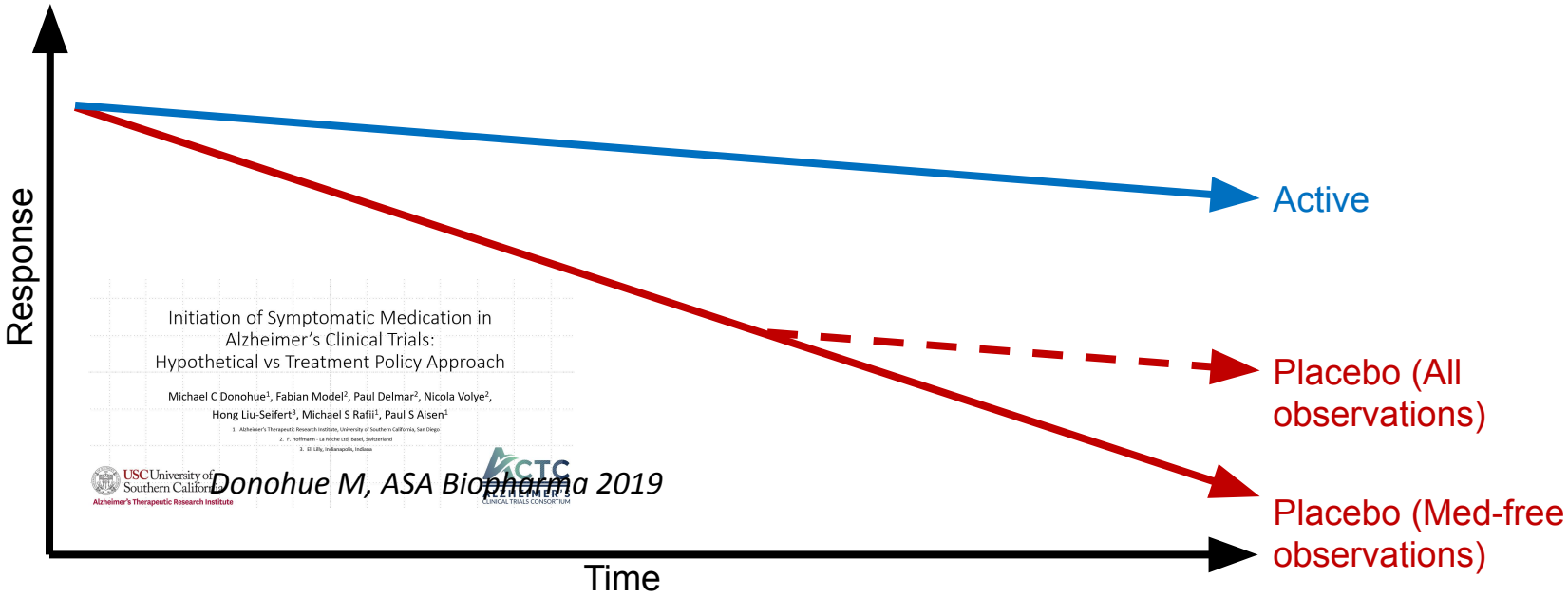
Intercurrent Events in early AD

Intercurrent Events: Treatment Policy or Hypothetical ?

Intercurrent Event	**Strategy**
Withdrawal from Study Treatment	Depends on reason for withdrawal **Trt Policy** ← AE , LoE... **Hypothetical** ← administrative, COVID-19, ...
Start of other AD medication	**Hypothetical** ← EMA guidelines
COVID-19 related treatment interruption	**Hypothetical** ← Effect in a world without COVID-19 pandemics
Death	**Hypothetical** **Treatment Policy**

Start of Symptomatic Treatment

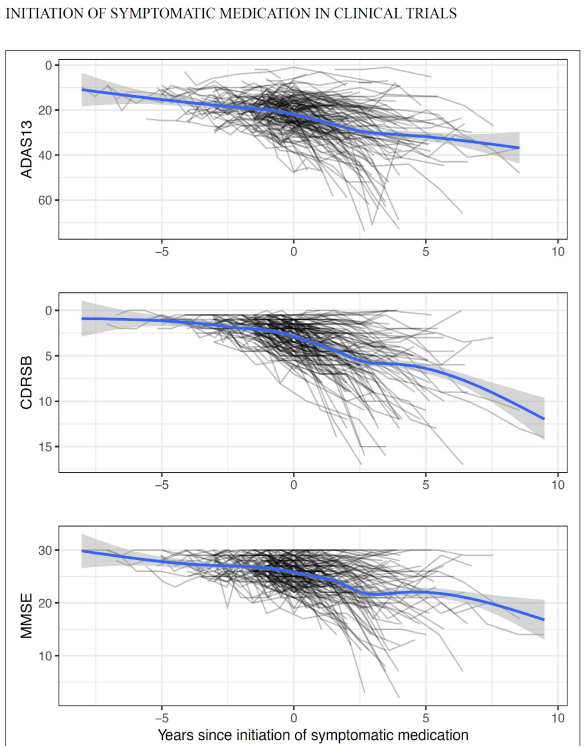
Treatment policy concern with Start of other AD medication

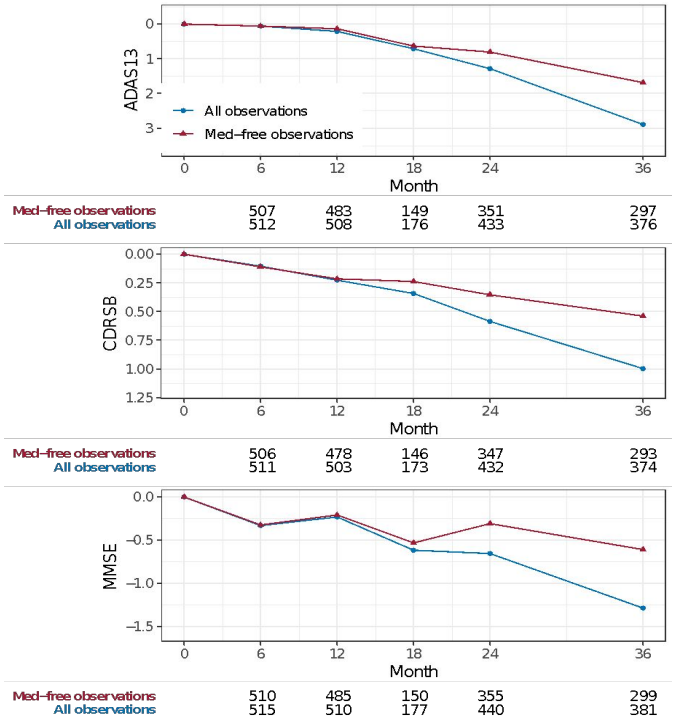


Therefore we might assume: E[Treatment policy effect] < E[Hypothetical effect | no symptomatic meds]

Is this assumption supported by available data?

Data from ADNI

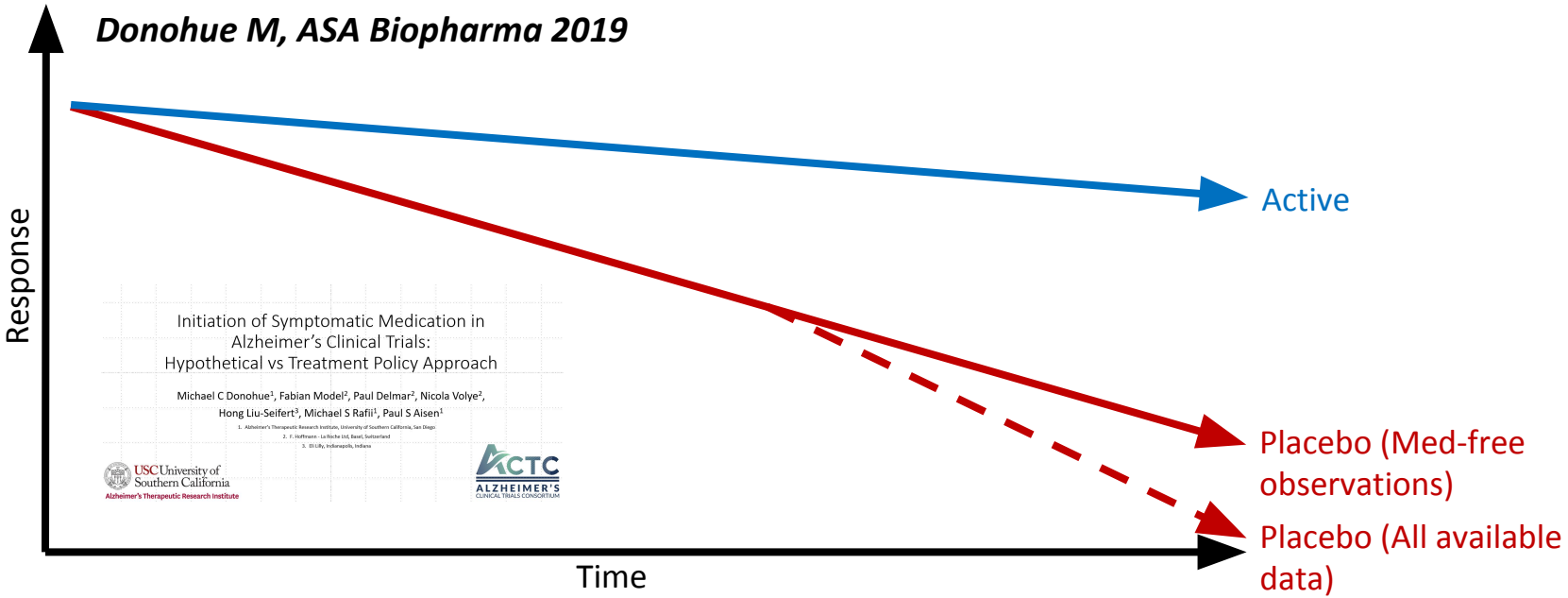




Initial theoretical assumptions don't necessarily match a data driven approach or clinician's observations

Donohue M, Alzheimer's Dement. 2020;16:797–803.

Treatment policy concern revisited



ADNI data suggests E[Treatment policy effect] > E[Hypothetical effect | no symptomatic meds]

The selection bias induced by requiring rescue is stronger than the benefit of symptomatic treatment

COVID-19 related treatment interruption

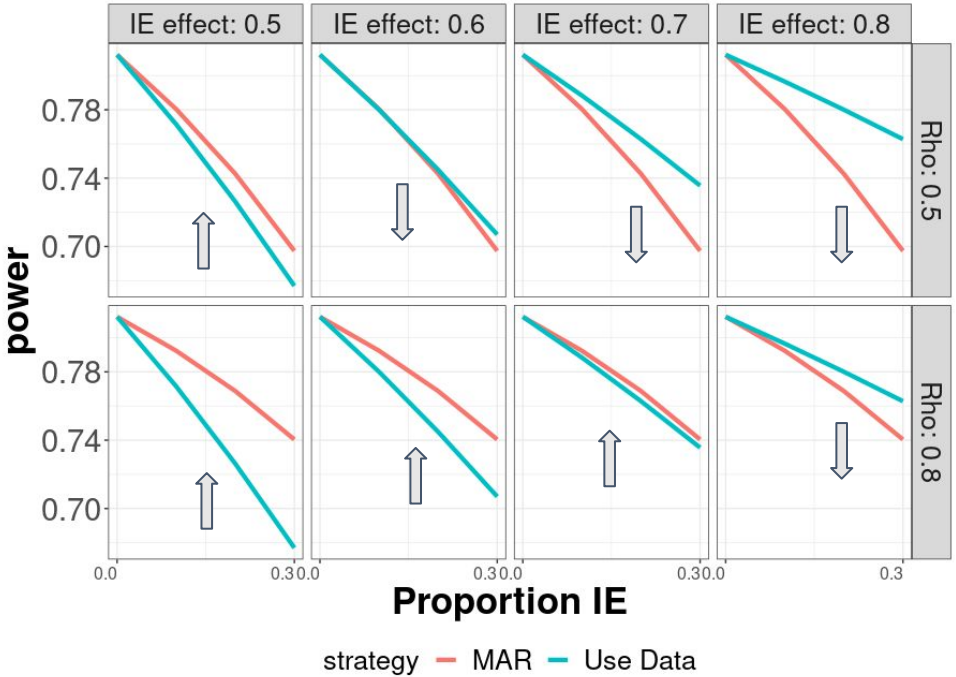
Treatment Policy Concern with COVID related treatment interruption

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%]



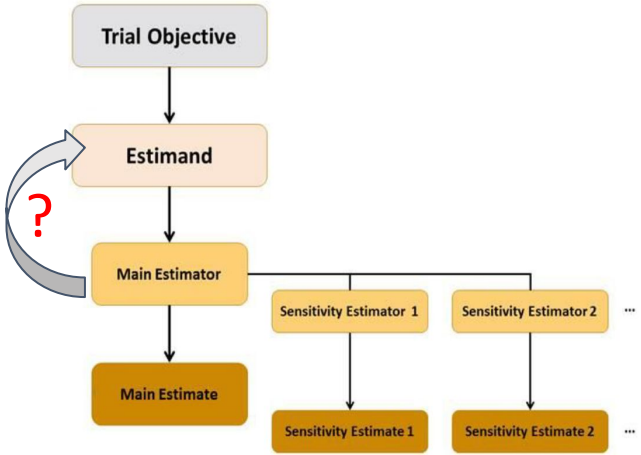
Whether or not MAR imputation improves power over using post-IE data depends on

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."

Meyer et al. (2020), Stat. in Biopharm. Res.

Doing now what patients need next