MHRA
Regulating Medicines and Medical Devices

Disease Modifying Drug Development: Statistical Design and Analysis

David Brown, MHRA

Medicines and Healthcare Products Regulatory Agency

Definition

- “From a regulatory point of view, a medicinal product can be considered as disease modifying, if the progression of the disease as measured by assessment tools addressing both cognition and function is reduced or slowed down and if these results are linked to a significant effect on adequately qualified and validated biomarkers.”

Disease modifying

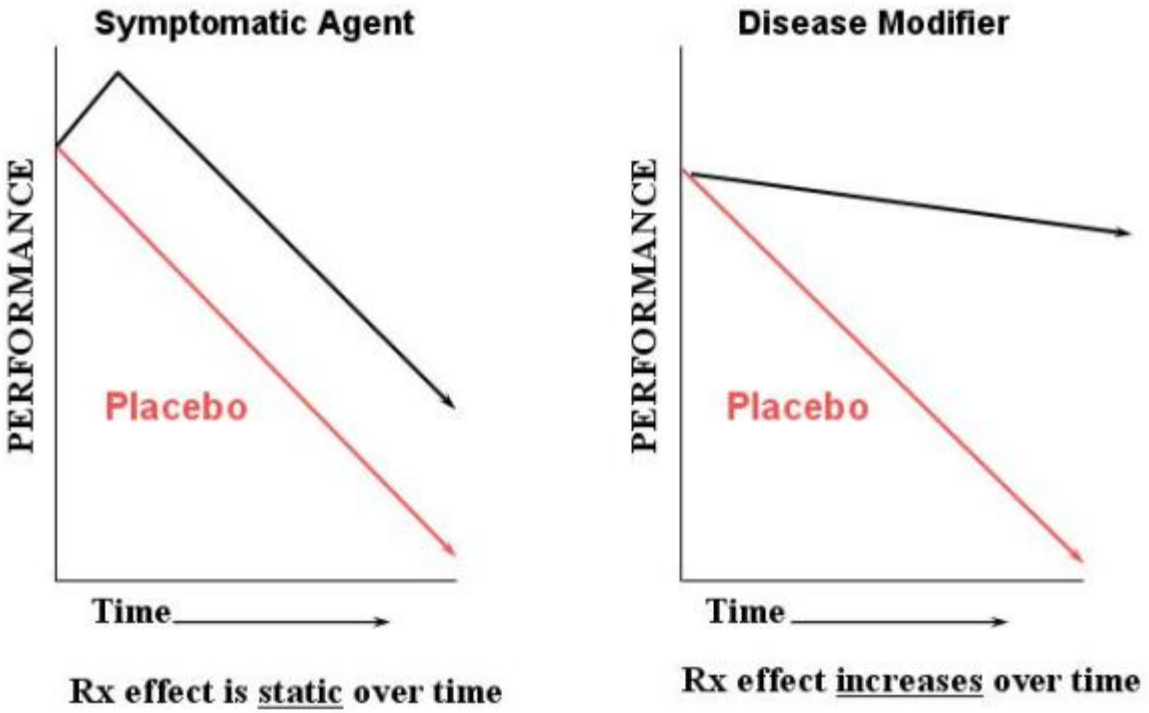


Figure from Alzheimer's association (2008)

Discussion paper

- “An improvement in the rate of decline of clinical signs and symptoms must be shown over a time period that is relevant to the proposed claim. Clinical outcomes in both study arms should be measured at regular intervals to establish a clinically relevant effect.”
- “So in a first approximation a hypothesis of disease modification seems most consistent with a statistical comparison of rates of change in clinical symptoms over time (slope analysis).”

Slope analysis

- For each patient fit a slope through the data
- Summary statistic of ‘average’ slope for each treatment group.
- Compare slopes between treatment groups

Slope analysis

- Problems:
  - Linearity assumption not clearly adequate
  - How to fit slopes in presence of initial improvement then subsequent decline
  - Problems with missing data – toxic treatments favoured

Alternative

- An alternative way to establish divergent slopes:
- "…a delay of progression over time in the pre-specified endpoints should be established at (at least) two distinct time points in a parallel group design."
  - Estimate the treatment difference at two (or more) time-points and look for an increasing difference over time

Further issue

- Establish divergent slopes but…
- "… a comparison of the rate of change in key clinical efficacy parameters based on slope analysis between active treatment and placebo using a standard parallel design does not solve the problem that a pharmacologically reversible effect that increases over time could also lead to such an outcome."
- How could we look at this?

Diverging slopes +

- How to establish effect not reversible?
- Enhanced parallel group designs:
  - Delayed start
  - Withdrawal design

Delayed start

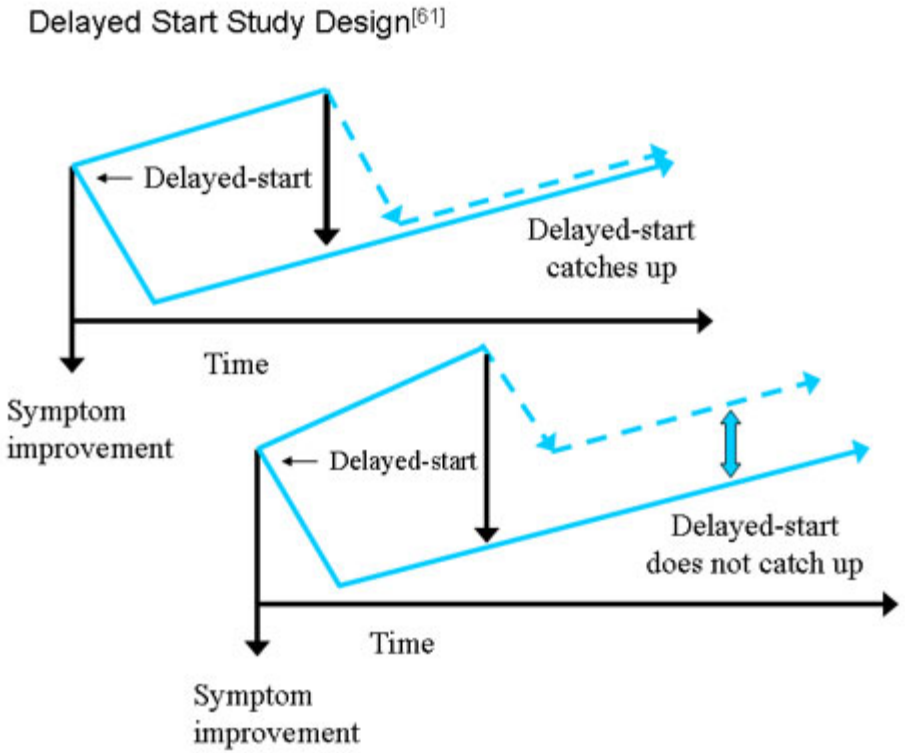


Figure from Langston et al 2010

Withdrawal trial (not randomised withdrawal)

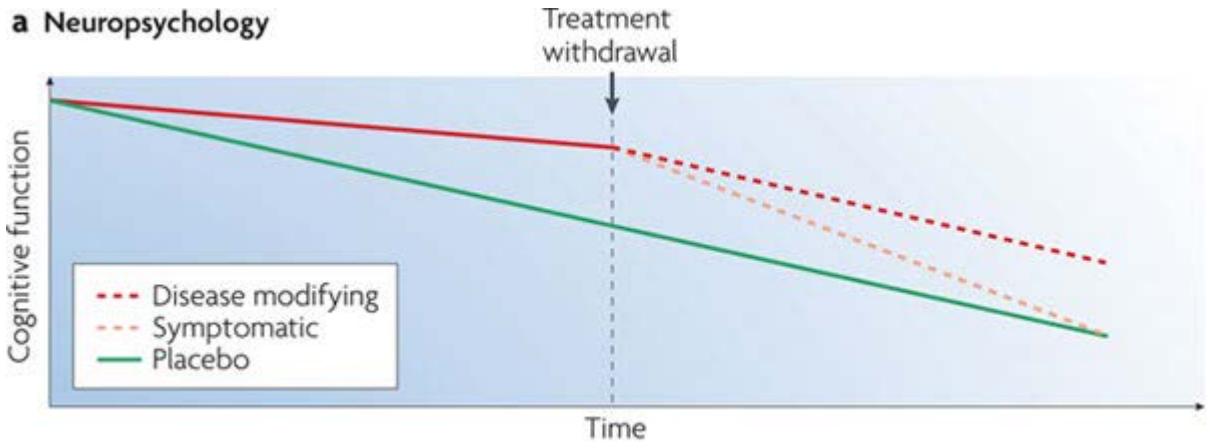


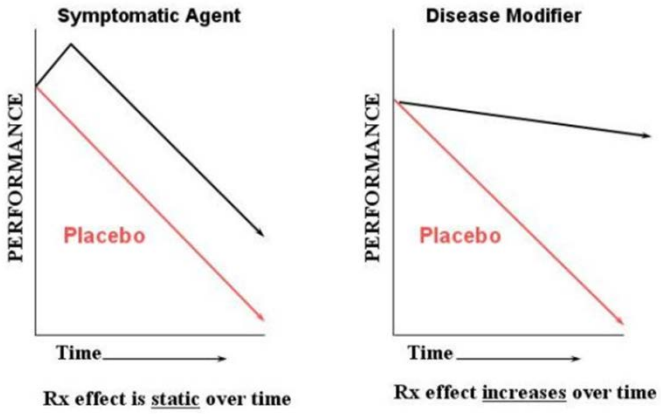
Figure from Hampel et al (2010)

Easier to analyse

- Both designs easier to analyses than looking for change of slopes
  - We only need to detect a difference
  - Don’t need to establish divergent slopes
- However length of follow-up critical
  - Too short follow-up could show a difference when the curves are actually still coming together

Time to event?

- Suggested in discussion paper
  - Does not seem to distinguish between symptomatic agents and disease modifying
  - Both would lead to difference in time-to-event



Biomarkers

- In the end effect on biomarkers is needed to finally establish disease modifying treatment
- Intermediate step
  - “If in a first step an improvement in the rate of decline of clinical sign and symptoms can be established, this may be acceptable for a limited claim (e.g. delay of disability) if efficacy in cognition and function is demonstrated.”

Delay of disability intermediate step?

- Wording suggests time-to-event
  - As noted above doesn't guarantee divergent slopes
- Desirable objective – but does it fit into indication framework?
- Time-to-event secondary analysis to aid clinical relevance assessment (and include in results in 5.1)?

Alternative intermediate

- Indication wording such as “slowing rate of decline” might be needed instead as the intermediate
- Could gain this wording with slopes/delayed start/withdrawal design on the clinical cognition/function etc. endpoints?
- Then biomarker for full disease modification?

P.S. Missing data

- Always causes additional problems
  - Toxic drugs – careful not to reward them
  - Withdrawal
  - Off treatment follow-up
  - Imputation
  - Establish disease modification in completers then likely size of average benefit in all subjects?