# Estimation of Treatment Policy Approaches for Repeatedly Collected COAs

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# Treatment Policy Estimation

## COA Analysis

- Most COAs are structured as discrete scales bounded at zero and a scale-specific upper bound
  - Typically assessed at baseline and repeatedly throughout a trial
  - Examples: KCCQ (0-100), PASI (0-72)
- Commonly assume they are continuous longitudinal data, analysable by MMRM
- ICH E9(R1) introduced concepts of Intercurrent Events (ICEs) and strategies for handling them
- Many regulators and HTAs require **treatment policy** approaches for COAs
- This is problematic: MMRM approaches most closely align with hypothetical estimands and are not able to handle missing data appropriately for treatment policy
- This talk will look at the problems with MMRM in this setting, and propose potential alternatives

# Treatment Policy Estimation

## What Is Needed?

- Treatment-policy includes ICEs within the treatment effect of interest
  - i.e. treatment changes (e.g. treatment discontinuation, use of rescue therapy) are part of the treatment regimens being compared.

- Its estimation requires continued data collection regardless of ICE occurrence
  - Nonetheless, missing data is almost inevitable

- Estimation of treatment policy in the presence of missing data is difficult
  - Treatment status within arms is heterogeneous (unlike other strategies)
  - ICEs highly correlated with missingness

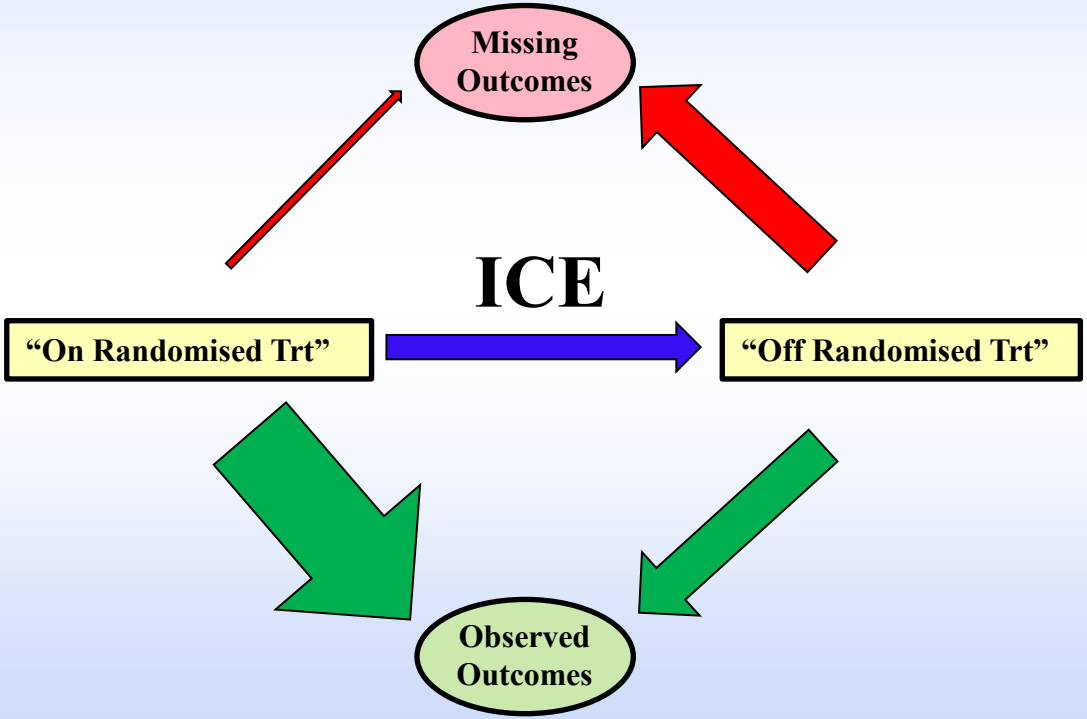
# Treatment Policy Estimation

## Missing Data

- Missing data in clinical trials is disproportionately "off randomised treatment" (off-trt)

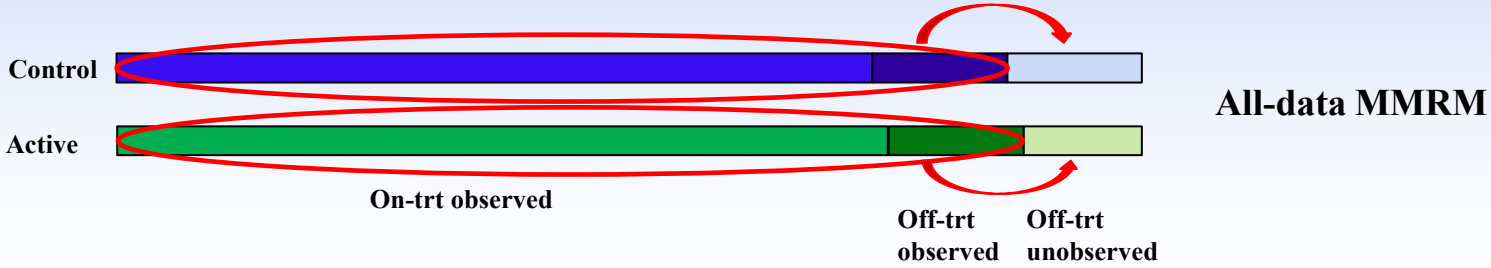
- Observed patients are 'different' to unobserved patients
→ Complex missing data problem

- Analysis must account for patients' trt status to solve missingness issues



# Treatment Policy Estimation

## All-Data MMRM

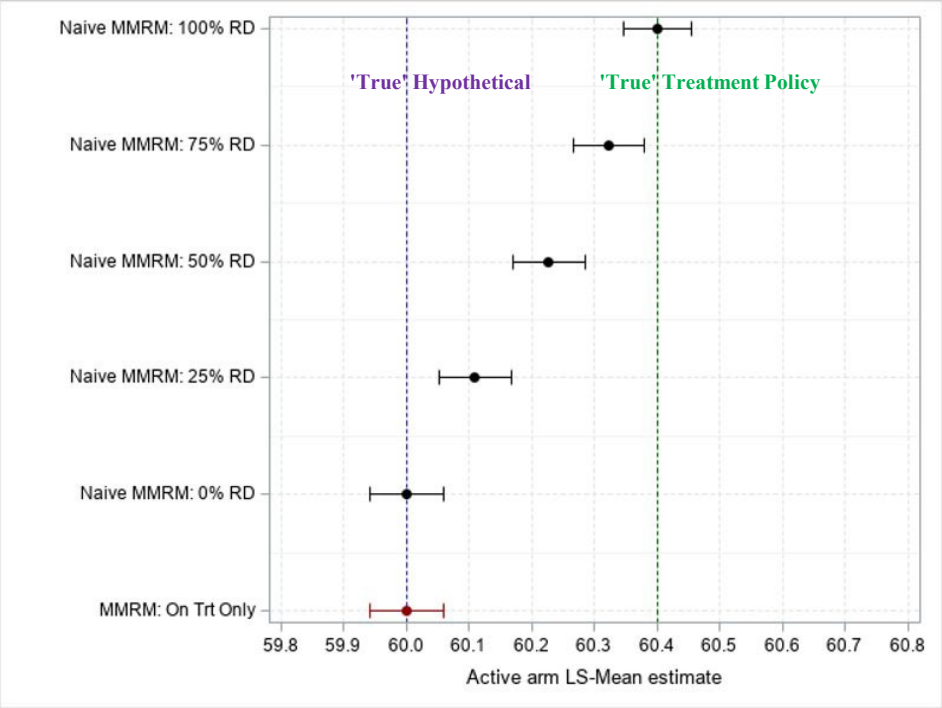



- MMRM on all available data assumes MAR;
  - Unobserved data 'same' as observed data, conditional on modelled variables, responses
  - **Assumes unobserved patients are observed mixture of on- and off-trt**
    - e.g. 90% observed data on-trt → 90% unobserved data on-trt
  - Observed off-treatment measurements are 0% on-treatment
    - **Analysis is inconsistent** w.r.t. observation status

- Without complete data: Ignores treatment status and is biased
  - **→ MMRM not suitable**

# Treatment Policy Estimation

## All-Data MMRM




- Different proportions of retrieved dropout (RD)
- All-data MMRM analysis
- Estimator increasingly biased for treatment policy as RD decreases

# Treatment Policy Estimation

## Control-Based


**Control-Based Approaches**

- Control-based approaches have been used for treatment policy estimation
  - When off-trt, assume zero treatment effects (or zero additional treatment effect over time)

- Advantages:
  - Only requires sufficient control arm data
  - Preserves type I error (in superiority trials)
  - 'Low variance'
- Disadvantage:
  - Assumes, rather than estimates, off-trt effects; can be (very) biased

# Treatment Policy Estimation — Implementations

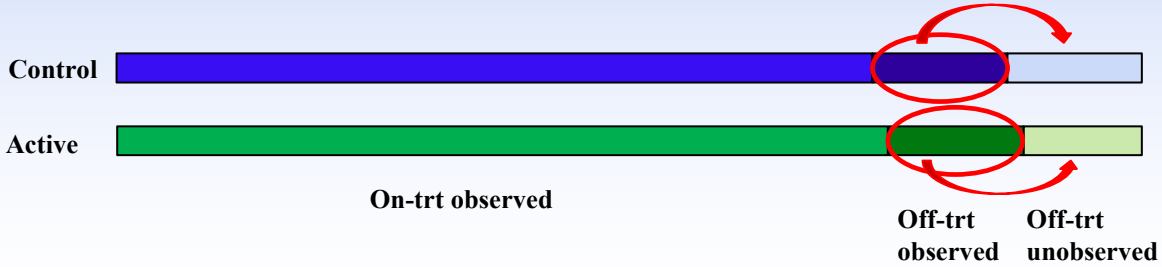
- **Jump to Reference**
  - Active arm patient trajectories 'jump' to control arm upon missingness, follow control distribution
  - Appropriate for short-acting symptomatic treatments
  - MI: Implementable by:
    - 'Five Macros' by James Roger † in SAS
    - rbmi R package, by Gower-Page et al.‡
    - PROC MI based SAS approaches that remove trt effects then impute on residuals
  - Note: there is a debate about what is the correct variance!

- **Copy Increment from Reference**
  - Active arm patient trajectories follow control arm upon missingness
  - Appropriate for disease modifying treatments
  - MI: Implementable by
    - Straightforwardly implementable in PROC MI using MNAR statement
    - 'Five Macros' by James Roger † in SAS

† *https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data*
‡ https://CRAN.R-project.org/package=rbmi

# Treatment Policy Estimation

## Retrieved Dropout




**Off-Trt-Based Approaches**

- Missing off-treatment data modelled using observed off-treatment data
  - Accounts for changing treatments
  - Estimates effect of changing treatments
  - Uses most relevant data to model missingness
  - Handles observed and unobserved data equivalently

- **Approach recommended in principle….**
- But…
  - Requires **strong** off-treatment data collection methods ( > 40% off trt observed at key visit)
  - Trade offs between model complexity and variance/estimability (e.g. time dependence vs independence)
  - Variance inflation realistically unavoidable, potentially serious

# Treatment Policy Estimation — Implementations

- **Time Dependent Retrieved Dropout Approaches**
  - Model aware of all off-trt visit statuses of patients
  - Very vulnerable to sparse off-trt data but appropriate for all types of treatment
  - Requires pre-specified 'step down procedures' for if/when model does not fit

  - MI: Straightforwardly implemented in PROC MI with off-trt indicator variable in model for each visit
    - Avoid simple MI model solely based on off-treatment data (inefficient, unlikely to fit)

- **Time Independent Retrieved Dropout Approaches**
  - Model only aware of 'current' off-trt status of patients
  - More robust to less data, appropriate for short-acting symptomatic treatments
  - Requires pre-specified 'step down procedures' for if model does not fit (usually OK)

  - MI: Implementable in %MISTEP SAS macros by James Roger† (also see Polverejan 2020‡)
  - Direct: implementable in PROC MIXED by 'time-dependent covariate pattern mixture model'
    - See recent EIWG presentation at PSI Conference 2022

† *https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data#dia-missing-data*
‡ Statistics In Biopharmaceutical Research 2020, Vol. 12, No. 2, 142–154

# Treatment Policy Estimation Summary

- Treatment policy analysis of longitudinal COAs is not straightforward
- MMRM is increasingly biased for it with increasing ICEs and missingness
- Reference-based approaches will provide precise estimates
  - But they often amount to ‘guessing’ what happens after an ICE; often quite biased
- Retrieved-dropout approaches provide relatively unbiased estimates
  - Can inflate variance or not fit at all if not enough observed post-ICE data
- Please try to collect all COA data possible after patients prematurely stop treatment!
- Treatment Policy estimation field is an underdeveloped but very active area of research
  - Stay tuned!

# Acknowledgements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Thank you for your attention!