IMPERIAL

ICTU
Imperial Clinical Trials Unit

Estimation for treatment policy strategies with missing data:

Introducing retrieved dropout reference-base centred multiple imputation

Suzie Cro
10th June 2025
s.cro@imperial.ac.uk
@suziecro.bsky.social

Outline

1 Motivating example: antidepressant trial

2 Estimation options for treatment policy strategies with missing data

3 A new option: Retrieved dropout reference-base centred multiple imputation

4 Bias and Root Mean Square Error exploration

5 Analysis of antidepressant trial

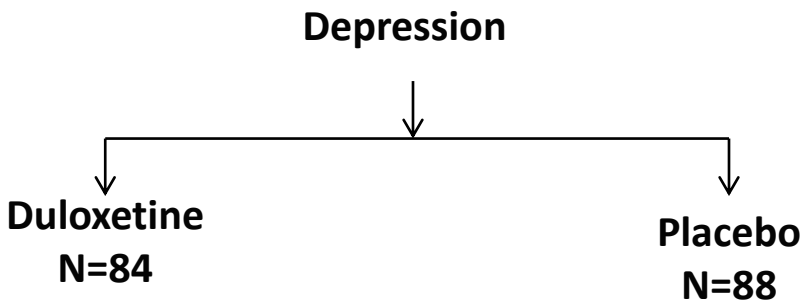
Acknowledgements - James[2]

- James Roger
- James Carpenter, LSHTM, MRC CTU @ UCL

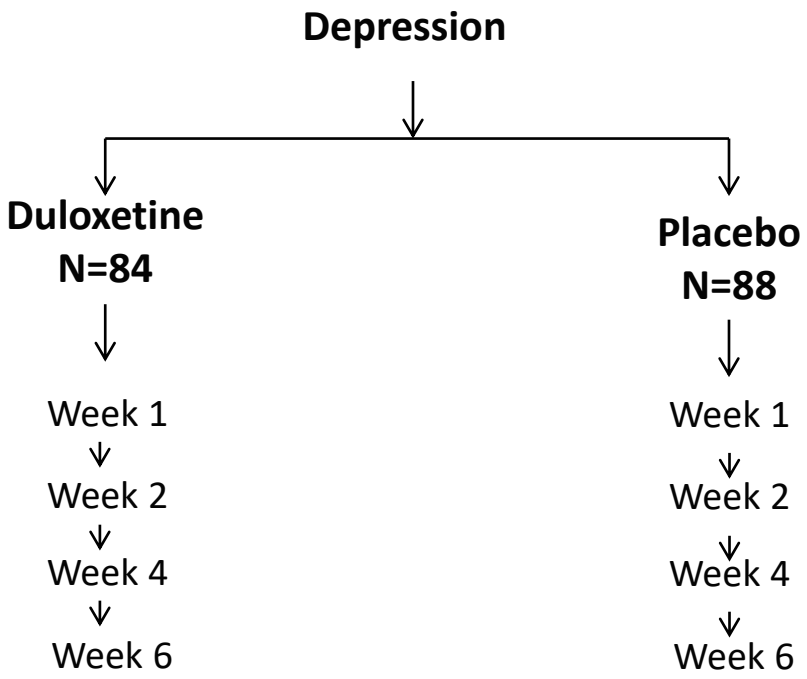
Suzie Cro was funded by an NIHR advanced fellowship (NIHR300593). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

FUNDED BY NIHR | National Institute for Health and Care Research

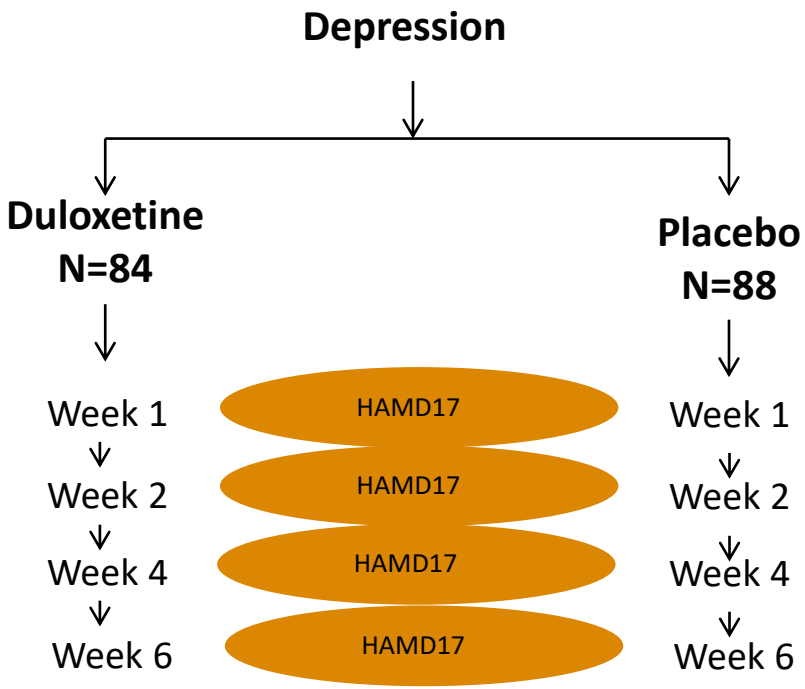
Antidepressant trial



Antidepressant trial



Antidepressant trial



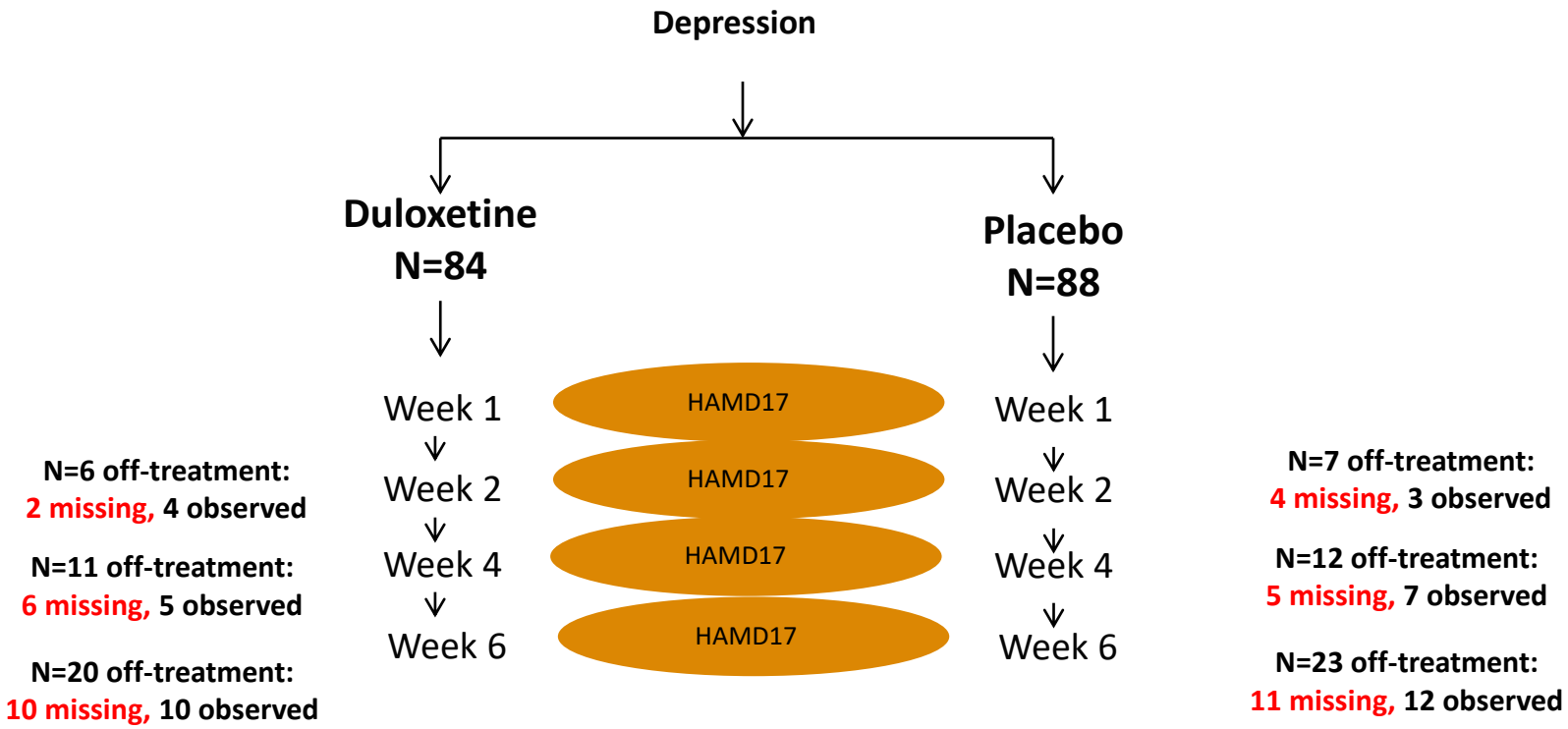
Antidepressant trial - Estimand

The mean difference in change in HAMD17 score at week 6 among the eligible trial population with depression for duloxetine treatment relative to placebo ***regardless*** of whether all treatment was received

Attribute	Description
Population	Patients with depression fulfilling trial eligibility criteria (as fully defined in trial protocol)
Treatment conditions	Duloxetine treatment versus placebo regardless of whether all doses of treatment were received
Endpoint	Change in HAMD17 score at week 6 from baseline
Handling of Intercurrent events	Stopping treatment early - **treatment policy**
Population level summary	Mean difference

Antidepressant trial

Intercurrent event:



Problem: Partial data missing after Intercurrent event

What about standard MAR analysis?

- Consider regression model (or Multiple Imputation) – ignoring whether or not had IE
- Imputing implicitly (or directly) based on mix of off- and on-treatment data with partial missing data after IE
- *Antidepressant example* : imputing missing week 6 HAMD17 data after stopping treatment data in active arm based on the combination of observed data of those on (n=64) and off treatment (n=10).
- Doesn’t fully align with treatment policy strategy - not technically appropriate unless no difference in outcomes after discontinuation versus still assigned to treatment/negligible amount of missing data

Alternative estimation options for treatment policy strategy with missing data

Retrieved Dropout Multiple Imputation – RD MI

- For participants who do/ do not have IE, Impute based on the observed data of those who do/do not have IE only (Wang & Hu 2022)
- Can be viewed as extended MAR Multiple Imputation (conditional on IE)
- Implementable in univariate outcome setting with IE covariate in imputation model or by IE status
- In repeated outcome measures setting various modelling options using sequential regression MI:

- *Simplest:* Incorporate a single indicator variable that denotes IE before end of trial (Polverejan & Dragalin 2019)

- *Most extreme :* Stratify by treatment and index of the last visit on treatment and impute within stratum (Wang 2023)

Retrieved Dropout Multiple Imputation – RD MI

For outcome Y measured at j visits in treatment arm t, where k is the last on-treatment visit:

- Full-pattern RD model: $E[Y_{tj}] = \gamma_{tkj} \; for \; all \; j, k$

  γ_{tkj} is the mean at visit j for the stratum defined by treatment t and last-on-treatment visit k (history)

- Historic RD model:

$$E[Y_{tj}] = \mu_{tj} \; for \; j \leq k$$
$$E[Y_{tj}] = \gamma_{tkj} \; for \; j > k$$

- Current RD model:

$$E[Y_{tj}] = \mu_{tj} \; for \; j \leq k$$
$$E[Y_{tj}] = \alpha_{tj} \; for \; j > k$$

α_{tj} is the mean at visit j for the stratum defined by treatment t and being off treatment at visit k

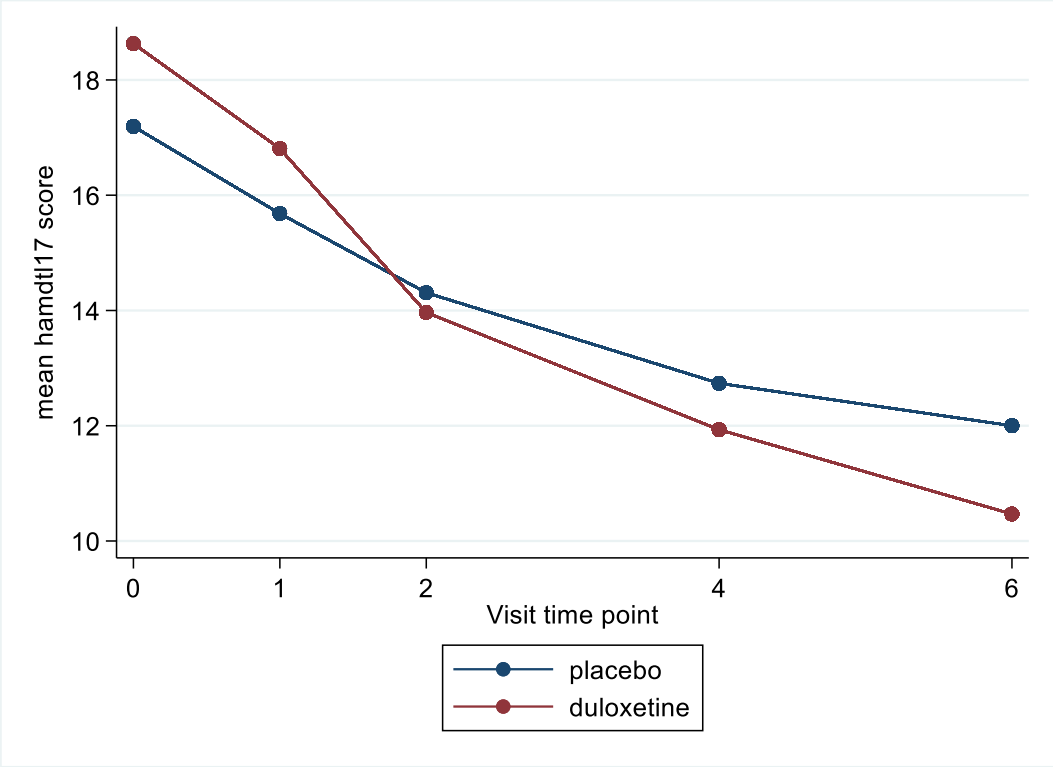
Retrieved Dropout Multiple Imputation – RD MI

- Requires post IE (‘retrieved dropout’) data to perform Multiple Imputation in this manner
- Performs poorly with limited observed off-treatment data
- If minimal post IE data (e.g. <50% observed) large inflation in variance with retrieved drop out MI or imputation model convergence issues or not estimable (Bell et al 2024, Wang and Hu 2022)

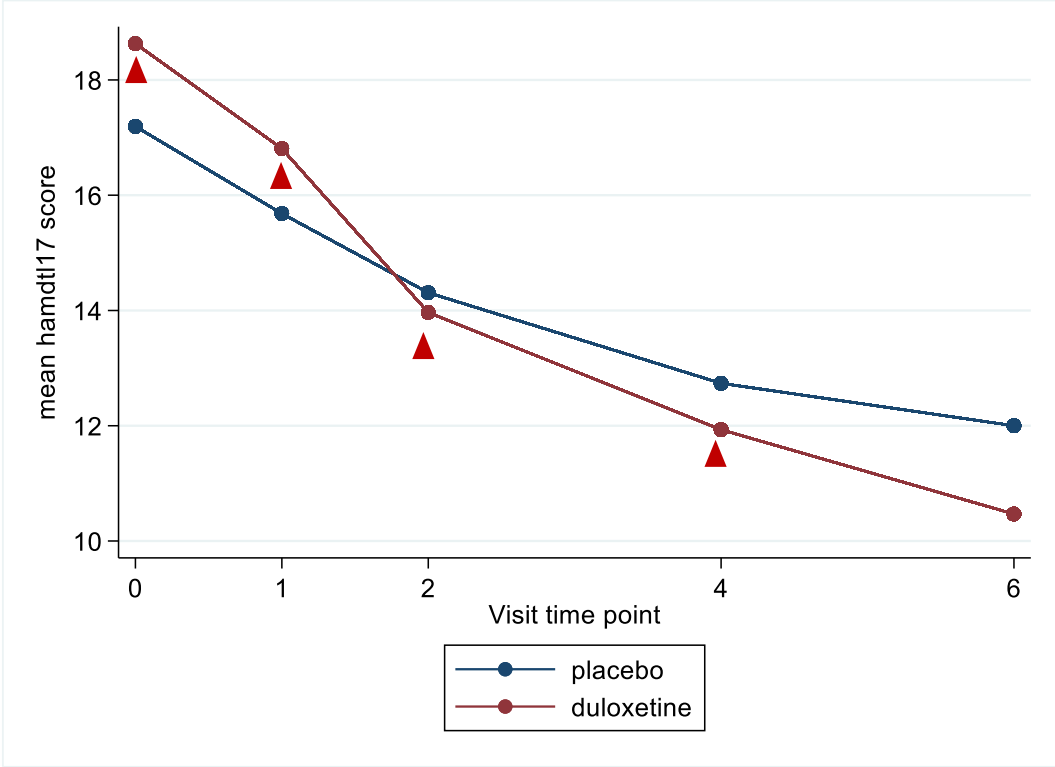
Reference-based Multiple Imputation – RBI

- Combines pattern-mixture modelling with multiple imputation (Carpenter, Roger, Kenward 2013)
- Pattern mixture models explicitly specify the distribution of the unobserved data using parameters from reference arm (e.g. placebo/control)
- Data is imputed several times from this reference-based model
- Analyse each imputed data set using the analysis model of interest and obtain overall treatment effect and estimate of variance using Rubin's rules

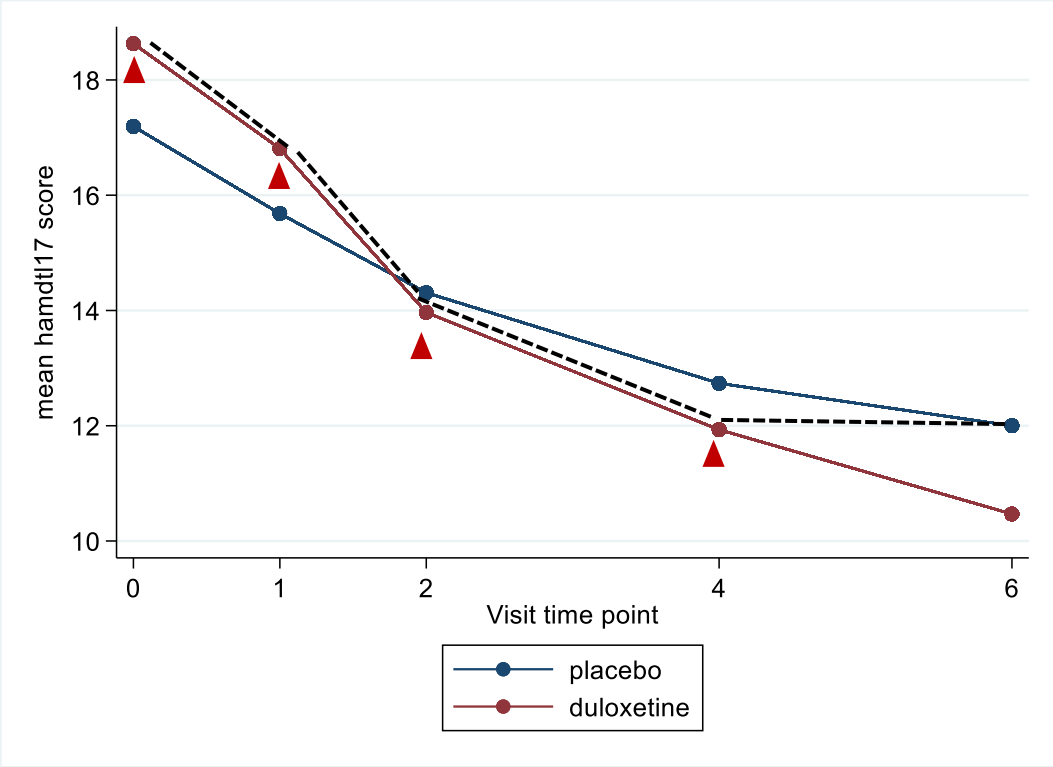
Antidepressant trial



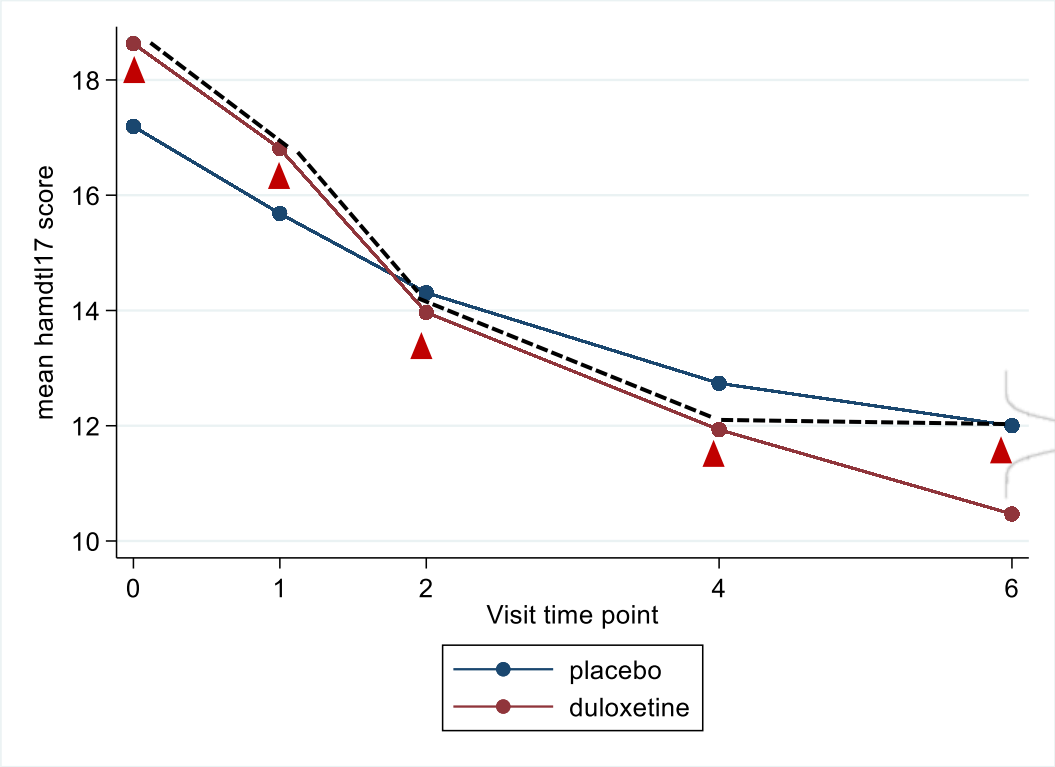
Antidepressant trial



Antidepressant trial: Jump to reference



Antidepressant trial: Jump to reference



Reference-based Multiple Imputation

- Useable with no data observed post treatment withdrawal
- But makes strong assumptions based on data from different arms – does not use observed post–IE data when available
- What if have some post IE data observed – but minimal amounts? i.e. <50%

Bell et al 2024 showed J2R MI useful:

- Impute using reference-based MI excluding post-IE data from dataset
- Merge back in observed off-treatment data

Retrieved Dropout Reference Base Centred MI

RD RBI-C

The concept

- Combines RD MI and RBI to form an extended model for multiple imputation
- Start with a core RBI model, which borrows the distribution of outcomes from a specified reference group (e.g. control/placebo).
- Extend it with additional parameters so that the extended model becomes equivalent to a RD model that uses post-treatment withdrawal data -*if available*
- Fit the extended model using a Bayesian framework with uninformative priors for the core reference-based model parameters and ***mildly informative zero-centred priors for the additional parameters***

Single outcome example

- Two arm trial (reference=0, active=1), single outcome Y_o or Y_1
- $Y_0 \sim N(\mu_0, \sigma^2)$ in reference arm and $Y_1 \sim N(\mu_1, \sigma^2)$ in active arm
- Active arm:
  Proportion p_1 stop treatment early in active arm;
  of which proportion q_1 have missing data
  $p_1 q_1$ are not observed off treatment,
  $p_1(1 - q_1)$ observed off-treatment,
  $(1 - p_1)$ observed on-treatment
- Treatment contrast of interest is:

$$TE = \left[(1 - p_1)\mu_{on,1} + p_1(1 - q_1)\mu_{off,1} + p_1 q_1 \mu_{miss,1}\right] - [\mu_0]$$

Single outcome example

- Two arm trial (reference=0, active=1), single outcome Y_o or Y_1
- $Y_0 \sim N(\mu_0, \sigma^2)$ in reference arm and $Y_1 \sim N(\mu_1, \sigma^2)$ in active arm
- Active arm:
  Proportion p_1 stop treatment early in active arm;
  of which proportion q_1 have missing data
  $p_1 q_1$ are not observed off treatment,
  $p_1(1 - q_1)$ observed off-treatment,
  $(1 - p_1)$ observed on-treatment

Not estimable!

- Treatment contrast of interest is:

$$TE = \left[(1 - p_1)\mu_{on,1} + p_1(1 - q_1)\mu_{off,1} + p_1 q_1 \mu_{miss,1}\right] - [\mu_0]$$

Single outcome example

reference=0, active=1

- Simple **RD** model sets to own arm off treatment mean: $\mu_{miss,1} = \mu_{off,1}$
  - As long as $n_{off,1} > 0$ and $n_{miss,1} > 0$ we can estimate this

- **RBI J2R** model does not require $n_{off,1} > 0$ and uses mean from reference arm $\mu_{miss,1} = \mu_0$

- **RD RBI-C** sets: $\mu_{miss,1} = \mu_{off,1} = \mu_0 + \gamma_1$ where $\gamma_1 \sim N(0, \sigma^2)$
  - when $\gamma_1 = 0$ this is equivalent to the J2R model
    - when $n_{off,1} = 0$ then γ_1 cannot be estimated.
    - BUT – using MI and a mildy informative prior for γ_1, then $\mu_{miss,1}$ can be estimated.

General algorithm for RD RBI-C

1. Choose a core RBI model (e.g. J2R) and a RD model (e.g. historic)
2. Parameterise an extended model as core RBI model plus additional parameters representing difference between RBI and RD model
3. Fit (2) in a Bayesian framework using uninformative priors for core model and mildly informative zero-centred priors for the additional parameters
4. Draw parameters and predict missing data based on patients' conditional distribution of post-deviation data given their pre-deviation data
5. Repeat (4) K times → K data sets
6. Fit model of interest to each K data set
7. Use Rubin's rules for final inference

Implementable in SAS using BGLIMM procedure
(steps4 + 5 combined in 1 step)

Choosing the prior

- Variance chosen for the zero-centred prior for the additional deviation parameters will impact results

- Three proposed options:

1. Expert elicitation on how far they expect the underlying compliance model might diverge from the chosen core model
2. Express prior in terms of effective no. of patients being added into the data to estimate the additional parameters e.g. 1 or 2 patients - residual variance of outcome at final visit from MMRM (~1 extra patient-visit worth of info)
3. Use simulation to quantify impact/selection of priors

Analytical examination of Bias + RMSE - methods

- Single outcome, 2 arm trial, 100 patients per arm, treatment withdrawal now in *both* arms:
  - 40% deviation active + 20% deviation reference arm – of which 50% missing

- Methods: RD RBI-C multiple imputation using J2R as core model & RD model based on own arms off-treatment mean:

$$\mu_{miss,0} = \mu_{off,0} = \mu_{on,0} + \gamma_0 \quad \text{and} \quad \mu_{miss,1} = \mu_{off,1} = \mu_{on,0} + \gamma_1$$

- Expected bias and RMSE analytically calculated (Cro, Carpenter, Roger 2024) for different values of the prior variance for the additional parameters:

$\gamma_0 \sim N(0, \sigma^2)$ and $\gamma_1 \sim N(0, \sigma^2)$

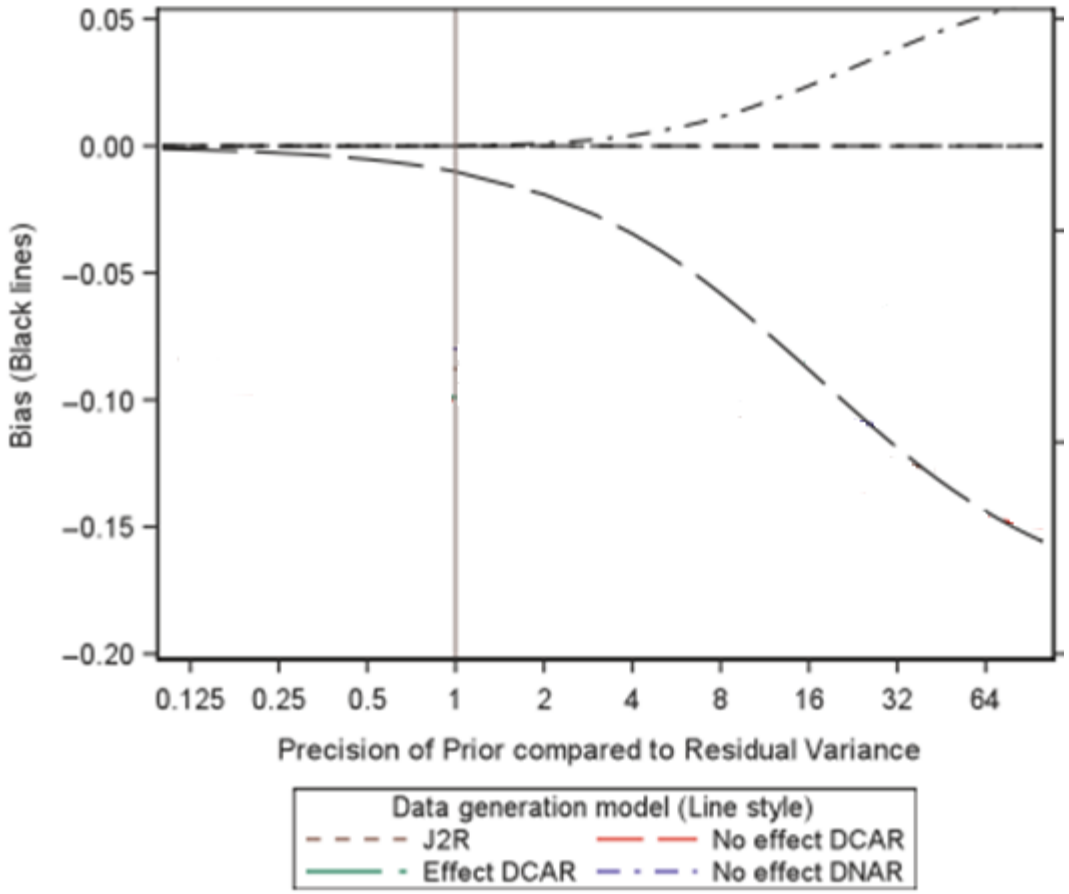
- Prior variance set to residual variance from a MMRM (~1 person, =1), then varied from: 0.125*residual variance up to 64*residual variance

Analytical examination of Bias + RMSE - methods

- Explored for 4 data generation models based on different values of $\mu_{off,0}, \mu_{on,0}, \mu_{off,1}, \mu_{on,1}, \gamma_0, \gamma_1$
  - No effect DCAR $[\mu_{off,0} = \mu_{on,0} = \mu_{off,1} = \mu_{on,1} = 1 \ and \ \gamma_0 = \gamma_1 = 0]$
  - J2R $[\mu_{off,0} = \mu_{on,0} = \mu_{off,1} = 1 \ and \ \mu_{on,1} = 2 \ and \ \gamma_0 = \gamma_1 = 0]$
  - Effect DCAR $[\mu_{off,0} = \mu_{on,0} = 1, \ \mu_{off,1} = \mu_{on,1} = 2 \ and \ \gamma_0 = \gamma_1 = -1]$
  - No effect DNAR $[\mu_{off,0} = \mu_{off,1} = 1, \mu_{on,0} = \mu_{on,1} = 2 \ and \ \gamma_0 = \gamma_1 = -1]$

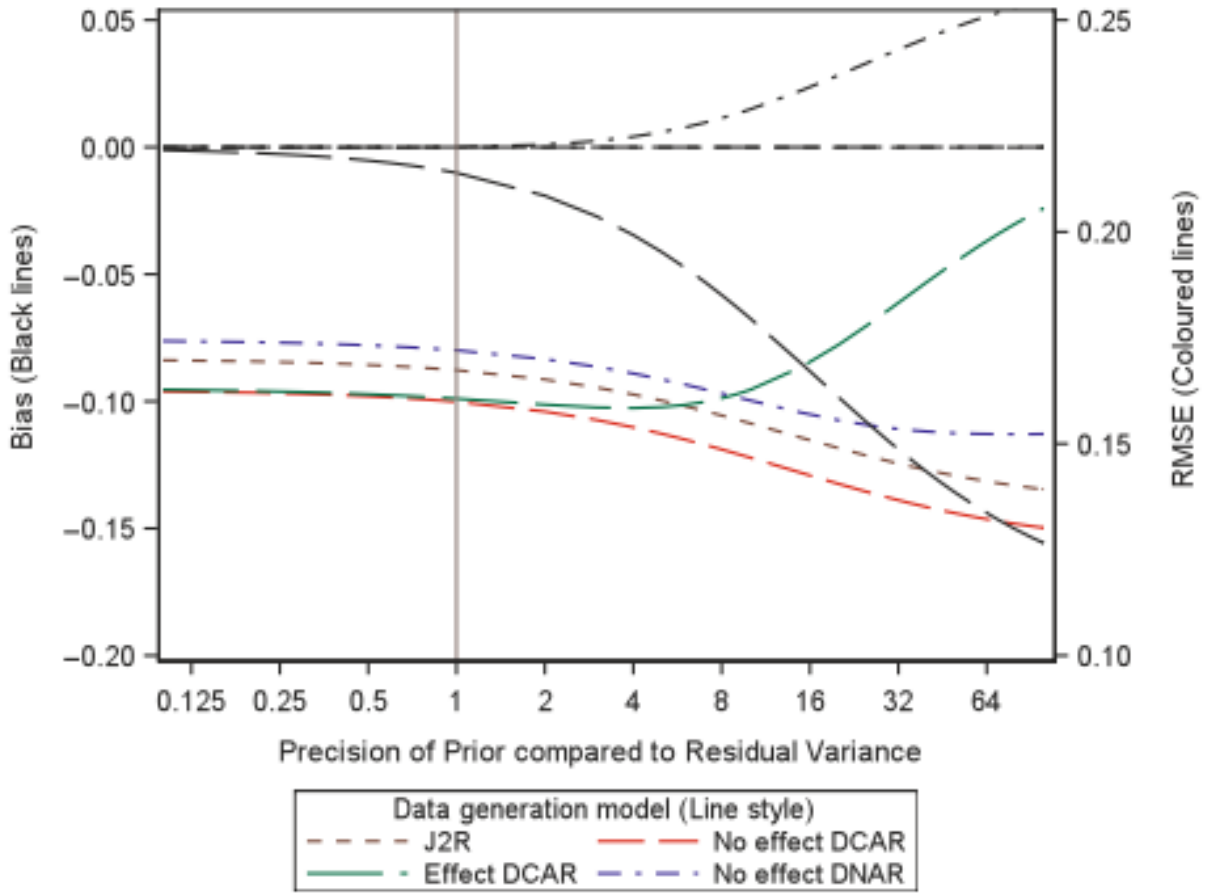
Bias + MCSE - results

40% deviation active, 20% deviation placebo – of which 50% missing



Bias + MCSE - results

40% deviation active, 20% deviation placebo – of which 50% missing



- With larger missingness prior has greater impact on bias for No effect DNAR + Effect DCAR and RMSE
- With smaller deviation the impact of prior lower

Prior using residual variance (=1) performs okay

Application – Antidepressant trial

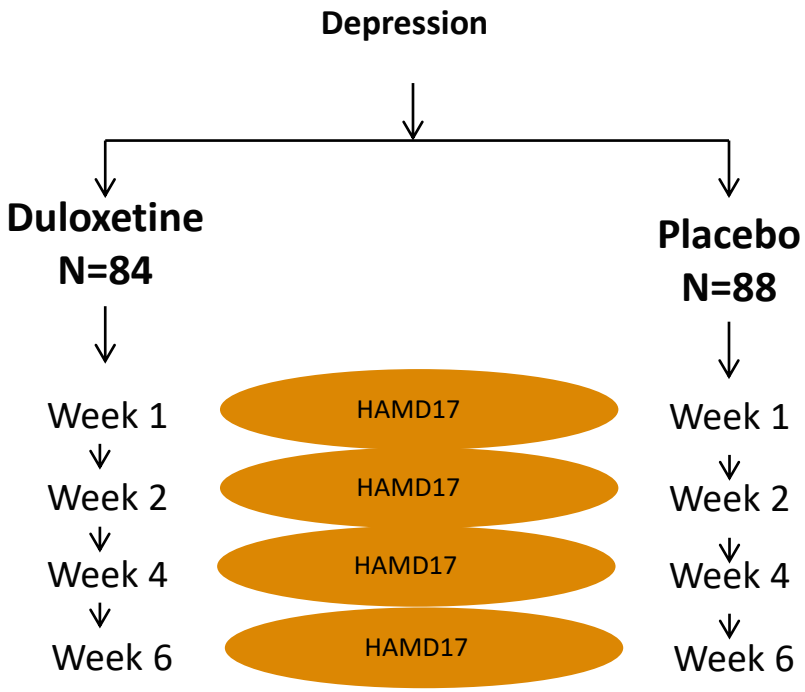
- Completion rates (on-treatment) were 76% (64/84) for active and 74% (65/88) for placebo

- On-treatment data are fully observed

- Apply RD RBI-C where observed off treatment data simulated to be:
  (1) “covered” - all parameters in RD model estimable
  (2) “perforated” - difficulties in fitting RD models

“Covered” – adequate data observed off-treatment data for RD model

Intercurrent event:



N=6 off-treatment:
2 missing, 4 observed

N=11 off-treatment:
6 missing, 5 observed

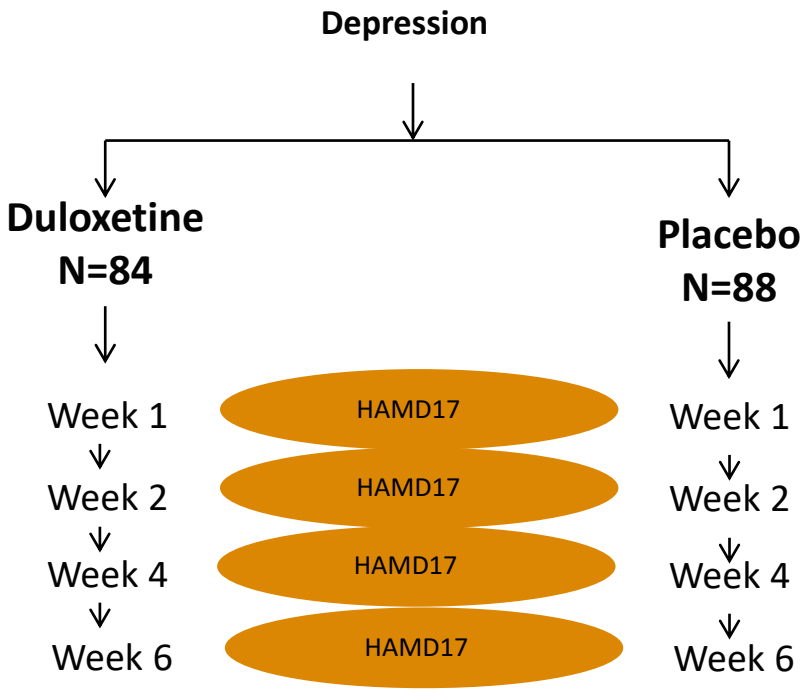
N=20 off-treatment:
10 missing, 10 observed

N=7 off-treatment:
4 missing, 3 observed

N=12 off-treatment:
5 missing, 7 observed

N=23 off-treatment:
11 missing, 12 observed

“Perforated” - Observed off-treatment data limited, do not allow for RD model



Intercurrent event:

N=6 off-treatment:
6 missing, 0 observed

N=11 off-treatment:
7 missing, 4 observed

N=20 off-treatment:
10 missing, 10 observed

N=7 off-treatment:
2 missing, 5 observed

N=12 off-treatment:
3 missing, 9 observed

N=23 off-treatment:
11 missing, 12 observed

Application – Antidepression trial

- Apply J2R RBI, RD MI and RD RBI-C using
  - J2R as core model
  - (a) historic (more parameters) and (b) current as RD models

- Varied prior variance for additional γ^* parameters:
  40 (residual variance of outcome from final visit from MMRM)
  1, 10, 160 and 1000 for comparison

- 10,000 imputations used leading to ~MCSE of 0.002

- Analysis model = ANCOVA based on change in HAMD17 at visit 6 with randomised treatment and baseline as covariates

Results of Application – “covered”

Method	Covered			
	Mean	SE	Mean	SE
RBI - J2R only	2.18	1.13		
RBI - J2R + observed off-treatment data	2.28	1.05		

With adequate data, the data over powers the priors

Results of Application – “covered”

Method	Covered			
	Mean	SE	Mean	SE
RBI - J2R only	2.18	1.13		
RBI - J2R + observed off-treatment data	2.28	1.05		
	Historic		Current	
RD MI	2.32	1.10	2.34	1.07

With adequate data, the data over powers the priors

Results of Application – “covered”

Method	Covered			
	Mean	SE	Mean	SE
RBI - J2R only	2.18	1.13		
RBI - J2R + observed off-treatment data	2.28	1.05		
	Historic		Current	
RD MI	2.32	1.10	2.34	1.07
RD RBI-C – J2R core				
Var=1	2.28	1.05	2.29	1.05
Var=10	2.31	1.06	2.33	1.06
Var=40	2.32	1.08	2.35	1.06
Var=160	2.32	1.09	2.36	1.06
Var=1000	2.32	1.10	2.36	1.06

With adequate data, the data over powers the priors

Results of Application – “covered” & “perforated”

Method	Covered				Perforated			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
RBI - J2R only	2.18	1.13			2.17	1.13		
RBI - J2R + observed off-treatment data	2.28	1.05			2.39	1.05		
	Historic		Current					
RD MI	2.32	1.10	2.34	1.07				
RD RBI-C – J2R core								
Var=1	2.28	1.05	2.29	1.05				
Var=10	2.31	1.06	2.33	1.06				
Var=40	2.32	1.08	2.35	1.06				
Var=160	2.32	1.09	2.36	1.06				
Var=1000	2.32	1.10	2.36	1.06				

With adequate data, the data over powers the priors

Application – “covered” & “perforated

Method	Covered				Perforated			
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
RBI - J2R only	2.18	1.13			2.17	1.13		
RBI - J2R + observed off-treatment data	2.28	1.05			2.39	1.05		
	Historic		Current		Historic		Current	
RD MI	2.32	1.10	2.34	1.07				
RD RBI-C – J2R core								
Var=1	2.28	1.05	2.29	1.05	2.38	1.04	2.42	1.04
Var=10	2.31	1.06	2.33	1.06	2.40	1.08	2.49	1.05
Var=40	2.32	1.08	2.35	1.06	2.41	1.16	2.51	1.05
Var=160	2.32	1.09	2.36	1.06	2.44	1.45	2.52	1.05
Var=1000	2.32	1.10	2.36	1.06	2.63	2.80	2.52	1.05

With adequate data, the data over powers the priors

With more missing data prior enables estimation

Discussion

- **RD RBI–C** offers a new estimation approach, implementable with limited observed off treatment data
- Combines RD MI and RBI to form extended model for imputation
- Current further work: Exploring the methods performance in more complex scenarios with different choices for the prior variance
- Retrieved dropout reference-base centred multiple imputation:

Cro, S., Roger, J. and Carpenter, J. (2024), Handling Partially Observed Trial Data After Treatment Withdrawal: Introducing Retrieved Dropout Reference-Base Centred Multiple Imputation. Pharmaceutical Statistics. https://doi.org/10.1002/pst.2416

References

IMPERIAL

Bell J, Drury T, Mutze T, Pipper CB, Guizzaro L, Mitroiu M, Rantell KR, Wolbers M, Wright D, Estimation methods for estimands using the treatment policy strategy; a simulation study based on the PIONEER 1 Trial, https://arxiv.org/ftp/arxiv/papers/2402/2402.12850.pdf

Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat. 2013;23(6):1352-71. doi: 10.1080/10543406.2013.834911. PMID: 24138436.

Cro S, Morris TP, Kenward MG, Carpenter JR. Sensitivity analysis for clinical trials with missing continuous outcome data using controlled multiple imputation: A practical guide. Statistics in Medicine. 2020. https://doi.org/10.1002/sim.8569

Cro, S., Roger, J. and Carpenter, J. (2024), Handling Partially Observed Trial Data After Treatment Withdrawal: Introducing Retrieved Dropout Reference-Base Centred Multiple Imputation. Pharmaceutical Statistics. https://doi.org/10.1002/pst.2416

Polverejan, E., & Dragalin, V. (2019). Aligning Treatment Policy Estimands and Estimators—A Simulation Study in Alzheimer's Disease. *Statistics in Biopharmaceutical Research*, *12*(2), 142–154. https://doi.org/10.1080/19466315.2019.1689845

Wang, S., Hu, H. Impute the missing data using retrieved dropouts. *BMC Med Res Methodol* **22**, 82 (2022). https://doi.org/10.1186/s12874-022-01509-9

Wang Y, Tu W, Kim Y, et al. Statistical methods for handling missing data to align with treatment policy strategy. *Pharmaceutical Statistics*. 2023; 22(4): 650-670. doi:10.1002/pst.2299

Thank you

Suzie Cro
June 2025
s.cro@imperial.ac.uk
@suziecro.bsky.social