# Pharmaceutical Statistics Journal Club
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## Missing data sensitivity analysis for recurrent event data using controlled imputation

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# Acknowledgements


- James Roger, LSHTM
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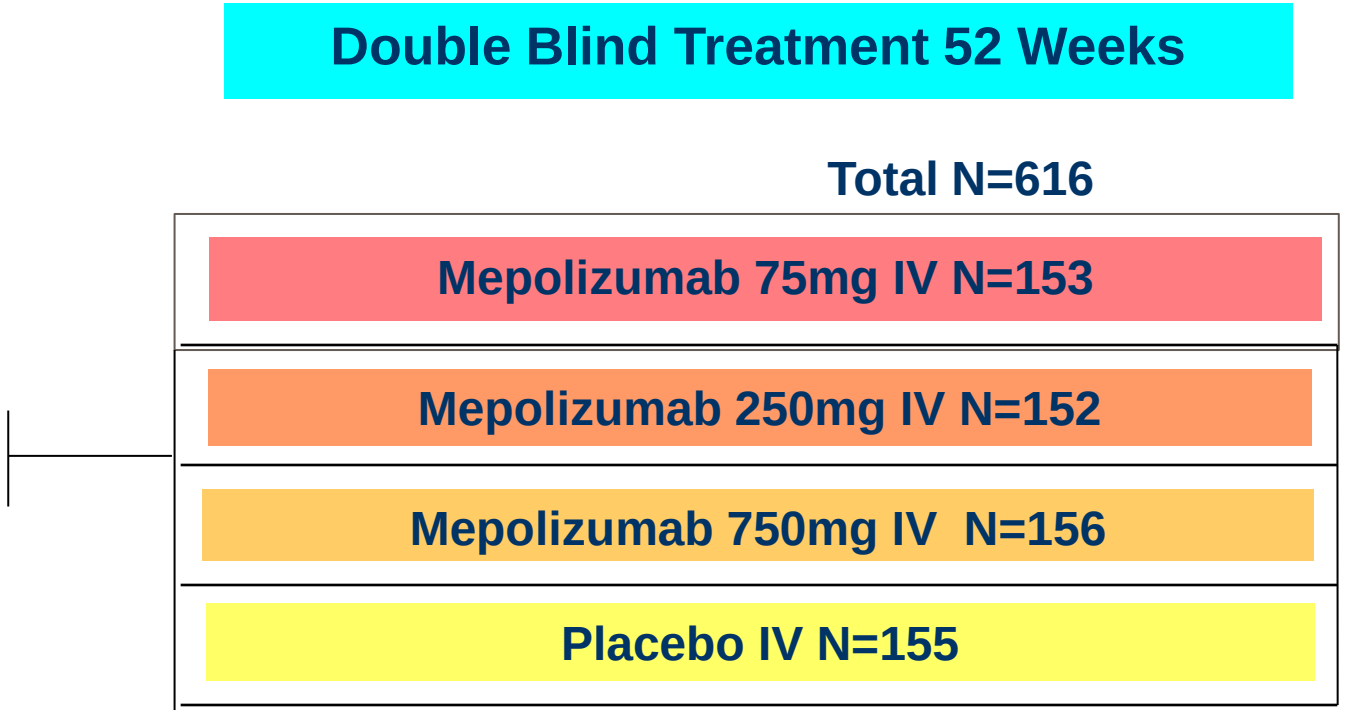
# Outline

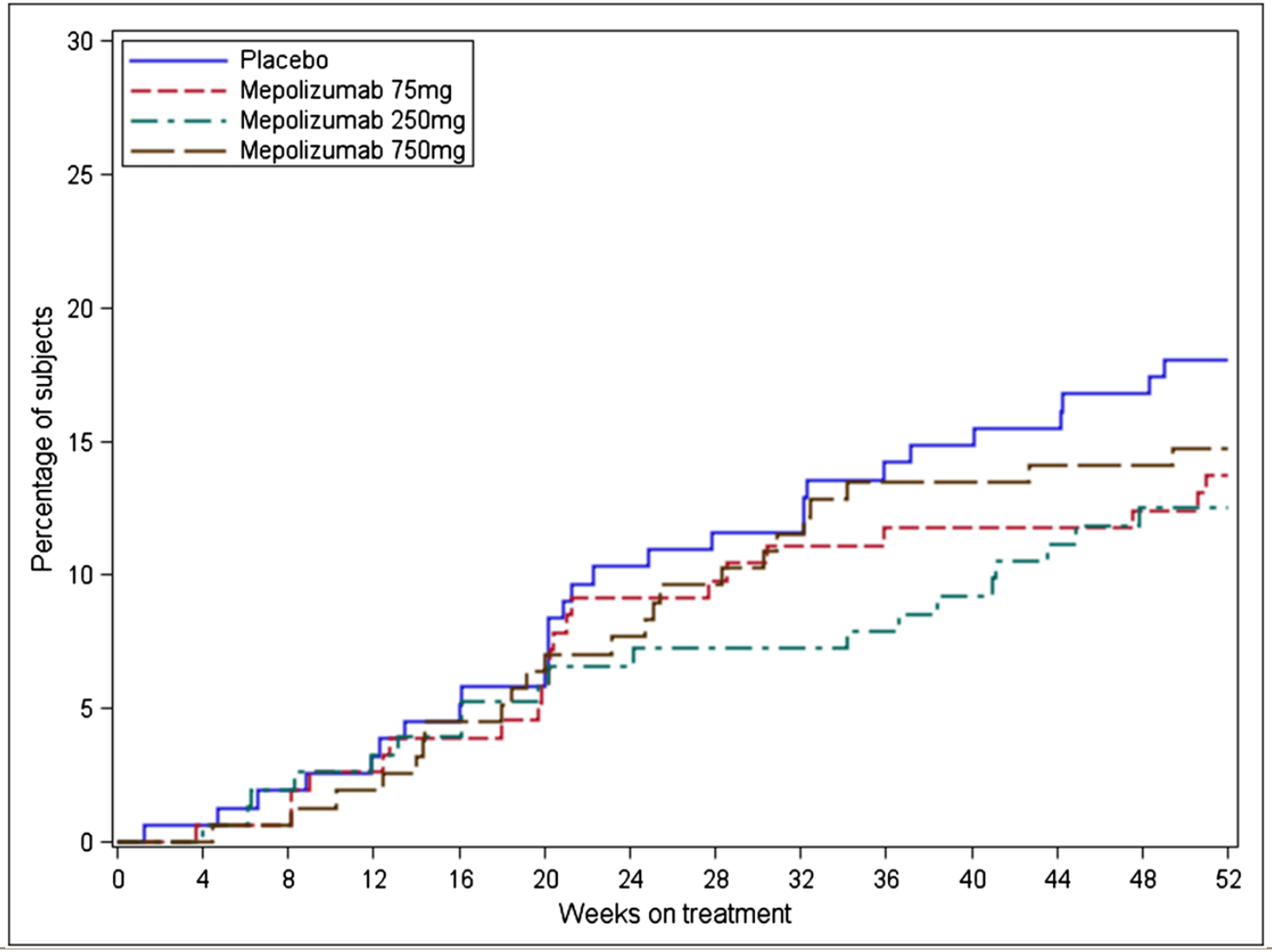
- DREAM trial: mepolizumab for severe uncontrolled eosinophilic asthma
- Analysis of recurrent event data
- De Jure and de Facto estimands
- Application of pattern mixture models to recurrent event data
- Options for modelling post-withdrawal period for discontinuations
- Results for DREAM trial

# DREAM study design




Subjects discontinuing randomised treatment not followed up off treatment

# Withdrawals over time



# Withdrawals

| | Placebo N=155 | 75mg N=153 | 250mg N=152 | 750mg N=156 |
|---|---|---|---|---|
| Withdrawn | 28 (18%) | 24 (16%) | 21 (14%) | 23 (15%) |
| Reason for withdrawal | | | | |
| Withdrew consent | 11 (7%) | 8 (5%) | 2 (1%) | 7 (4%) |
| Adverse event | 6 (4%) | 5 (3%) | 8 (5%) | 9 (6%) |
| Lack of efficacy | 8 (5%) | 6(4%) | 4 (3%) | 4 (3%) |
| Investigator discretion | 1 (<1%) | 3 (2%) | 3 (2%) | 3 (2%) |
| Lost to follow-up | 1 (<1%) | 1 (<1%) | 4 (3%) | 0 |
| Protocol deviation | 1 (<1%) | 1 (<1%) | 0 | 0 |

# DREAM trial: model for primary analysis

- Primary endpoint: frequency of clinically significant asthma exacerbations
- Primary analysis: negative binomial model
- Each person has own Poisson rate of events
  - As a set follow a gamma distribution across patients
- Variation among patients explicitly captured as part of the model
  - No “correction” needed
- Model allow for different lengths of follow-up for each patients
- Generalised linear model, can incorporate baseline covariates

# Estimands: De Jure and De Facto


– De jure (efficacy) estimand: expected treatment effect if treatments were taken as specified in the protocol


– De facto (effectiveness) estimand: difference in outcome improvement for all randomized patients, assesses benefit of a treatment strategy relative to a control

# DREAM trial

- Primary analysis: negative binomial model
  - Missing at random (MAR) assumption
    - conditional on the data observed (including covariates and data prior to withdrawal) unavailable data are randomly missing.
    - Implies future statistical behaviour of outcomes is the same for those who remain in the trial and those who withdraw conditional on their history
    - Addresses a De Jure estimand

- Need for alternative De Facto estimand

# Pattern mixture models

- General framework described in earlier talk by Bohdana Ratitch et al
- Control-based imputation for longitudinal continuous data described by James Carpenter/ James Roger / Mike Kenward in 2013 paper
  - Model post-withdrawal outcome for active (test) to reflect the behaviour of later outcomes on placebo (reference)

- Can this be applied to recurrent event data (exacerbations)?

# Recurrent event trials: early withdrawals


- If a patient has y1 exacerbations during period 1 and then withdraws
- We want to estimate y2, the number of unobserved exacerbations, given what we have actually seen

# Multinomial models (Roger/Kenward)

- Negative binomial is special case of negative multinomial model
- Conditional distribution of the missing values for partially observed negative multinomial data is also negative multinomial
- Missing data can be imputed using the appropriate negative multinomial models
- Numbers of events before and after withdrawal are seen as two periods with a joint negative multinomial distribution, with $Y_1$ observed and $Y_2$ unobserved

# Impute unobserved exacerbations

For a given patient, distribution Y2|Y1 is a function of:

- Observed y1
- Estimated dispersion (assumed same in both periods)
- Estimated mean (model predicted) rate period 1
- Imputed mean rate period 2
  - Options for this described on next slide

Multiple imputation

- Take a random sample from Y2|Y1, add this to the y1 we observed for the patient
- Analyse the data using PROC GENMOD as usual
- Repeat analysis multiple times
- Combine estimates using Rubin's rules

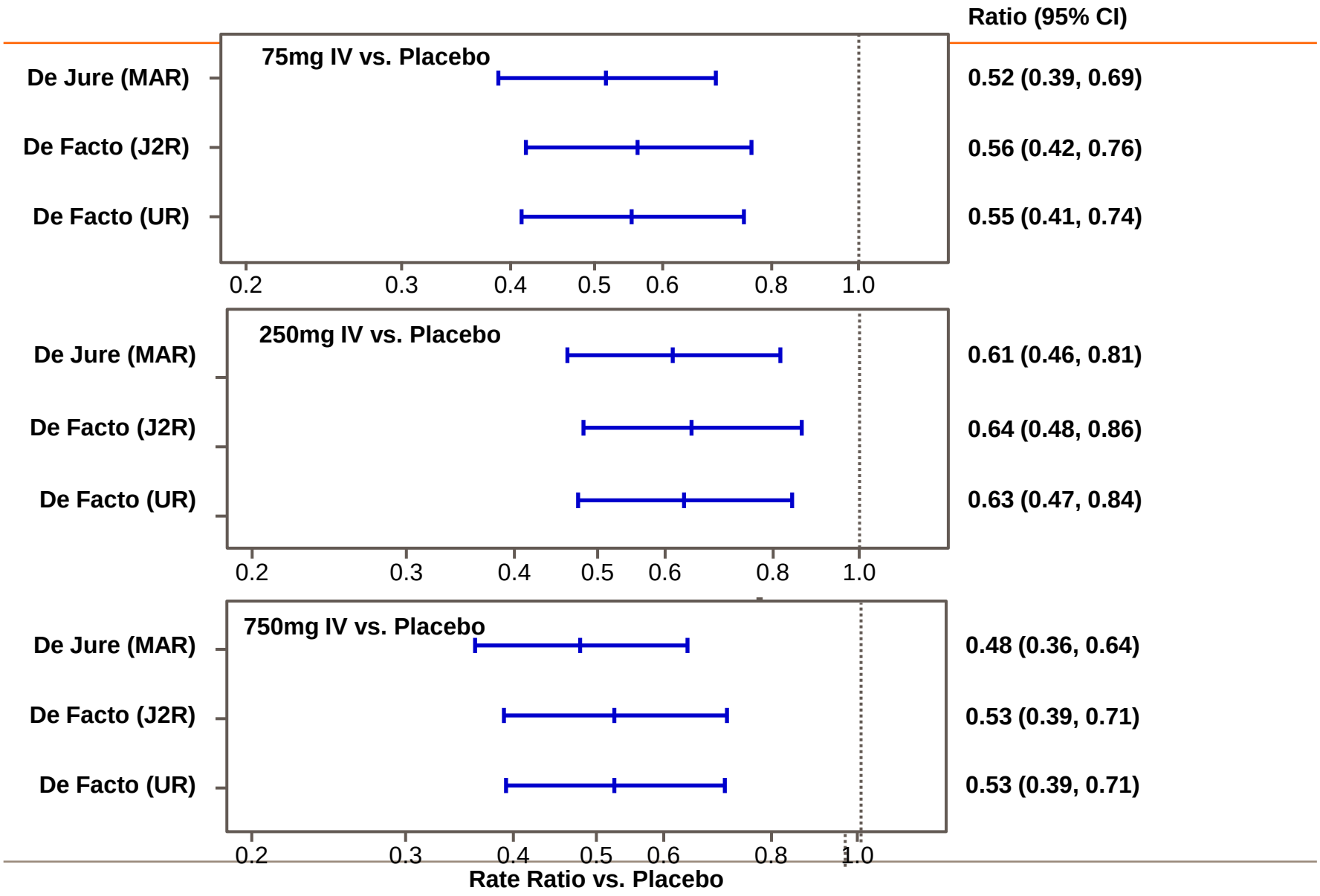
# Imputing patient's expected rate during period 2

Placebo patients imputed under MAR

| Method for Active Treatment | Period 1 | Period 2 | Residual from period 1? |
|---|---|---|---|
| MAR | Active | Active | Yes |
| Copy Reference (CR) | Placebo | Placebo | Yes |
| Jump to Reference (J2R) | Active | Placebo | Yes |
| Unconditional Reference (UR) | Active | Placebo | No |
| Delta methods | Active | Active - Delta | Yes |
| Specific off treatment say κ | Active | Kappa | No |

– Can make imputation method depend on reason for withdrawal

# DREAM: de jure and de facto estimands




MAR = Missing at Random, J2R = Jump to Reference, UR = Unconditional Reference

# Conclusions

- Likelihood analyses produce De Jure estimands under MAR assumption
  - What would happen if patient continued on treatment
- Need De Facto (ITT) estimands
  - Compare results of initial randomisation
  - Requested by regulatory authorities
- One possible approach is to use controlled imputation for recurrent event data

# References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