Treatment policy estimation based on standard and reference-based conditional mean imputation

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A stylized randomized trial of intervention vs. placebo

- **Continuous endpoint** longitudinally assessed at baseline and J follow-up visits (visits 1, …, J)
- **Clinical trial objective:** Effect of the active drug vs control assessed at visit J irrespective of study drug discontinuations (treatment policy strategy)
- **Analysis of complete data:** `outcome[visit J]` ~ trt + <baseline covariates> (ANCOVA)
- **Missing data:** Predominantly in subjects who discontinue study drug and subsequently drop out

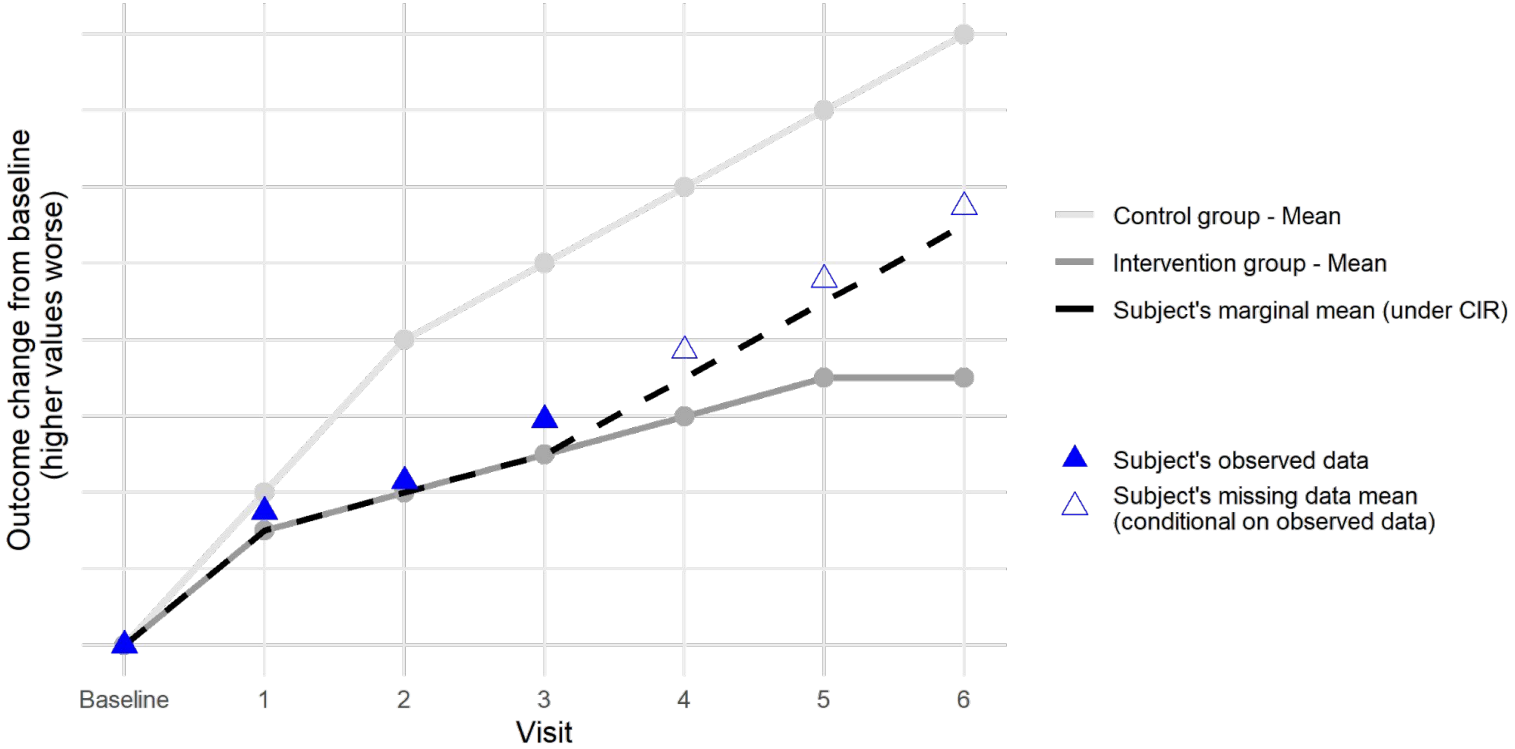
Note: All methods described in this presentation are based on **multivariate normal (MVN) models** for longitudinal outcomes.

Possible missing data assumptions

- **Standard MAR** (missing-at-random)
  - Imputation conditional on the treatment group, baseline variables, and observed outcomes
  - Does not distinguish between on- and off-treatment data
- **Extended MAR**
  - Additionally condition on subject's time-varying on/off-treatment status
  - Only feasible if sufficient off-treatment data is observed
- **Reference-based**
  - Imputation of missing post-discontinuation data in both treatment groups based on the placebo group
  - Several variants exist, e.g. jump-to-reference (JR), copy-reference (CR), and copy-increments-in-reference (CIR)

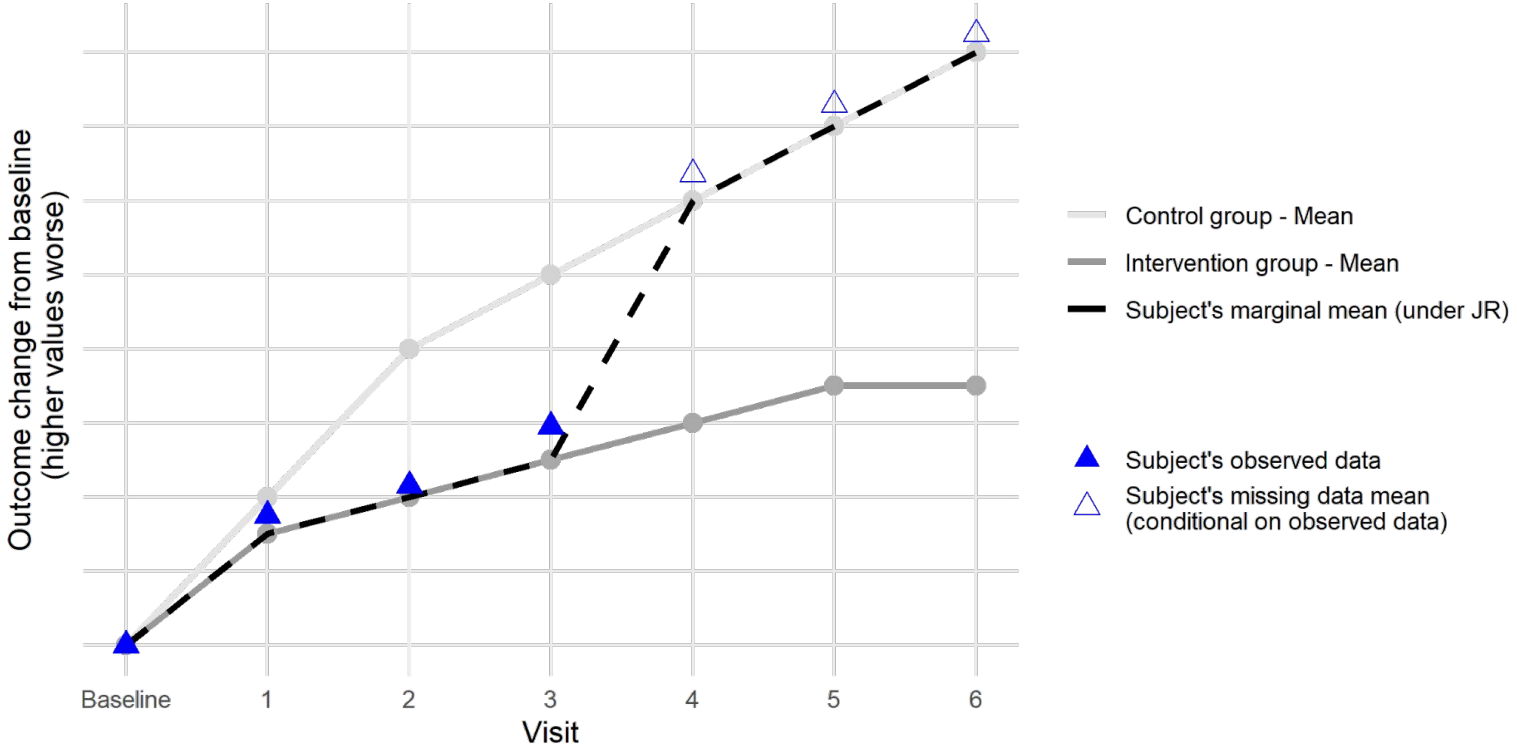
Missing data distribution implied by CIR

For one subject in the intervention group who discontinued treatment after visit 3 with missing afterwards

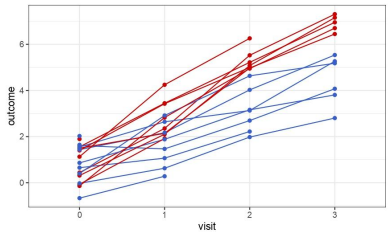


Missing data distribution implied by JR

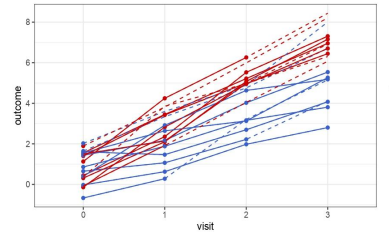
For one subject in the intervention group who discontinued treatment after visit 3 with missing post-ICE data

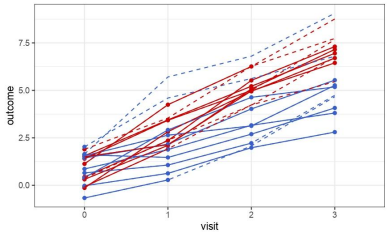


Conventional Bayesian multiple imputation approach



draws(): Fit MVN imputation model using a Bayesian approach





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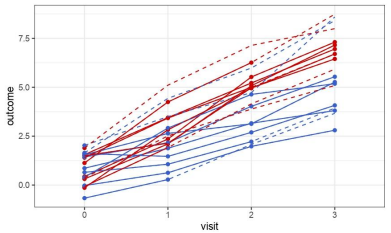


impute(): Use posterior draws of imputation model parameters to create complete datasets consistent with missing data assumptions

analyse(): Analyse completed dataset with ANCOVA

$$\hat{\theta}_1 = q(Y_{obs}, Y_{mis}^{(1)})$$

$$\hat{\theta}_2 = q(Y_{obs}, Y_{mis}^{(2)})$$

o o o

$$\hat{\theta}_M = q(Y_{obs}, Y_{mis}^{(M)})$$

$$\hat{\theta}^*, V(\hat{\theta}^*)$$

pool(): Get treatment effect and variance estimates using Rubin's rules

Conditional mean imputation approach plus jackknife

- **Deviations** from conventional approach
  - Impute based on REML estimates from a **frequentist** MVN imputation model
  - Point estimation based on ANCOVA from a **single conditional mean imputation**
  - Inference based on **jackknife** resampling (computationally intensive)

- **Why deviate** from the conventional approach
  - Comparable point estimates (and SE, for MAR imputation) to conventional approach
  - **Equivalent to REML-based multiple imputation** with an infinite number of random imputation in our setting
  - **Deterministic** point estimates, standard errors, p-values
  - **Frequentist consistent** estimates of the standard error leading to **accurate type I error control** and substantial **power gains** for reference-based methods (see publication for details & simulations)

Equivalence between conditional mean imputation and random imputations for M→∞ and a linear analysis model

- Z_m : **random** imputation of visit J outcome based on the REML estimate of the imputation model
  Z_{CMI} : **conditional mean** imputation

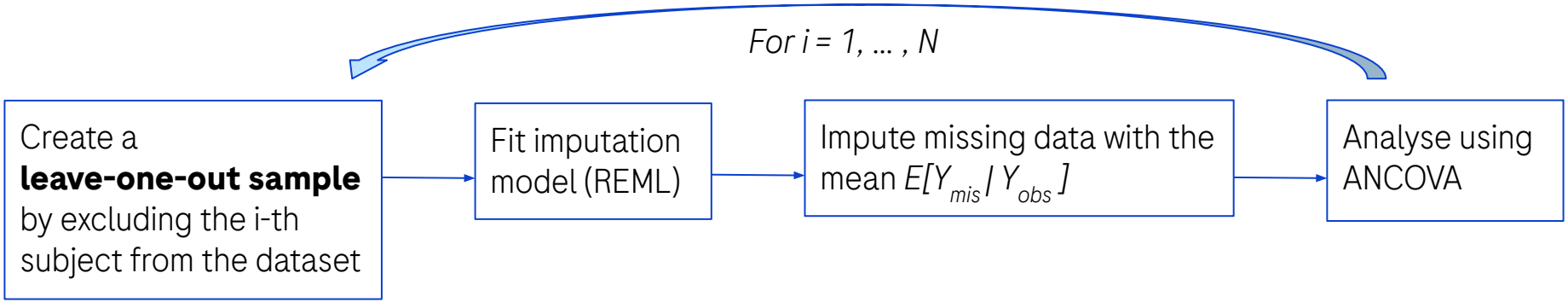
  Then $\sum_{m=1}^{M} \frac{1}{M} Z_m \to Z_{\text{CMI}} \text{ as } M \to \infty (\text{a.s.})$ (law of large numbers)

- $\hat{\beta}_{SI,m}$: treatment effect from ANCOVA analysis of m^{th} imputed dataset
  $\hat{\beta}_{CMI}$: treatment effect from ANCOVA analysis of conditional mean imputation

  Because regression coefficients in linear models are linear transformations of the outcome:

$$\hat{\beta}_{\text{MI},M} = \frac{1}{M}\sum_{m=1}^{M}\hat{\beta}_{\text{SI},m} = \frac{1}{M}\sum_{m=1}^{M}(X^tX)^{-1}X^tZ_m = (X^tX)^{-1}X^t\sum_{m=1}^{M}\frac{1}{M}Z_m \to (X^tX)^{-1}X^tZ_{\text{CMI}} = \hat{\beta}_{\text{CMI}}$$

Jackknife-based inference for conditional mean imputation



→ **Jackknife variance estimator:** $V(\hat{\theta}^*) = (N-1)/N \cdot \sum_i (\hat{\theta}^{(-i)} - \hat{\theta}^{(\cdot)})^2$

$\hat{\theta}^{(-i)}$ = treatment effect estimate from sample without subject *i*; $\hat{\theta}^{(\cdot)}$ = mean of $\hat{\theta}^{(-i)}$

→ Hypothesis testing is based on the **Z-statistics** $\hat{\theta}^* / \sqrt{V(\hat{\theta}^*)}$ using a **normal approximation**

Standard error of treatment effect estimate

- Methods for **variance estimation**
  - Conventional Bayesian multiple imputation ⟶ Rubin's rules
  - Conditional mean imputation ⟶ Jackknife
- **MAR** imputation: both methods provide frequentist consistent SE
- **Reference-based**: imputation and analysis model uncongenial. Consequences:

	Rubin's variance	Jackknife variance
Frequentist consistent (i.e. converges to true repeated sample variance)	No tends to overestimate	Yes
Type I error and power	Conservative	As advertised
Information-anchored (information loss due to missing data under MAR is approximately preserved for reference-based imputation)	Yes	No $Var_{ref-based}(\hat{\theta}) < Var_{MAR}(\hat{\theta})$

Example: Simulation for estimands in early Parkinson's disease

- **Estimand:** Treatment effect irrespective of discontinuation of the study drug but in the absence of the effect of rescue medication. → "Mixed" estimand for the two intercurrent events:

Intercurrent event (ICE)	Strategy
Study treatment discontinuation	Treatment policy
Start of symptomatic treatment	Hypothetical strategy

- **Simulation set-up:** "Realistic" clinical trial simulations motivated by analyses of the observational PPMI cohort study.

- See **Noci et al (2022)** for full details.

Example: Estimators for the “mixed” estimand

Estimator	Specification
MAR	Impute based on baseline characteristics and assigned treatment group.
CIR-Bayes	As for MAR prior to study treatment discontinuation, according to CIR after discontinuation. Use Bayesian Multiple Imputation with Rubin’s rules.
CIR-Cond Mean	As for CIR-Bayes, but use Conditional Mean Imputation + Jackknife.
TV1-MAR	Impute based on baseline characteristics, assigned treatment group, and a time-varying binary post treatment discontinuation indicator. Use multiple imputation.
TV2-MAR	Impute based on baseline characteristics, assigned treatment group, and a time-varying time since treatment discontinuation variable. Use multiple imputation.

Important: Data after the start of symptomatic treatment are considered as missing as they are not compatible with the hypothetical strategy that is defined for this intercurrent event

Example: Results (300 subjects/group; 10`000 simulated trials)

Estimator (implemented using `rbmi`)	Targeted effect ("truth")	Mean estimate	Bias	Mean SE
MAR	-3.60	-3.77	**-0.18**	**0.92**
CIR-Bayes	-3.60	-3.59	**0.01**	**0.91**
CIR-Cond mean	-3.60	-3.60	**0.00**	**0.86**
TV1-MAR	-3.60	-3.68	**-0.08**	0.93
TV2-MAR	-3.60	-3.59	**0.01**	0.94

- **Standard MAR imputation** overestimates the size of the treatment effect.
- **CIR-based estimators** provide consistent TEs for the mixed estimand (in our simulation setting) with smaller SE for conditional mean imputation + jackknife.
- **Extended-MAR imputation** reduces bias compared to standard MAR and does not increase SEs too much.

Software implementation - `rbmi` R package

https://cran.r-project.org/web/packages/rbmi

- **Open-source fully unit-tested R package** for the analysis of longitudinal continuous endpoints (aligned with the estimand) based on imputation of missing data
- **Two input datasets**
  - Dataset with baseline characteristics and longitudinal outcomes
  - ICE dataset: timing of intercurrent events and associated imputation strategies for missing post-ICE data
- **Four core functions**
  - draws() fits the imputation models and stores their parameters
  - impute() creates multiple imputed datasets
  - analyse() analyses each of the multiple imputed datasets
  - pool() combines the analysis results across imputed datasets
- **Vignettes**: Quickstart, advanced functionality, statistical specifications

`rbmi` functionality

- Supported **imputation strategies**
  - Missing-at-random (based on baseline and/or time-varying covariates)
  - Reference-based imputation (impute based on control group)
  - **δ**-adjustment (for sensitivity & tipping point analyses)

- Supported **imputation methods**
  - Conventional Bayesian MI + Rubin's rules
  - Approximate Bayesian MI (based on bootstrapping) + Rubin's rules
  - **Conditional mean imputation** based on (RE)MLE of imputation model + **jackknife** or bootstrap
  - Random imputation based on (RE)MLE of imputation model + bootstrap

- Package **flexibility**: User-defined imputation strategy and analysis function

- Recent update: Internal MMRM fits based on **`mmrm` package**

Conclusions

- Conditional mean imputation + jackknifing provides deterministic & frequentist consistent inference for standard and reference-based missing data assumptions in clinical trials
- The `rbmi` package provides a fully unit-tested open-source implementation of conditional mean imputation and alternative imputation approaches and is well-aligned with the ICH E9(R1) estimands addendum

Associated manuscripts and R package

Marcel Wolbers, Alessandro Noci, Paul Delmar, Craig Gower-Page, Sean Yiu, and Jonathan W. Bartlett (2022), "Standard and Reference-Based Conditional Mean Imputation." *Pharmaceutical Statistics*. https://doi.org/10.1002/pst.2234.

Craig Gower-Page , Alessandro Noci, and Marcel Wolbers (2022), "rbmi: A R package for standard and reference-based multiple imputation methods." *Journal of Open Source Software*. https://doi.org/10.21105/joss.04251
[CRAN-link: https://cran.r-project.org/web/packages/rbmi/]

Alessandro Noci, Marcel Wolbers, Markus Abt, Corine Baayen,Hans Ulrich Burger, Man Jin, Weining Zhao Robieson (2022). "A Comparison of estimand and estimation strategies for clinical trials in early Parkinson's disease." Statistics in Biopharmaceutical Research. https://doi.org/10.1080/19466315.2022.2116476,

Thank you very much for your attention. Any questions?