Imputation strategies within the estimand framework to evaluate patient improvement in longitudinal trails

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Background

- PatiePatient-reported endpoints can be evaluated by comparing proportions of patients achieving a meaningful change threshold (MCT) across arms.
- Advances in missing data approaches have highlighted the need to better define trial estimands [1, 2]
- Estimands are what is being estimated and encompass four components:
  1. Research objective
  2. Target population
  3. Analytical approach
  4. Handling of post-randomization events (e.g., protocol deviations, and missing data)
- Most estimands fall into two broad categories
  - Efficacy estimands (de jure) quantify benefits of treatment taken as planned
  - Effectiveness estimands (de facto) quantify the treatment as actually taken
- When a patient drops out or deviates from the treatment protocol, responder status becomes unclear
- Accounting for such situations depends on the estimand(s)

Objective

We defined estimands for responder analysis of patient-reported outcomes (PROs) and demonstrated the use of missing-at-random (MAR) and missing-not-at-random (MNAR) imputation methods considering protocol adherence and dropout by evaluating bias relative to the true value

- Here, the de jure estimand is difference in proportions where all subjects adhered to the protocol
- Here, the de facto estimand is the difference in proportions from a combination of subjects who adhered and who did not adhere

Methods

Simulation

- 6 scenarios to represented different patterns of adherence and dropout in a randomized trial with two arms, N=200

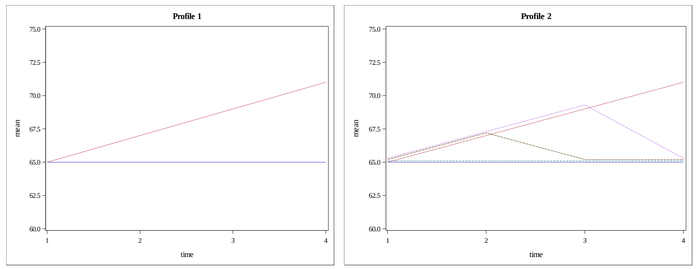
Data Generating Model

Let Y_{ij} represent a continuous PRO measure, range [1, 100] for the i^{th} subject at the j^{th} time where $j = 1, \dots, 4$:

$$Y_{ij} = (\beta_0 + b_i) + \beta_j + \delta_j * x_{trt} + \epsilon_{ij}$$

- β_j: the effect of the j^{th} timepoint,
- $\delta_j * x_{trt}$: interaction of treatment and time,
- $x_{trt} = 1$ for the treatment arm and $x_{trt} = 0$ for the control arm
- $b_i \sim N(0, \sigma_b^2)$: random subject effect
- $\sigma_b = 12$ and $\sigma_\epsilon = 7$

Response profiles



Linear response profile (1)

- The true values for the de jure estimand

Patterned response profile (2)

- Included an indicator of adherence: $AD_{ij} = 1$ for adherers, 0 otherwise
- At the time of non-adherence and after, subject responses came from the control group mean vector
- Response patterns did not change in the control arm
- The true values for the de facto estimand

Creating Missingness

Dropout model 1 (MAR): the probability of missing was dependent on Y_{j-1}

Dropout model 2 (MAR): same as above but with differential attrition

Dropout model 3 (MNAR): Y_{ij} and subsequent responses to missing when $AD_{ij} = 0$

Imputing Missing

1. Non-response imputation (NRI), missing imputed as non-responders
2. Standard multiple imputation (MI) with fully conditional specification
3. Control-based MI (CMI), within a pattern mixture model (PMM) framework, estimated missing Y_j from the control arm distribution of responses

Table 1 Simulation Results

	Response profile	Non-adherence	Dropout	Method	% Responders Trt	% Responders Ctl	Difference (95% CI)	% Bias
1	**Linear**	**0%**	-		**34.2**	**15.5**	**18.7 (7.0, 30.3)**	-
2	Linear	0%	Dependent on Y_{j-1}	MI	34.2	15.6	18.6 (7.0, 30.3)	-0.3
				CMI	30.9	15.7	15.2 (3.8, 26.7)	-18.6
				NRI	26.9	11.8	15.1 (4.4, 25.8)	-19.0
3	Linear	0%	Dependent on Y_{j-1} and Tx	MI	34.3	16.1	18.2 (6.5, 29.9)	-2.5
				CMI	31.1	16.5	14.6 (3.0, 26.1)	-22.0
				NRI	26.9	6.7	20.2 (10.3, 30.1)	8.1
4	**Patterned**	**Equal across arms**	-		**28.8**	**15.6**	**13.2 (1.9, 24.5)**	-
5	Patterned	Equal across arms	Dependent on AD	MI	34.3	15.7	18.6 (6.9, 30.2)	41.2
				CMI	29.4	15.9	13.5 (2.1, 24.9)	2.5
				NRI	24.4	11.1	13.3 (3.0, 23.7)	1.1
6	**Patterned**	**Differential across arms**	-		**30.4**	**15.5**	**14.9 (3.5, 26.3)**	-
7	Patterned	Differential across arms	Dependent on AD	MI	34.3	15.9	18.5 (6.8, 30.1)	23.9
				CMI	30.9	16.1	14.8 (3.3, 26.3)	-0.8
				NRI	27.2	8.9	18.3 (8.0, 28.6)	23.0

Results

NRI estimated under- and over-estimated the difference in responder proportions

MI estimated

- Proportions of responders in the treatment arm was 34.2 – 34.3%
- Proportions of responders in the control arm was 15.6 – 16.1%
- The difference in proportions was 18.2 – 18.6%

CMI estimated

- Proportions of responders in the treatment arm was 29.4 – 31.1%
- Proportions of responders in the control arm was 15.7 – 16.5%
- The difference in proportions was 13.5 – 15.2%

Conclusions

MI best estimated the true difference in proportions when subjects adhere to the protocol, making it a good choice to evaluate the de jure estimand

CMI best estimated the true difference in proportions when subjects were both adherers and non-adherers, making it a good choice to characterize the de facto estimand

References

1. Panel on Handling Missing Data in Clinical Trials, Committee on National Statistics Division of Behavioral and Social Sciences and Education. *The Prevention and Treatment of Missing Data in Clinical Trials Panel on Handling Missing Data in Clinical Trials ; National Research .*; 2010.
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