MSR86

Ensuring Patient Inclusion When Baseline Is Missing: Utilizing Constrained Longitudinal Data Analysis (cLDA) for Patient-Reported Outcomes (PROs)

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OBJECTIVE

Our aim was to compare and assess the performance of two methods; change from baseline (CfB) mixed-model for repeated measures (MMRM) and cLDA linear model for the estimation of treatment effect on PROs using longitudinal data in the presence of missing baseline data.

CONCLUSIONS

Using a cLDA model allows for all patients who provided PRO at any time in the study to be included in the analysis, aligning more closely with the intent-to-treat principle.

cLDA models use the raw PRO scores, following recommendations from the FDA and SISAQOL (1, 2), and are more efficient as they allow both PRO scores and CfB to be estimated from one model.

cLDA models improve the precision of the treatment effect estimates compared to MMRM. The difference in performance between the two model approaches will depend on the study and the amount and reasons for missing data.

AbbVie and the authors thank the participants, study sites, and investigators who participated in the clinical trial that provided the data for the simulations used in this analysis.

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.

Financial arrangements of the authors with companies whose products may be related to the present report are listed as declared by the authors: EM and RL are employees of Adelphi Values. AK is a former contractor of AbbVie, currently employed by GSK. IN is a former employee of AbbVie, and may hold AbbVie stock. RK, RS, YX, and SJ are employees of AbbVie, Inc. and may hold stock or options.

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INTRODUCTION

- Longitudinal analysis of PRO data in oncology clinical trials is commonly used to assess patient-reported quality of life (QoL), functioning, and disease symptoms. CfB over time in PROs is a critical endpoint in oncology clinical trials to assess how treatment has impacted QoL and symptoms. Our aim was to compare two methods for the estimation of treatment effect on PROs using longitudinal data in the presence of missing baseline data—CfB MMRM and cLDA linear models.

CfB MMRM versus cLDA LINEAR MODEL

- Linear mixed-models (eg, MMRMs) are recommended by the FDA, SISAQoL, and others for the analysis of longitudinal data (1,2,3). Traditional CfB MMRMs are often used for evaluating the magnitude of change over time. We compared the following two linear mixed-modelling approaches:

	CfB MMRM		cLDA Linear Model	
	• Uses patients' CfB score at each postbaseline visit over time to account for correlated measurements within patients, while adjusting for patient's baseline PRO response • MMRMs only include patients who have a CfB score. This leads to the exclusion of all patients lacking a valid baseline measurement		• Models patients' PRO scores including the baseline measurements as part of the outcome vector • Enables the inclusion of patients with missing baseline, or no postbaseline data • The treatment effect at baseline is constrained to be zero to respect randomisation	
	[Visit 1 – Baseline Visit 2 – Baseline Visit 3 – Baseline]		[Baseline Visit 1 Visit 2 Visit 3]	
Patient 1	[77 – 80 = −3 75 – 80 = −5 73 – 80 = −7]	✓ patient included	[80 77 75 73]	✓ patient included
Patient 2	[76 – missing = n/c 73 – missing = n/c 74 – missing = n/c]	✗ patient excluded	[missing 76 73 74]	✓ patient included

RESULTS

- With no baseline missingness, estimates of treatment effect from the cLDA and CfB MMRM models were equivalent. The estimated overall mean treatment difference and 95% CI was 3.6 (95% CI [−2.2, 9.4]) for both models, which favours the treatment arm over the control arm. The LSMeans estimates from the cLDA model over time were consistently slightly higher for both treatment groups when compared with the traditional MMRM.
- In the presence of missing baseline data, using a cLDA model allows all patients with any postbaseline data to now be included, resulting in more patients in the analysis (Figure 1). In the case of baseline missingness being random at 30%, the total number of patients included in the cLDA model was all 392, compared with only 193 included using a traditional MMRM.
- Across all LoM and SoM, the estimated treatment effects from the two modelling approaches LSMeans were similar. However, the cLDA model resulted in increased precision and narrower CIs (Table 2). The improvements in precision for the cLDA model over the CfB MMRM was greater as the LoM increased, and in scenarios with higher missingness in the control arm (95% CI width 11.9 [cLDA] vs 13.3 [MMRM] in SoM 2 with 20% missing, 12.0 versus 14.4 with 30% missing).

References
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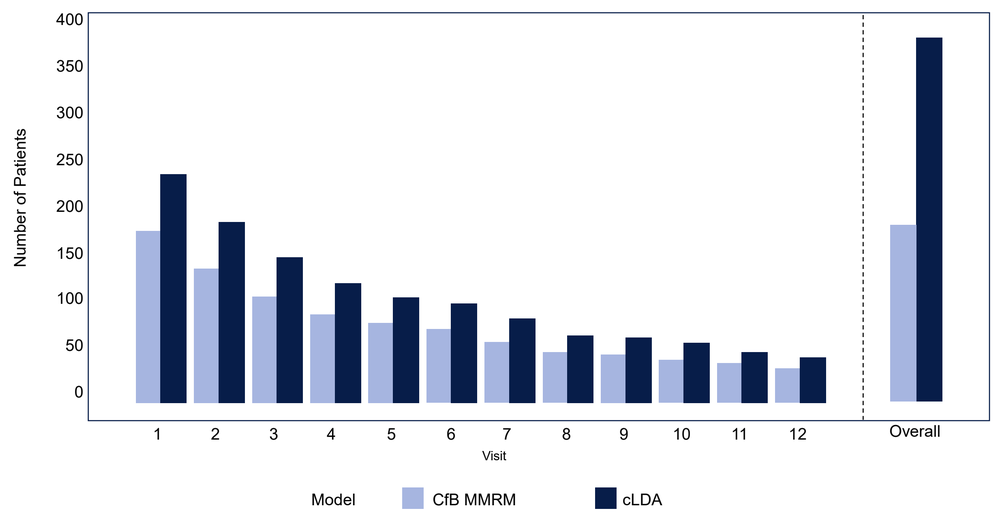
CASE STUDY AND SIMULATION METHODS

- The 2 models were compared using PRO data from a phase 3 trial in patients with acute myeloid leukaemia (NCT02993523, N=431, randomised 2:1 treatment to control). The overall treatment effect on longitudinal magnitude of change in EORTC QLQ-C30 physical functioning was estimated using the subset of patients with valid baseline data (N=392). The treatment effect estimates measured by Least Squares Means (LSMeans) and precision of the estimates measured by width of confidence interval (CI) were compared.
- To assess the impact of missing baseline data, we simulated datasets based on the N=392 patient dataset, with increasing levels of missingness (LoM) at baseline (10%, 20%, and 30% overall between treatment arms) and three scenarios of missingness (SoM) as detailed in Table 1 below.
- For each scenario, 100 datasets were simulated, both models were fitted to each simulated dataset, and the LSMeans and CI widths were estimated.

Table 1: Summary of the simulated missing data scenarios

Scenario	Missing data pattern	Arm	LoM A	LoM B	LoM C
0	No missing	Treatment and control			
SoM 1	Baseline missing at random	Treatment and control	10%	20%	30%
		Overall	10%	20%	30%
SoM 2	Baseline missing differs by treatment arm	Treatment	10%	10%	10%
		Control	10%	30%	50%
		Overall	10%	20%	30%
SoM 3	Baseline missing differs by baseline PRO value (by PRO baseline quartile [Q])	Treatment and control	Q1–20% Q2–15% Q3–5% Q4–0%	Q1–40% Q2–25% Q3–15% Q4–0%	Q1–60% Q2–35% Q3–25% Q4–0%
		Overall	10%	20%	30%

Figure 1: Number of patients in analysis



Number of patients with data included at each timepoint using each model when baseline data is missing at random at 30% level.

Table 2: CI widths by scenario

		Missingness		
		10%	20%	30%
1. At random	cLDA	11.7	11.8	11.9
	CfB MMRM	12.2	13.05	13.6
2. By treatment	cLDA	11.7	11.9	12.0
	CfB MMRM	12.2	13.3	14.4
3. By PRO score	cLDA	11.7	11.7	11.8
	CfB MMRM	12.2	12.8	13.5

CI widths for each model by LoM and SoM.