

Impact of different aggregation methods and dropout types on MBMA models

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Aim

This simulation study aims to analyze how different strategies to handle clinical trial dropout impact the model-based meta-analysis (MBMA) models of continuous and event data.

Background

- Dropout in clinical trial results in missing data, which may impact analyses with MBMA.
- Dropout classification:
 - Completely random dropout (CRD): dropout does not depend on observed or unobserved variables of relevance
 - Random dropout (RD): dropout depends on observed variables, but not unobserved variables
 - Informative dropout (ID): dropout depends on unobserved variables
- The simulated data types used in this study followed the COPD MBMA model¹:

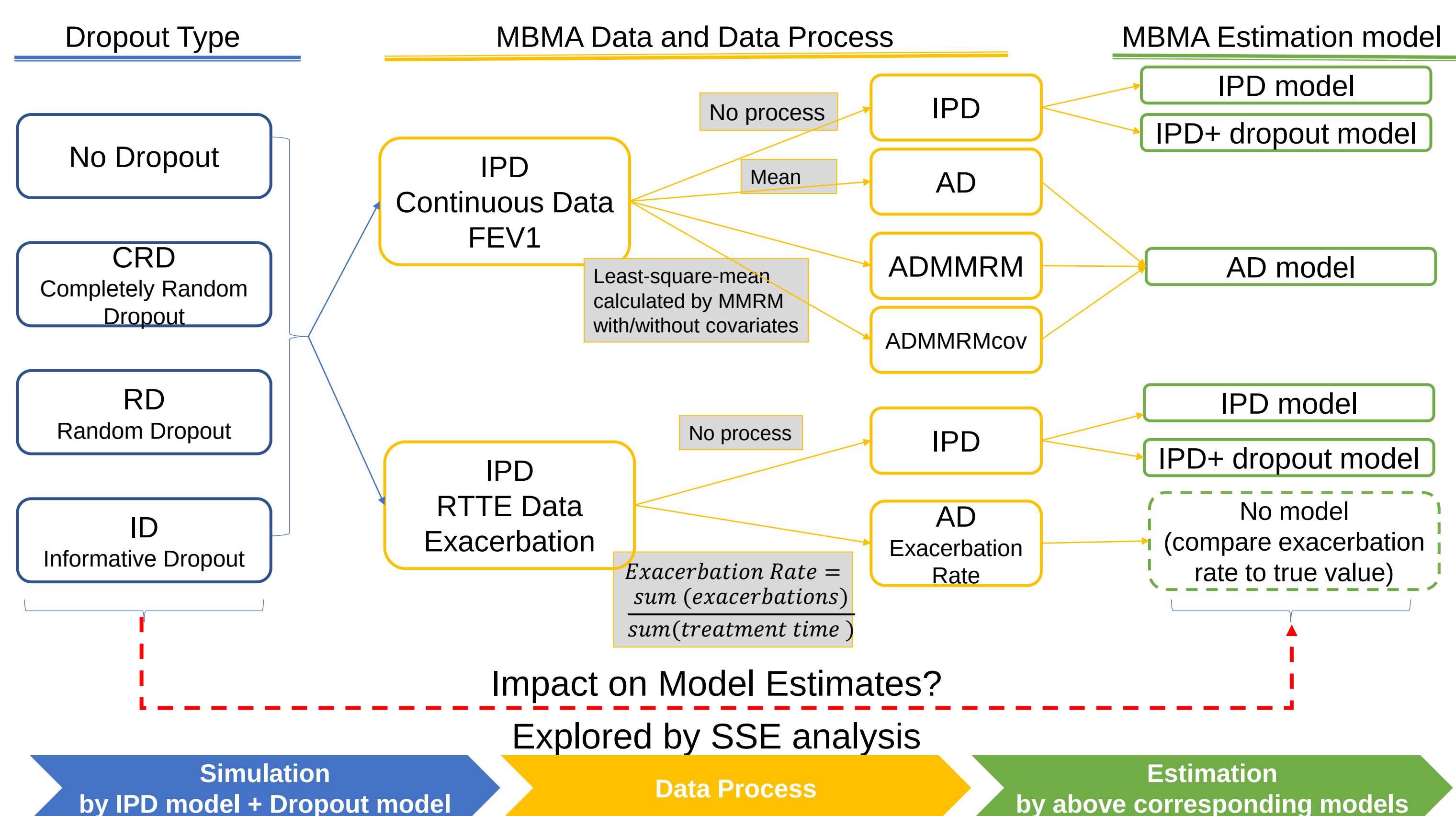
Continuous data – Forced Expiratory Volume in 1 sec (FEV1):

- Individual-patient-level data (IPD)
- Aggregated data (AD): (1) mean of observations ignoring dropout; (2) least-square-mean based on mixed model for repeated measures (MMRM)

Repeated-time-to event (RTTE) exacerbation:

- IPD
- AD of exacerbation rate: sum of exacerbations divided by sum of treatment times of all patients

Method



$$FEV1 = B + DPS \cdot TIME + placebo\ effect + DE_{VIL} + DE_{FF} \quad Eq. 1$$

Eq. 1 Model structure of FEV1 model. FEV1: The biomarker, forced expiratory volume in one second; B: baseline; DPS: disease progression slope. TIME: study time. Placebo effect: immediate constant placebo effect. DE: Drug effect responses of vilanterol (VIL) and fluticasone furoate (FF).

$$Exacerbation\ Hazard = LM \cdot e^{(SHP \cdot TIME)} \cdot DE_{VIL} \cdot DE_{FF} \quad Eq. 2$$

Eq. 2 Model structure of RTTE model. Hazard: the hazard of an exacerbation event. LM: the hazard constant parameter. SHP: the coefficient of time. DE: Drug effect responses of VIL and FF.

Results: impact of dropout on models of continuous data

Table 1. Stochastic simulation and estimation (SSE) results of continuous FEV1 models

Dropout Type	Model	Relative Diff% TH_B	Relative Diff% TH_DPS	Relative Diff% TH_FF	Relative Diff% TH_VIL	Relative Diff% OM_B	Relative Diff% OM_DPS	Relative Diff% OM_VIL
No Dropout	IPD	-0.07	5.10	-2.80	1.00	-0.94	0.61	-0.88
	AD	0.16	-8.68	-22.44	4.14	.	.	.
	ADMMRM	0.12	-15.66	-18.35	3.79	.	.	.
CRD	IPD+dropout	-0.11	3.91	-2.56	1.00	-0.74	0.16	-1.00
	IPD	-0.07	3.91	-2.57	1.00	-1.01	0.16	-0.88
	AD	0.31	-26.56	-12.36	-1.43	.	.	.
RD	ADMMRM	0.16	-24.33	-19.79	5.17	.	.	.
	IPD+dropout	0.05	3.46	-2.72	0.91	-0.85	0.21	-0.84
	IPD	0.05	3.47	-2.75	0.95	-1.01	0.21	-0.78
ID	AD	0.17	-91.25 ¹	-74.29	17.76	.	.	.
	ADMMRM	0.14	-97.91	-76.47	17.71	.	.	.
	ADMMRMcov	-0.06	-10.35	-3.50	3.63	.	.	.
ID	IPD+dropout	-0.11	4.42	-2.47	0.86	-0.74	0.20	-0.97
	IPD	-0.07	1.96	-2.52	0.91	-1.07	0.17	-0.85
	AD	0.73	-99.00	-7.90	7.15	.	.	.
	ADMMRM	0.73	-99.00	-7.37	7.22	.	.	.

¹The above table shows the relative differences (%) in parameters compared to the true values. Underlined values indicate student t-test p<0.01. Colors range from red to blue, representing small to large values, respectively. TH: theta, typical value; OM: omega, variance of inter-individual variability; SI: sigma, variance of residual error. TH_FF and TH_VIL are the typical values of drug effects of FF and VIL, respectively. Parameter definitions are same for the following figures/tables.

References: [1] Llanos-Paez, C. et al. Joint longitudinal model-based meta-analysis of FEV1 and exacerbation rate in randomized COPD trials. J. Pharmacokinet. Pharmacodyn. 50, 297–314 (2023).

Conflict of Interest: LY, MJ and MOK declare that they have no conflict of interest. SY, CA and AB are GSK employees and hold GSK shares.

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Conclusions

For continuous (FEV1) data:

- ✓ The IPD models showed advantages in dealing with dropout compared to AD models, regardless of including a dropout model or not.
- ✓ AD models were biased under the conditions of RD and ID but not CRD.
- ✓ Adding dropout-relevant covariates in MMRM analysis may improve AD model estimation.

For RTTE (exacerbation) data:

- ✓ IPD model and IPD-dropout model performed well under the conditions of no-dropout and CRD, but were more biased under RD and ID.
- ✓ AD (exacerbation rate) was biased under the conditions of RD and ID but not CRD.

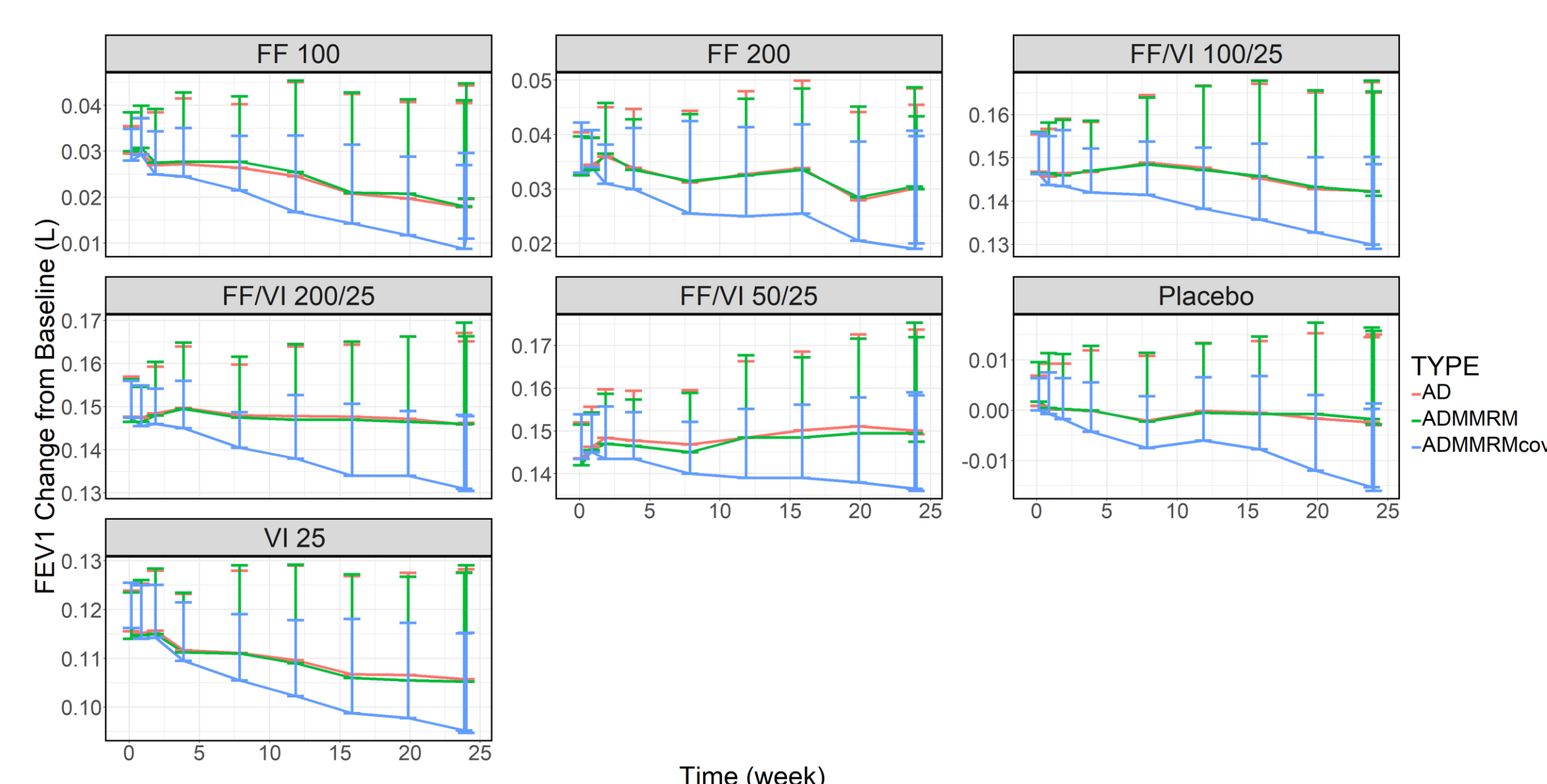


Fig 1. Different types of AD generated by IPD (20 times simulation) under the condition of RD with disease severity as the covariate for dropout hazard. Disease severity was also included as covariate in one MMRM (blue line, ADMMRMcov). The treatments included placebo, mono-, and dual-therapies of FF (50, 100, 200 µg) and VIL (25 µg).

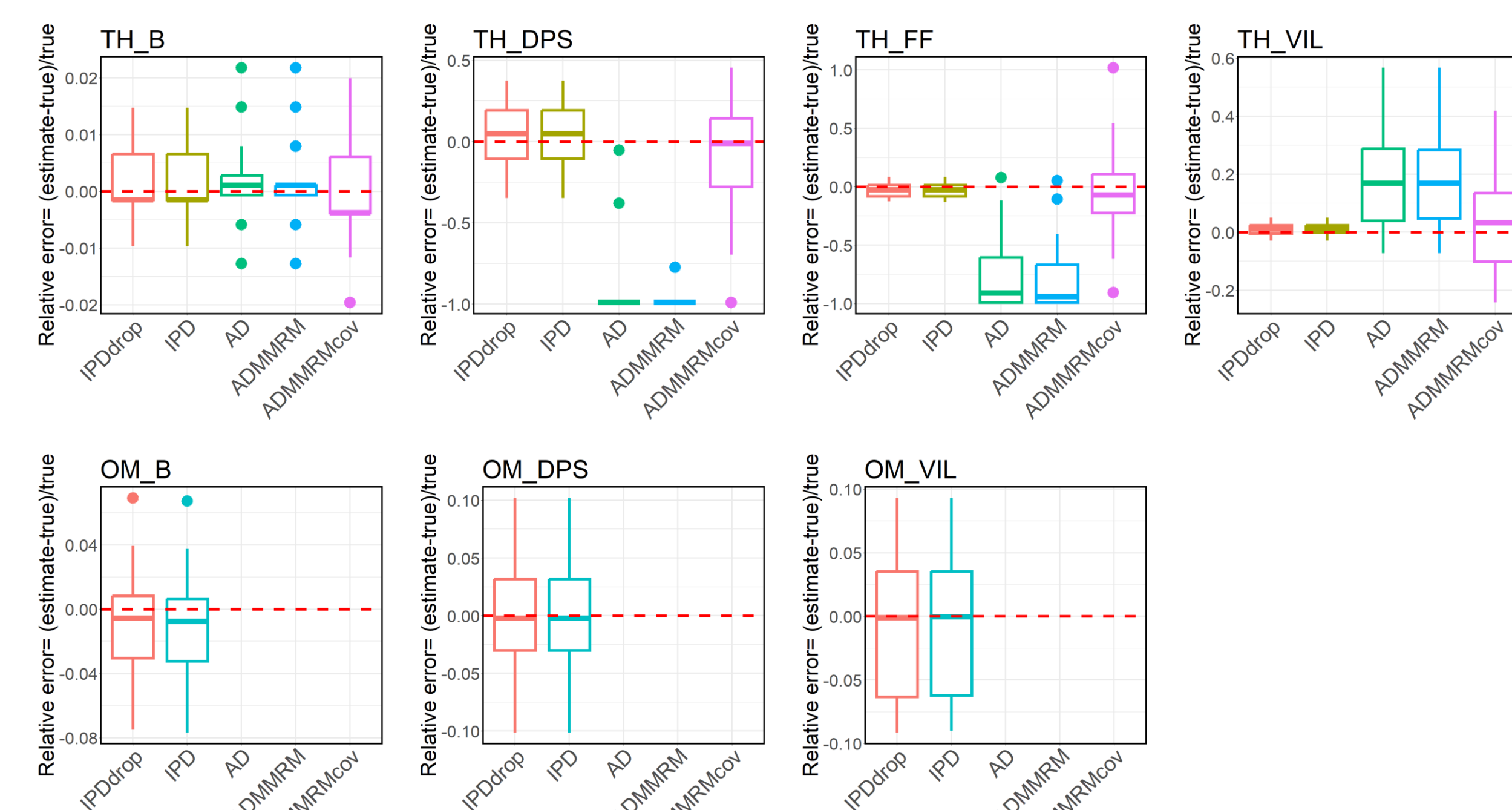


Fig 2. Parameter errors (SSE results, 20 times) of continuous FEV1 models under the condition of RD with disease severity as the covariate for dropout hazard.

Results: impact of dropout on models of RTTE data

Table 2. SSE results of RTTE models

Dropout Type	Model	Relative Diff% TH_LM	Relative Diff% TH_SHP	Relative Diff% TH_FF	Relative Diff% TH_VIL	Relative Diff% OM_LM
No Dropout	IPD	-5.00 ¹	-8.99	2.68	-5.80	0.46
	AD	-5.85	0.35	-4.12	-5.00	4.00
CRD	IPD+dropout	-5.85	0.39	-4.12	-5.05	3.99
	IPD	-6.09	-10.39	1.03	-7.78	1.62
RD	IPD+dropout	-6.07	-10.44	1.07	-7.80	1.61
	IPD	-7.82	30.04	-8.20	-4.73	-2.24
ID	IPD+dropout	-11.60	-12.68	-4.08	-0.25	13.45

¹Same as the note of Table 1.

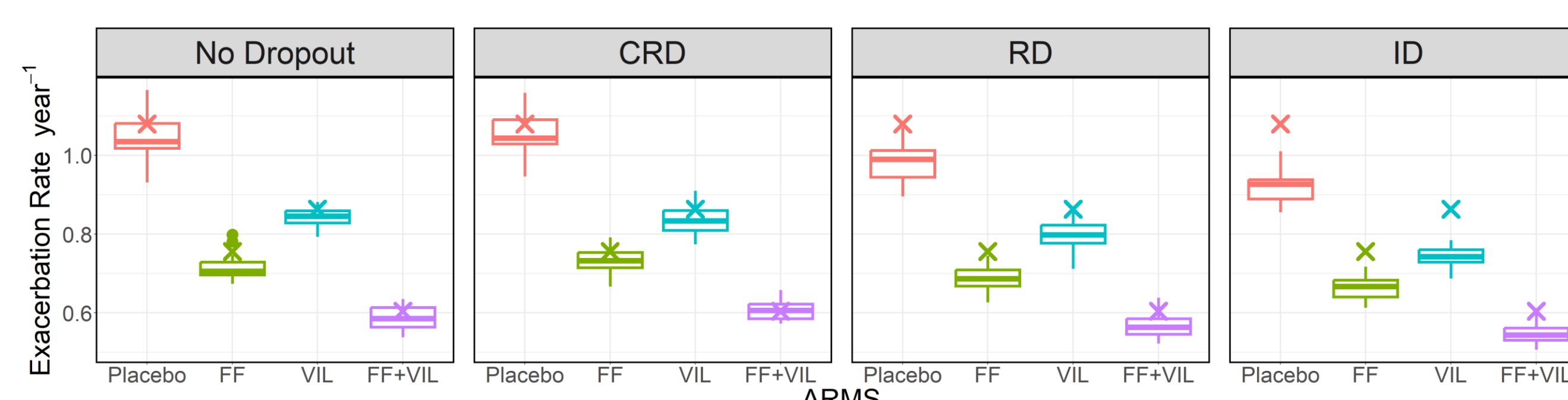


Fig 3. Exacerbation rates on AD level by simulation (boxplot, 20 times) compared to the true value (cross) under the conditions of No dropout, CRD, RD and ID.