Case Example: Bayesian approach to conduct sensitivity analysis for missing data

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Abstract

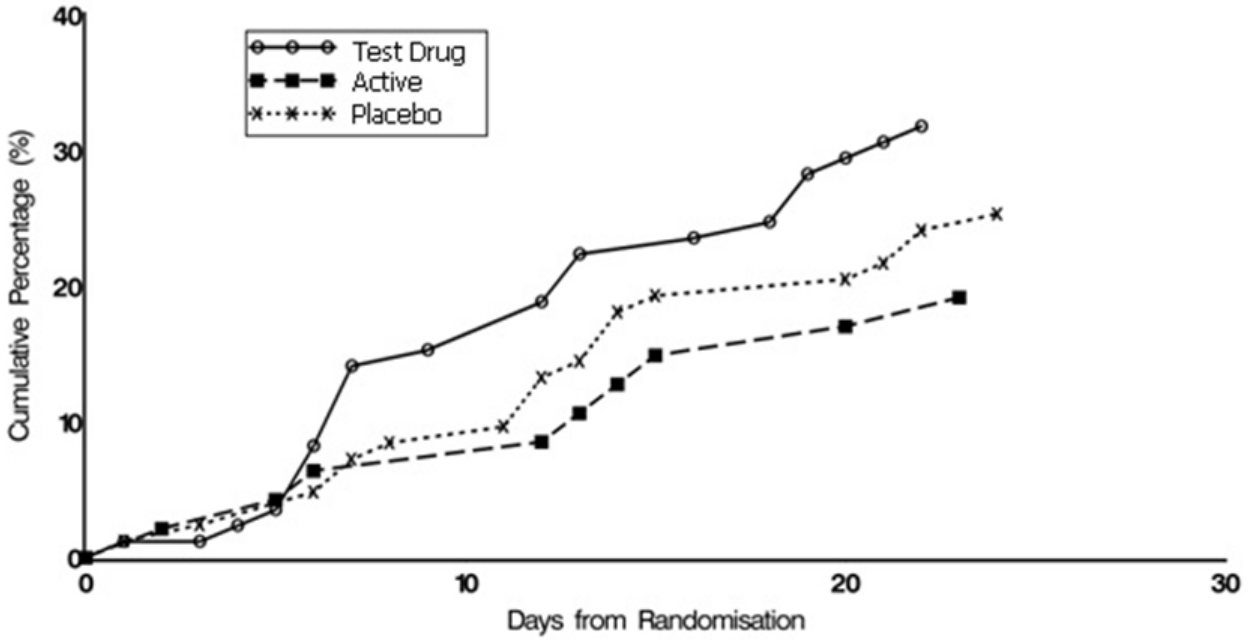
- Sensitivity analysis is recommended by regulatory guidance for clinical trials with missing data
- Bayesian methods provide flexible ways to implement complex sensitivity analysis models for missing data
- We demonstrate the application of Bayesian methods for missing data analysis through a case study with a schizophrenia clinical trial.

Background

- In a schizophrenia trial
  - ~ 200 patients were randomized with 2:1:2 ratio to Test, Active, and Placebo groups
  - Primary endpoint: treatment difference in change from baseline at week4 on Positive and Negative Syndrome Scale (PANSS)
    - A high score means worse condition
  - PANSS scores were measured at baseline, Day2, and weeks 1, 2, 3, and 4

Background

- Dropout rates at week4 were about
  - 33% in Test
  - 27% in Placebo
  - 20% in Active



Background

Number (%) of Patients Discontinued by Reason

	Active	Placebo	Test
	N=45	N=78	N=81
	n (%)	n (%)	n (%)
Adverse Event			3 (3.7)
Lack Of Efficacy	4 (8.9)	15 (19.2)	16 (19.8)
Physician Decision			1 (1.2)
Pregnancy	1 (2.2)		
Progressive Disease	1 (2.2)		1 (1.2)
Protocol Violation	1 (2.2)		
Withdrawal by Subject	2 (4.4)	6 (7.7)	6 (7.4)

Statistical analysis plan

- Protocol planned primary analysis: mixed model for repeated measures (MMRM) on change from baseline in PANSS,

  CFB = base, visit, trt, visit*base, visit*trt

  with unstructured covariance

- Sensitivity Analyses
  - Analysis on completers
  - Selection model
  - Shared parameter model
  - Pattern mixture model

Tools for Analyses

- For selection model, shared parameter model, pattern mixture model, no general software
- With frequentist method, we used SAS macros developed by DIA Missing Data Working Group (available at www.missingdata.org.uk.)
- For Bayesian method, we used
  - SAS Proc MCMC (Stat v13.1)
  - STAN

Selection Model

- MMRM for response
  - Y | X ~N (μ(x), Σ)
- Missing data mechanism:

$R_{ji} \sim \text{Bernoulli}(q_{ji})$, dropout index for i-th patient at j-th visit

$$\text{logit}\{q_{ji}\} = \phi_1(1 - trt_i) + \phi_2 trt_i + \phi_3(1 - trt_i)y_{j-1} + \phi_4 trt_i y_{j-1}$$
$$+\phi_5(1 - trt_i)y_j + \phi_6 trt_i y_j \, , j = 2, \ldots, v_i$$

- Bayesian method with vague prior
  - $N(0, 100^2)$ for all regression parameters in MMRM
  - $\Sigma \sim \text{invWishart}(\text{I}_5)$
  - $\phi_1, \phi_2, \sim logistic(0,1)$ and $\phi_3, \phi_4, \phi_5, \phi_6 \sim N(0, 5^2)$

Shared Parameter Model

- A quadratic model
  - Response model;

$$y_{ij} = (\beta_0 + \beta_1 w_j + \beta_2 w_j^2)(1 - trt_i) + (\beta_3 + \beta_4 w_j + \beta_5 w_j^2) trt_i + \beta_6 bl_i + U_{i0} + U_{i1} w_j + U_{i2} w_j^2 + \epsilon_{ij}$$

  - Missing mechanism model

$$\text{logit}\{q_{ji}\} = \zeta_j + a\, trt_i + (a_0 + b_0 trt_i) U_{i0} + (a_1 + b_1 trt_i) U_{i1} + (a_2 + b_2 trt_i) U_{i2}$$

$$(U_{i0}, U_{i1}, U_{i2}) \sim N(0, \Sigma_U), \quad \epsilon_{ij} \sim N(0, \sigma^2).$$

- Bayesian method with vague prior
  - $N(0, 100^2)$ for all regression parameters in response
  - $\Sigma_U \sim \text{invWishart}(I_3)$
  - $\zeta_j \sim logistic(0,1)$ and, $a_0, a_1, a_2, b_0, b_1, b_2 \sim N(0, 5^2)$

Pattern Mixture Model

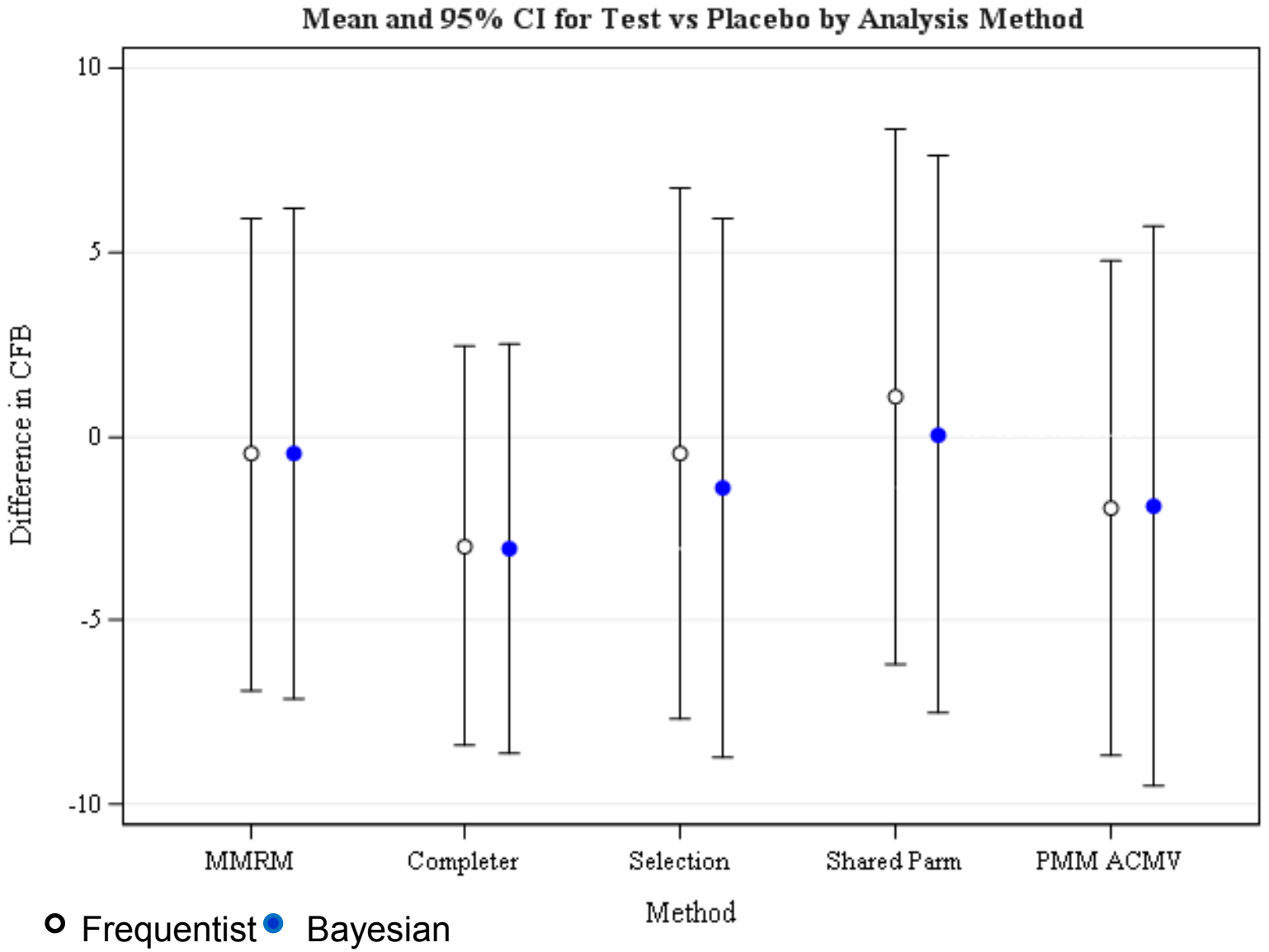
- Distribution decomposition (little 1993, 1994)

  $[Y_{obs}, Y_{mis}, R \mid X] = [Y_{obs}, Y_{mis} \mid M, X] \; [R \mid X]$

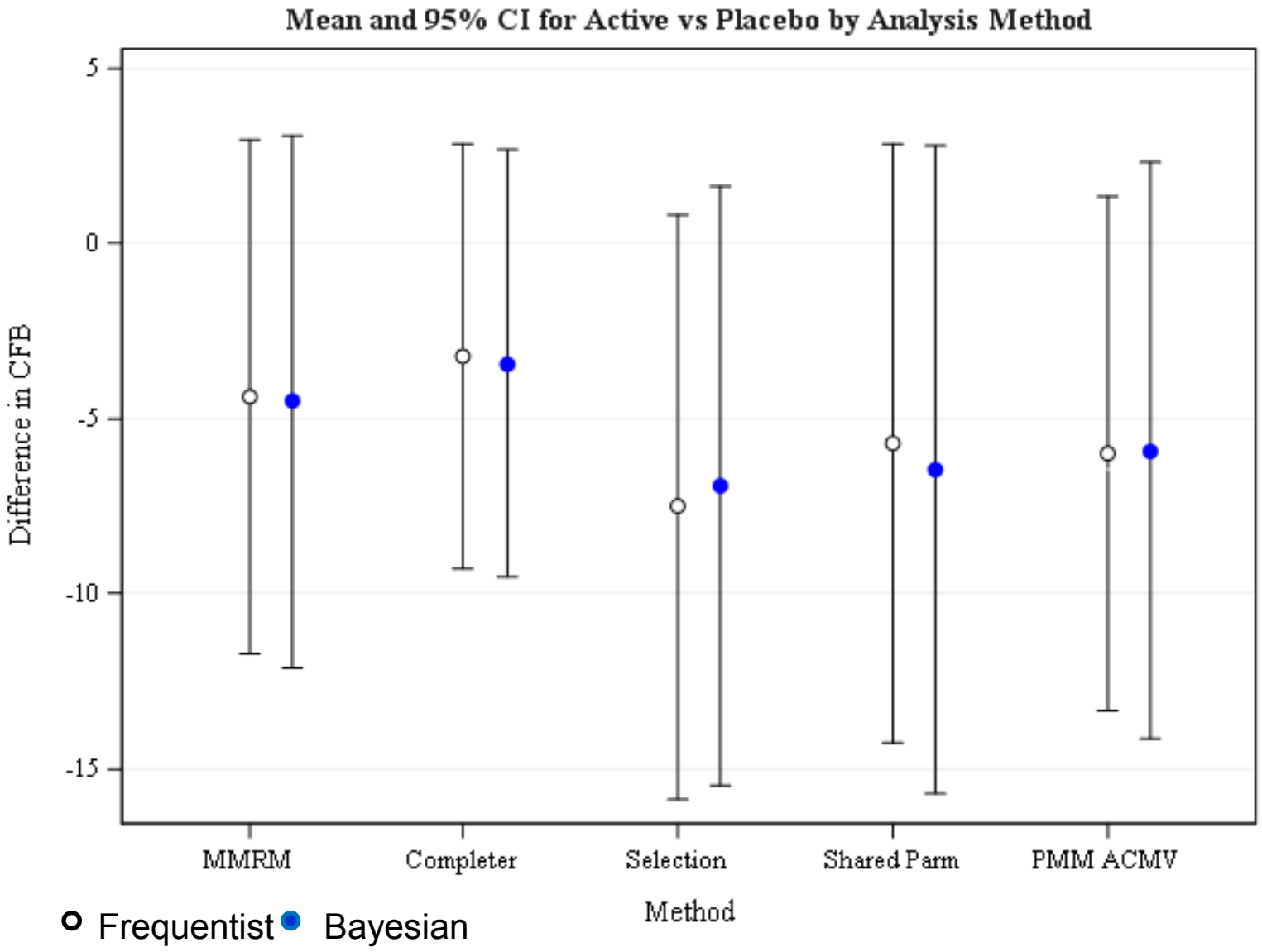
- This model can be fit using MI approach,
  - Impute missing data per pattern with ACMV restriction
  - Analyze and combine results

- Bayesian: using STAN with vague prior
  - Pattern indicator $(\phi_1, \phi_2, \phi_3, \phi_4, \phi_5)$ ~ Dirichlet
  - All standard deviation ~ Uniform (0,50)
  - All regression parameters ~ N(0, 100^2)

Analysis Results: Test vs Placebo



Analysis Results: Active vs Placebo



Selection model specification

- With vague prior (non-informative),
  - the Bayesian analysis ≈ frequentist method

- Primary vs sensitivity analysis
  - some differences were seen
  - may depend on model specifications, e.g.
    - In selection model

$$\text{logit}\{q_{ji}\} = \phi_1(1 - trt_i) + \phi_2 trt_i + \phi_3(1 - trt_i)y_{j-1} + \phi_4 trt_i y_{j-1} + \phi_5(1 - trt_i)y_j + \phi_6 trt_i y_j$$

Parameters did not depend on time points ➔ a strong restriction when the proportions of dropout diff over time.

Selection model w modified dropout

- Modify the dropout model

$$\text{logit}[q_{ji}] = \zeta_j + \gamma_0 y_{ij} + \gamma_1 y_{i(j-1)},\ j = 2, 3, 4, 5.$$

  – allow different parameter for each time point

- Bayesian analysis with vague prior

	Selection Model	Modified Selection Model	MMRM
Test vs Placebo	-1.4 (3.7)	-0.6 (3.3)	-0.5 (3.3)
Active vs Placebo	-6.9 (4.4)	-4.4 (3.8)	-4.4 (3.8)
γ_0	N/A	-0.01 (0.05)	
γ_1	N/A	0.15 (0.06)	

Bayesian non-parametric model

- All Bayesian models assumed that the response ~ normal distribution
- To relax this assumption, Linero and Daniels (2014) proposed a non-parametric model
  - Assume Y ~ a Dirichlet process mixture
  - Model can be fit under MAR, or MNAR with non-future dependence (NFD)

	BNP w MAR	BNP w MNAR	MMRM
Test vs Placebo	-0.7 (2.7)	-0.3 (2.9)	-0.5 (3.3)
Active vs Placebo	-4.5 (3.0)	-4.7 (3.0)	-4.4 (3.8)

Conclusions

- For the case study, we illustrate some application of Bayesian methods for sensitivity analysis
  - With vague prior, produce similar results as the frequentist models
  - Tools available: STAN, winBUGS, SAS Proc MCMC (Stat v13.1)

- Advantage of Bayesian method:
  - Can be implemented with available software package such as STAN, SAS Proc MCMC, winBUGS, etc.
  - More flexible to handle model specification
  - Have posterior distribution besides point/SE estimates.

Conclusions

- Need to be careful:
  - Understand specification and prior
  - Check for convergence
- Sensitivity analysis require additional assumption:
  - important to clearly specify and understand them
- Tools/software are still needed for fitting these models
- Acceptance by regulatory