Clinical trials with incomplete daily diary data

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Example used throughout

- Randomized Phase 2 double-blind parallel-group placebo-controlled trial in insomnia
- Placebo, 15, 30, 45, 60 mg doses
- Sample size of approximately 135 per dose group
- 10 patients were randomized but never dosed. They are excluded throughout.
- One week blinded placebo run-in, primary endpoint after 4 weeks of dosing

Visit schedule and data

- Weekly clinic visits: 0(one week of placebo run-in), $1, 2, 3, 4$
  - There were 13 efficacy items collected at each weekly visit
- Daily morning phone call by patients to an automated diary
  - There were 5 items collected
  - SWASO (wake after sleep onset, minutes) is primary
  - Study days: $-5, \ldots, 0$,**1**,$2, \ldots, 29$ $(30, \ldots, 36)$
- Other variables collected
  - Adverse events
  - Reason for stopping dosing/study
  - Baseline covariates: age, sex, race, and clinical site

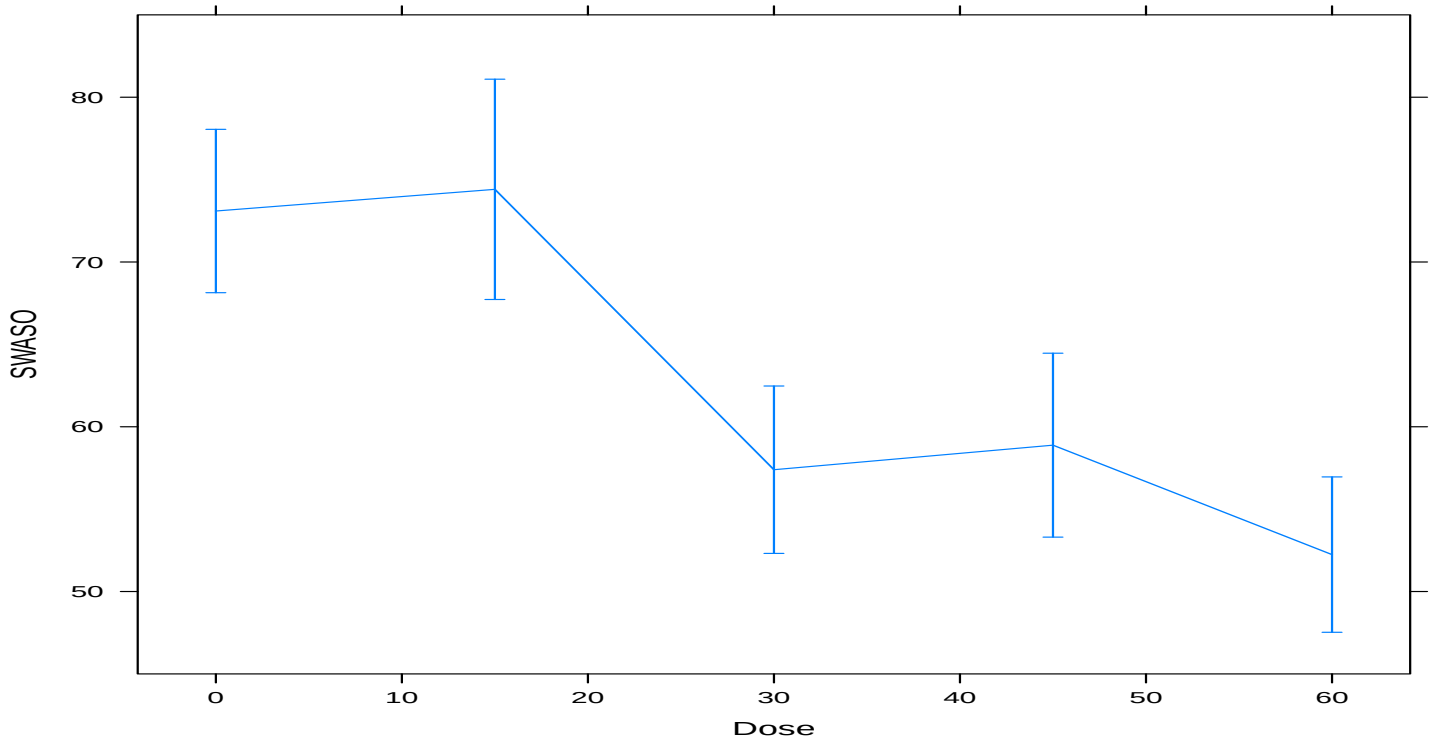
Primary analysis: Daily values aggregated to weekly level

- The primary endpoint is the average value of the daily SWASO values during Week 4 of the study.
- If there were $<$ 4 SWASO diary reports during a Week, the 'Weekly' SWASO is set to **MISSING**. Otherwise, it is computed from the available SWASO values.
- Averaging daily diary data ubiquitous, as is the practice of regarding the data as 'complete' provided a minimum number is available.

Primary analysis (cont)

- Much less common is the lack of windowing to determine 'Weeks'
  - 'Week' is based on the dates of the clinic visits and the visit number recorded by the investigator. The number of days in a 'week' varied noticeably from 7.
- Primary analysis was a mixed effect model with dose*week and unstructured variance. It included the baseline SWASO and the other covariates already mentioned.

Primary analysis: Results



	15mg vs PBO		60mg vs PBO		Pooled
Method	Est	SE	Est	SE	Res SD
MLLM-week	-2.93	5.97	-26.61	6	44.7

Table: Estimates and standard errors for the Week 4 SWASO endpoint.

Outline

Analyses to better assess the consequences of missing data

- Describe patterns of missing data and potential reasons for them.
- Multiple imputation under the MAR assumption
  - Pre-specified imputation model likely to be 'numerically' successful.
  - More refined models to check model sensitivity. Less confidence they could be successfully implemented.
  - Models that better matched the variances/correlations observed in exploratory analyses.
- Pattern mixture models to assess sensitivity to MNAR deviations from MAR
  - Models that impute independent of dose group.
  - Models that impute 'unfavorable' values only in the active groups.
    - ★ Models indexed by a parameter increasing the deviation from the MAR assumption to form a 'tipping point' analysis.
    - ★ For one choice of the indexing parameter, there is an alternative interpretation as estimate when dropouts change to placebo.

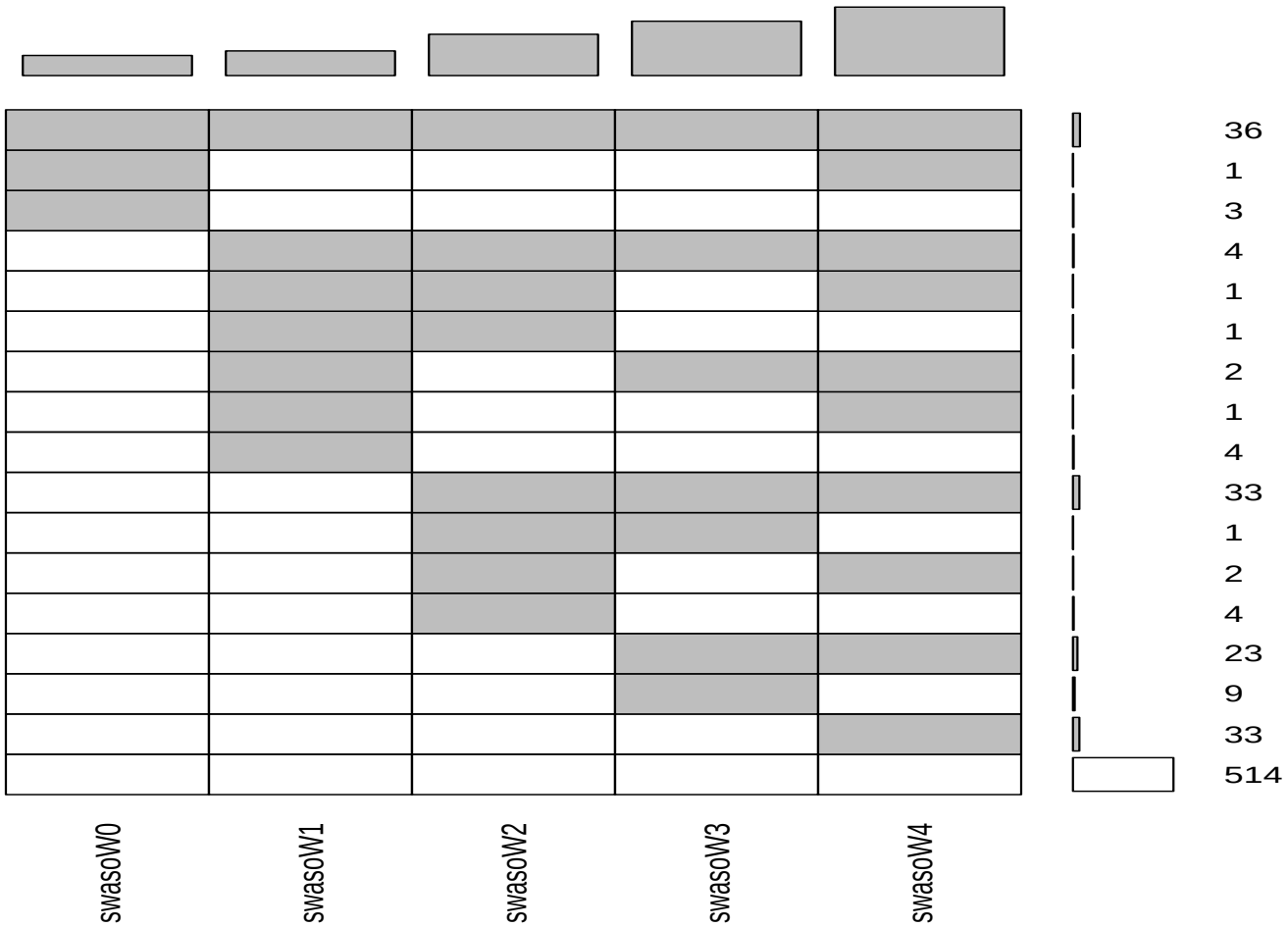
Outline

Missing data rates

Dose	Cumulative Dropout Rates Week				Intermittent Missing Rates Week				
	1	2	3	4	0	1	2	3	4
0	0.06	0.08	0.10	0.14	0.06	0.02	0.02	0.03	0.04
15	0.04	0.11	0.15	0.20	0.04	0.01	0.01	0.04	0.05
30	0.04	0.09	0.13	0.14	0.04	0.00	0.00	0.02	0.02
45	0.04	0.10	0.13	0.16	0.05	0.02	0.01	0.02	0.00
60	0.09	0.15	0.18	0.22	0.09	0.04	0.04	0.00	0.03

Table: Dropout and intermittent missing rates for the weekly (per protocol) SWASO endpoint.

Patterns of missing data



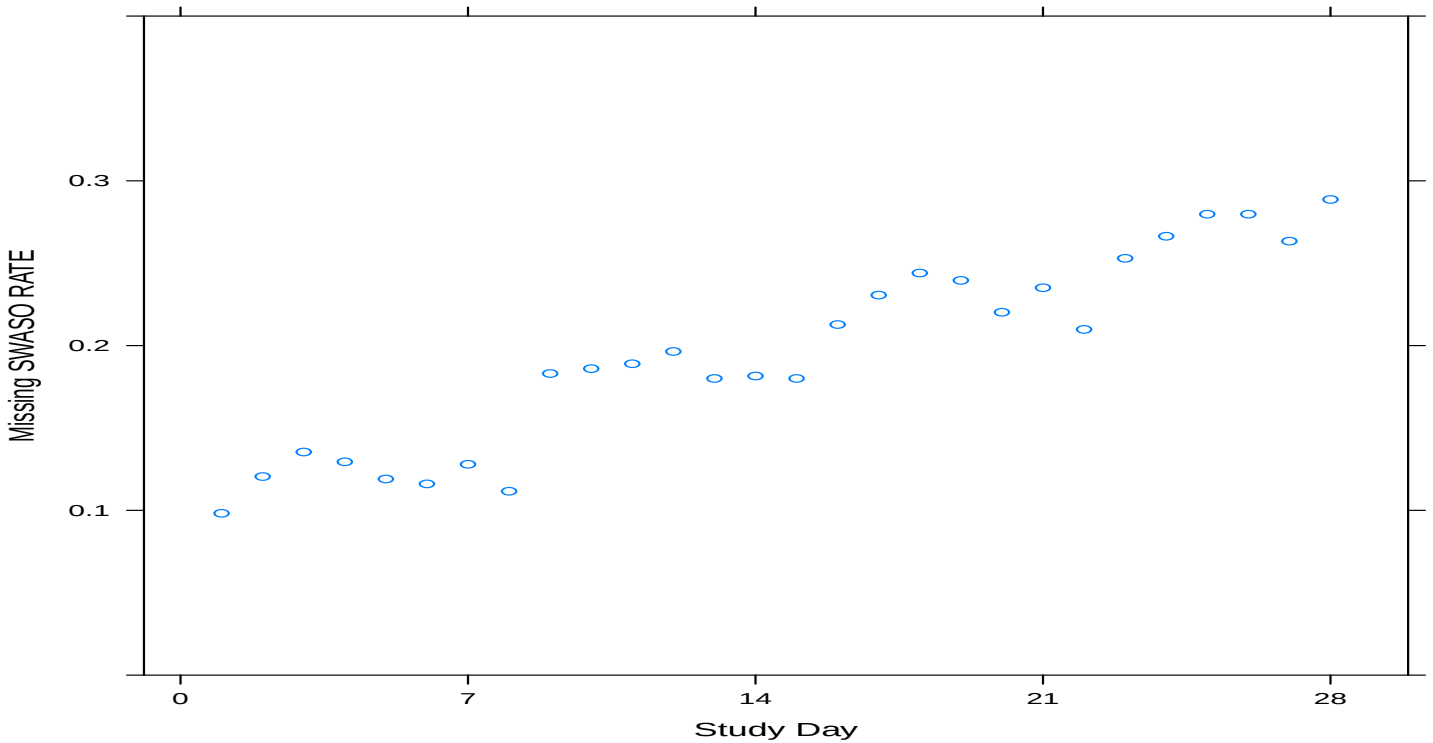
Missing data patterns for weekly-averaged SWASO. R package **VIM** (Templ et al., 2013).

Compliance with visit schedule

Days Between Visits 3 and 4	Row Total	Days Contributing to the Weekly Average											
		1	2	3	4	5	6	7	8	9	10	11	14
2	1	1	0	-	-	-	-	-	-	-	-	-	-
3	1	0	0	1	-	-	-	-	-	-	-	-	-
4	4	0	0	1	3	-	-	-	-	-	-	-	-
5	31	0	3	2	11	15	-	-	-	-	-	-	-
6	81	1	0	1	12	24	43	-	-	-	-	-	-
7	342	1	0	5	7	32	81	216	-	-	-	-	-
8	64	0	1	0	2	4	9	19	29	-	-	-	-
9	21	0	0	0	0	1	1	4	4	11	-	-	-
10	5	0	0	0	1	0	1	1	0	1	1	-	-
11	1	0	0	0	1	0	0	0	0	0	0	0	-
12	2	0	0	1	0	0	0	0	0	0	0	1	-
13	1	1	0	0	0	0	0	0	0	0	0	0	-
16	1	0	0	0	0	0	0	0	0	0	0	0	1

Daily diaries contributing to SWASO at Week 4. Counts are the number of patients amongst those with Week 3,4 visits.

Missing rates for daily diaries



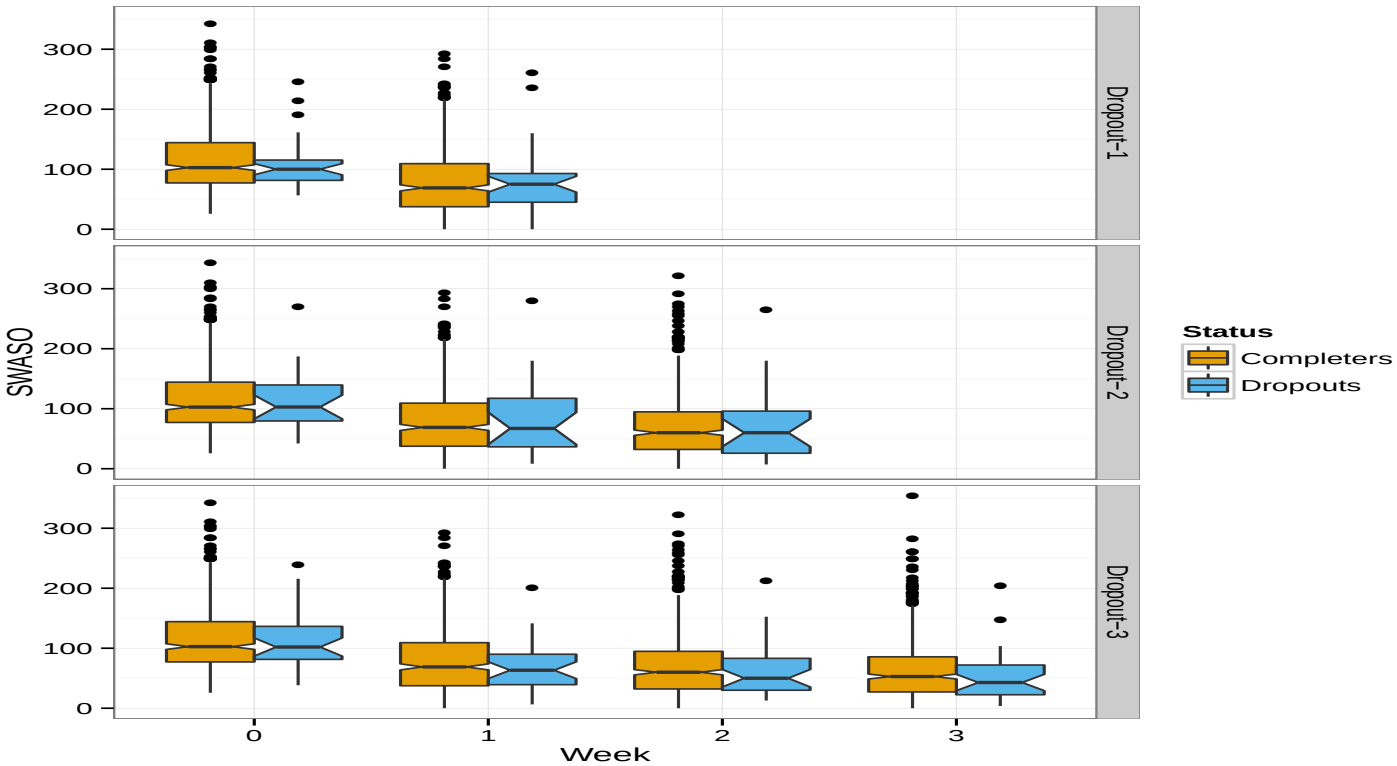
The proportion of missing SWASO values for study days 1-28.

Reasons for discontinuing dosing

	Dose				
	0	15	30	45	60
RANDOMIZED	143	134	134	124	137
COMPLETED STUDY	124	110	115	104	109
ADVERSE EVENT	3	4	1	5	13
SUBJECT DIED	0	0	0	0	1
PROTOCOL VIOLATION	4	5	2	3	3
LOST TO FOLLOW UP	1	1	3	5	4
OTHER	2	0	2	0	1
FAILED ENTRANCE CRITERIA	1	0	1	0	0
SUBJECT WITHDREW CONSENT	8	13	10	7	6
PREGNANCY	0	1	0	0	0

Table: Reason for end of dosing.

Observed responses from different missingness patterns



Response for patients with monotone missing (dropout) patterns compared to completers for SWASO. Software to produce this graphic is included with Thomas et al. (2015).

Outline

General considerations

- Impute any missing SWASO values for Days -5,..., 29 so all patients have 'complete' data in this range.
- Weekly averages formed based on planned visit schedule, e.g., Week 4 is average of Days 22-29.
- All of the imputation models assume multivariate normality.
- Imputation models based on square-root transformation. SWASO was back-transformed before analyses of 'complete' data.

General considerations (cont)

- Usual formulas for combining MI data sets were applied (Rubin, 1987), implemented in R package **mitools** (Lumley, 2014).
- Imputations were created using Bayesian models with diffuse conjugate prior distributions.
  - The simpler models were fit using the R package PAN (Schafer and Yucel, 2002). All models were fit (or re-fit) using the general Bayesian software STAN (Stan Development Team, 2013) called from R package **rstan** (Stan Development Team, 2015).

Pre-specified imputation model

- Compound-symmetric variance-covariance matrix
- Variance-covariance matrix assumed common across treatment groups
- Baseline covariates are additive
- Daily mean values allowed to change only weekly to further reduce the number of parameters estimated
- Priority was ease and stability of model estimation.

Pre-specified model (MVNMI1)

$$Y_{ij} = X_i'\beta + \Delta^{T_i}_{\lceil (j-1)/7 \rceil} + \theta_i + \epsilon_{ij} \ . \tag{1}$$

- The β and Δ parameters were assigned diffuse independent normal distributions. The variance component and residual variance were assigned conjugate diffuse inverse gamma distributions.

Refined imputation models (MAR)

- Fit model (1) separately for each treatment group (MVNMI2).
- Fit model (1) with mean SWASO allowed to change daily (MVNMI3):

Refined model in pre-specified sequence (MVNMI3)

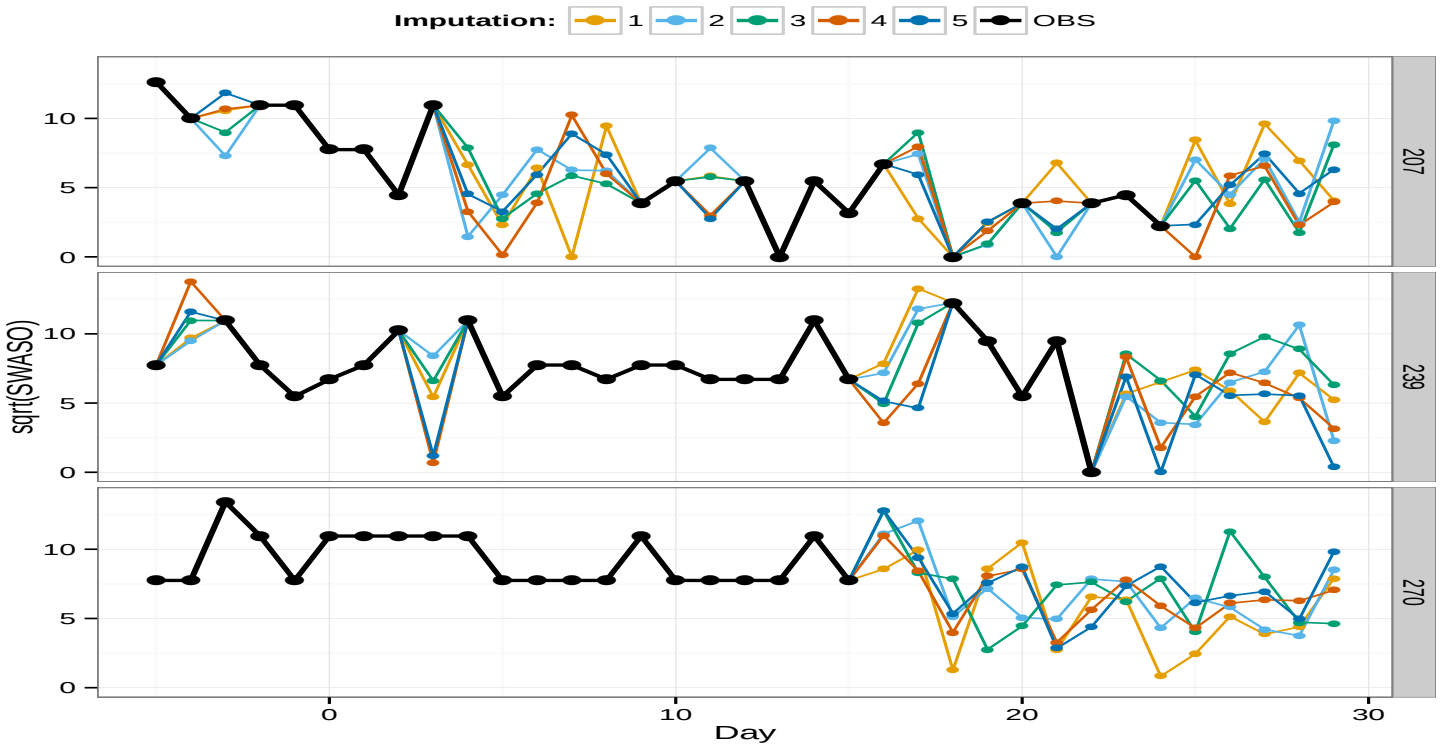
$$Y_{ij} = X_i'\beta + \delta_j^{T_i} + \theta_i + \epsilon_{ij} \quad (3)$$

Imputation results (MAR)

	15mg vs PBO		60mg vs PBO		Pooled
Method	Est	SE	Est	SE	Res SD
MLLM-week	-2.93	5.97	-26.61	6	44.7
MVNMI1-day	-4.43	5.15	-26.57	5.15	39.4
MVNMI2-day	-4.23	5.17	-26.22	5.09	39.5
MVNMI3-day	-5.2	5.16	-26.17	5.07	39.3

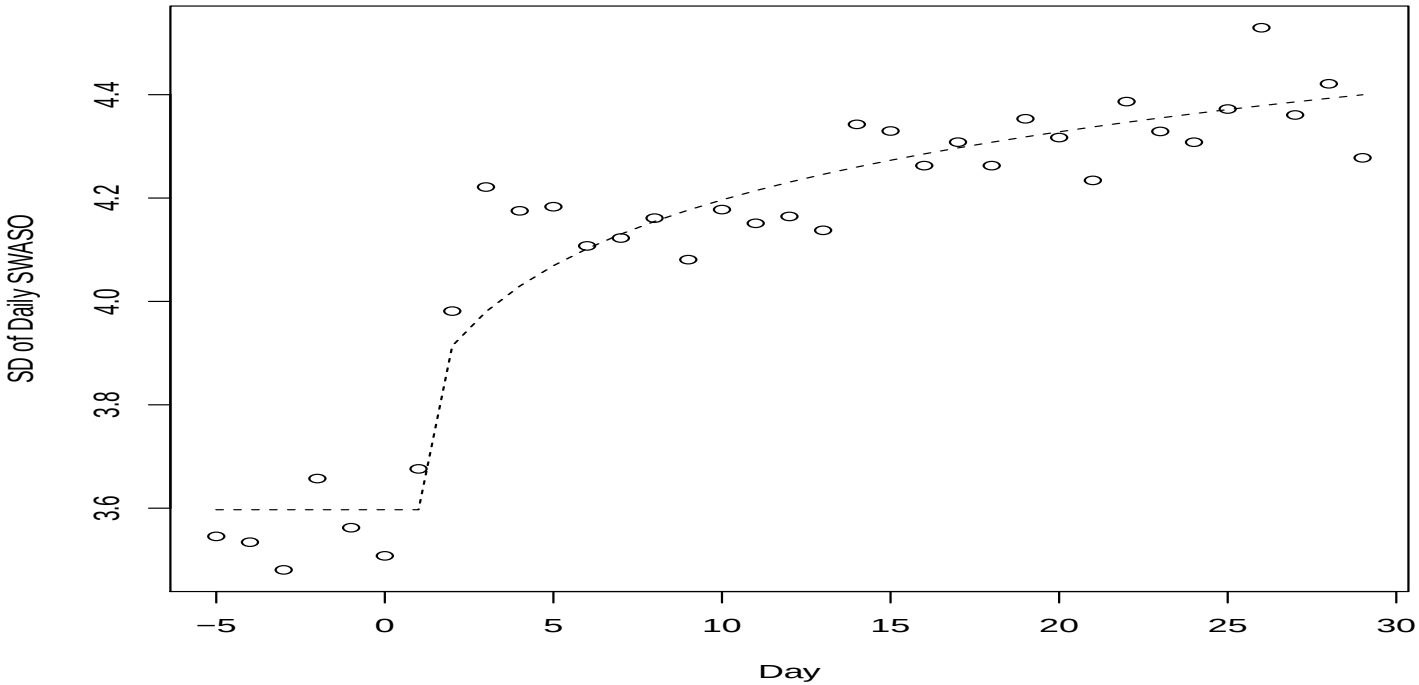
Table: Estimates and standard errors for the Week 4 SWASO endpoint.

Quality of the imputed values



Longitudinal plot of $\sqrt{SWASO}$ for 3 patients treated with the 60 mg dose. The first 5 sets of imputed values from model MVNMI3 are displayed. Software to produce this graphic is included with Thomas et al. (2015).

Exploratory analyses to refine imputation model



Trend in SDs of daily $\sqrt{\text{SWASO}}$ after removing dose group mean differences. The dashed function through the SDs is denoted by 'f'.

Exploratory analyses to refine imputation model (cont)

- Empirical $(5^{th}, 95^{th})$ percentiles for correlations including at least one baseline value are $(0.23, 0.45)$
- Empirical $(5^{th}, 95^{th})$ percentiles for correlations between post-baseline values are $(0.46, 0.67)$
- Approximate compound-symmetric correlations observed within baseline and post-baseline periods

Exploratory model (MVNMI5)

$$Y_{ij} = X_i'\beta + \delta_j^{T_i} + f(j)\theta_i + \epsilon_{ij} \; . \tag{5}$$

Exploratory imputation result (MAR)

	15mg vs PBO		60mg vs PBO		Pooled
Method	Est	SE	Est	SE	Res SD
MLLM-week	-2.93	5.97	-26.61	6	44.7
MVNMI1-day	-4.43	5.15	-26.57	5.15	39.4
MVNMI2-day	-4.23	5.17	-26.22	5.09	39.5
MVNMI3-day	-5.2	5.16	-26.17	5.07	39.3
MVNMI5-day	-4.19	5.23	-26.33	5.27	40.1

Table: Estimates and standard errors for the Week 4 SWASO endpoint.

Outline

Pattern mixture model

- Add an unfavorable (positive) value to each imputation.
- The model implied by the shifted imputations is similar to the model used in Giusti and Little (2011).
  - The unfavorable shift they recommend is $c\mathrm{SD}$
  - The values of $c = 0.8, 1.2, 1.6$ (low, medium, high),
- In the current setting, there are two variances in the imputation model (on the square-root scale):
  - The within-patient variance $\sigma^2 = 8.9$
  - The between-patient variance $\psi^2 = 8$
  - The variance estimates are posterior means.
- Two different shifts considered:
  - Apply the shift $c\sigma$ to all missing values.
  - Apply the shift $c\sigma$ to intermittent missing values, and apply the shift $c\sqrt{\sigma^2 + \psi^2}$ following drop-out.
  - For now, the shifts are applied regardless of dose group.

Results for MNAR model applied symmetrically across treatment groups

	15mg vs PBO		60mg vs PBO		Pooled
Method	Est	SE	Est	SE	Res SD
MVNMI3-day	-5.2	5.16	-26.17	5.07	39.3
AllLow-day	-2.39	5.74	-27.48	5.63	42.7
AllMed-day	-0.58	6.23	-27.9	6.12	46.1
AllHigh-day	1.49	6.86	-28.16	6.75	50.8
DropLow-day	-1.6	5.99	-26.92	5.89	44.5
DropMed-day	0.77	6.78	-26.94	6.68	50.4
DropHigh-day	3.49	7.83	-26.75	7.74	58.6

MNAR model applied to the active groups only

- Use previous imputation model that had different shifts for intermittent and dropout missingness.
  - Use corresponding MAR imputations for placebo patients.
- Interpret the results as sensitivity to MAR assumption
- Interpret the results as an estimate of the effect if dropouts change treatment (to placebo).
  - The effect (on the square-root scale) of the high dose under MAR is approximately $0.4\sqrt{\sigma^2 + \psi^2}$.
  - The 'low' recommendation for Giusti and Little (2011) is still extreme relative to 'return-to-placebo'.

Results for MNAR model applied to the active groups only

	15mg vs PBO		60mg vs PBO		Pooled
Method	Est	SE	Est	SE	Res SD
MVNMI3-day	-5.2	5.16	-26.17	5.07	39.3
DiffLow-day	5.48	5.77	-16.22	5.69	43.7
DiffMed-day	12.28	6.51	-9.64	6.45	49.8
DiffHigh-day	20.03	7.6	-1.99	7.55	58.6

- The 'low' sensitivity shift is roughly twice the high-dose effect. With 20% dropout the resulting reduction in treatment effect is approximately $.2 * 50 = 10$ minutes.
- The corresponding change with 'change-to-placebo' estimate is $.2 * 25 = 5$ minutes.

Conclusions

- The common practice of computing weekly-averaged available-cases diary reports conceals the extent of missing data.
- Desktop computers and software are now sufficient to support better analyses even in regulated environments that emphasize pre-specification.

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