Missing Data in Longitudinal Studies: Mixed-effects Pattern-Mixture and Selection Models

Hedeker D & Gibbons RD (1997). Application of random-effects pattern-mixture models for missing data in longitudinal studies. Psychological Methods, 2, 64-78.

Chapter 14 in Hedeker & Gibbons (2006), Longitudinal Data Analysis, Wiley.

Example: Treatment-Related Change Across Time

Data from the NIMH Schizophrenia collaborative study on treatment related changes in overall severity. IMPS item 79, *Severity of Illness*, was scored as:

1 = normal
2 = borderline mentally ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill

	Sample size at Week							
Group	0	1	2	3	4	5	6	*completers*
PLC (n=108)	107	105	5	87	2	2	70	65%
DRUG (n=329)	327	321	9	287	9	7	265	81%

Drug = Chlorpromazine, Fluphenazine, or Thioridazine

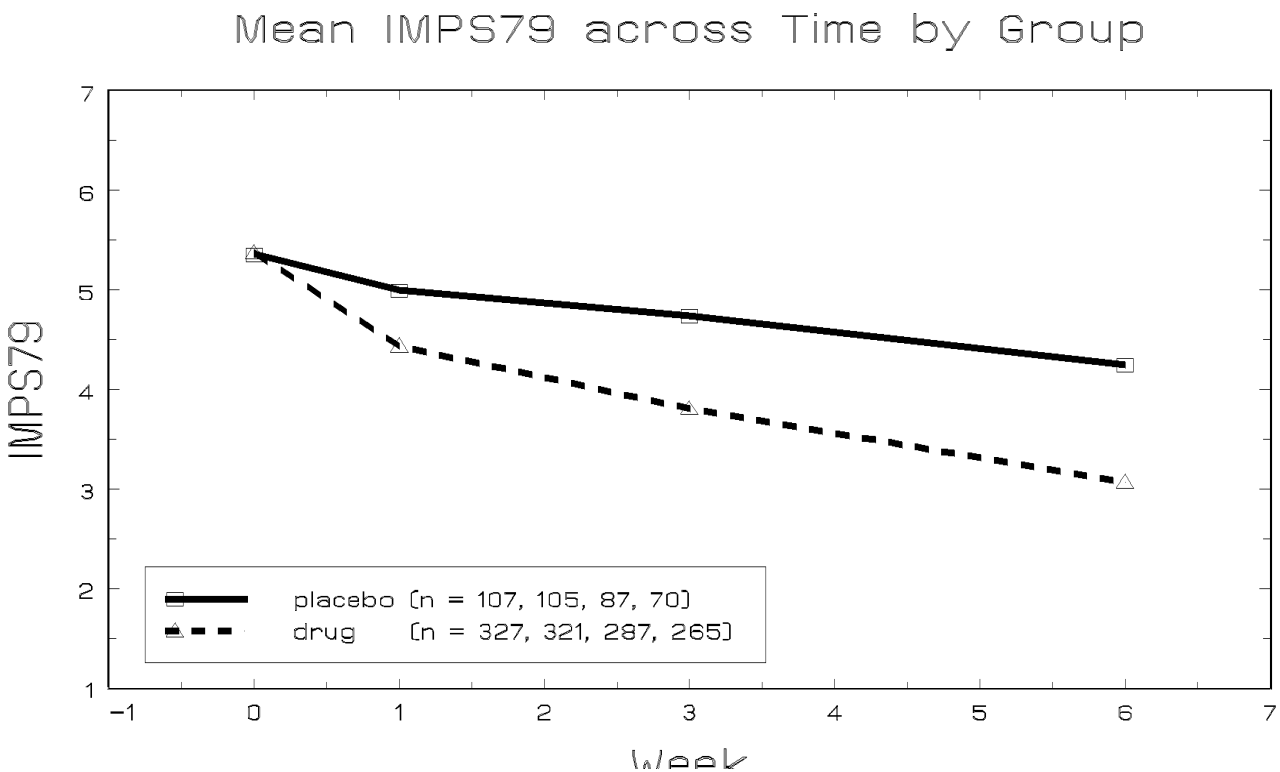
Descriptive Statistics - NIMH Schizophrenia study

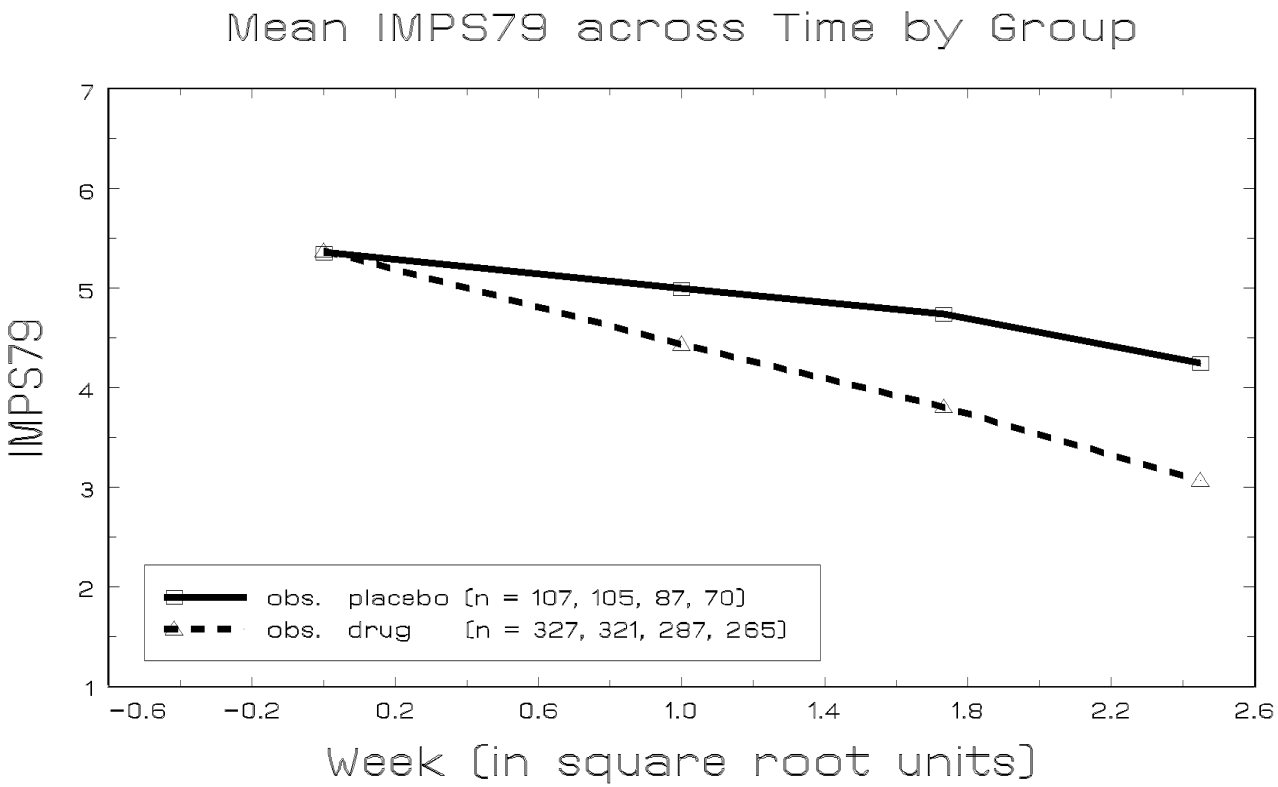
Observed IMPS79 Means, n, and sd

	week 0	week 1	week 3	week 6
placebo	5.35	4.99	4.74	4.25
n	107	105	87	70
drug	5.37	4.43	3.80	3.06
n	327	321	287	265
pooled sd	.87	1.23	1.44	1.48

Correlations: $\mathbf{n = 313}$ and $\mathit{321} \leq n \leq \mathit{424}$

	week 0	week 1	week 3	week 6
week 0	1.0	*.41*	*.25*	*.15*
week 1	**.43**	1.0	*.67*	*.47*
week 3	**.29**	**.67**	1.0	*.67*
week 6	**.14**	**.47**	**.68**	1.0


Mean IMPS79 across Time by Group
IMPS79
Week
placebo (n = 107, 105, 87, 70)
drug (n = 327, 321, 287, 265)


Mean IMPS79 across Time by Group
IMPS79
Week (in square root units)
obs. placebo (n = 107, 105, 87, 70)
obs. drug (n = 327, 321, 287, 265)

Mixed-effects regression model (MRM) - Schizophrenia study

$$IMPS79 = Drug + Time + (Drug \times Time) + Subj + (Subj \times Time) + Error$$

$$\texttt{IMPS79}_{ij} = \beta_0 + \beta_1 \texttt{Drug}_i + \beta_2 \texttt{SWeek}_j + \beta_3 (\texttt{Drug}_i \times \texttt{SWeek}_j) + \upsilon_{0i} + \upsilon_{1i} \texttt{SWeek}_j + \varepsilon_{ij}$$

$i = 1, \ldots, N$ subjects $\quad j = 1, \ldots, n_i$ obs

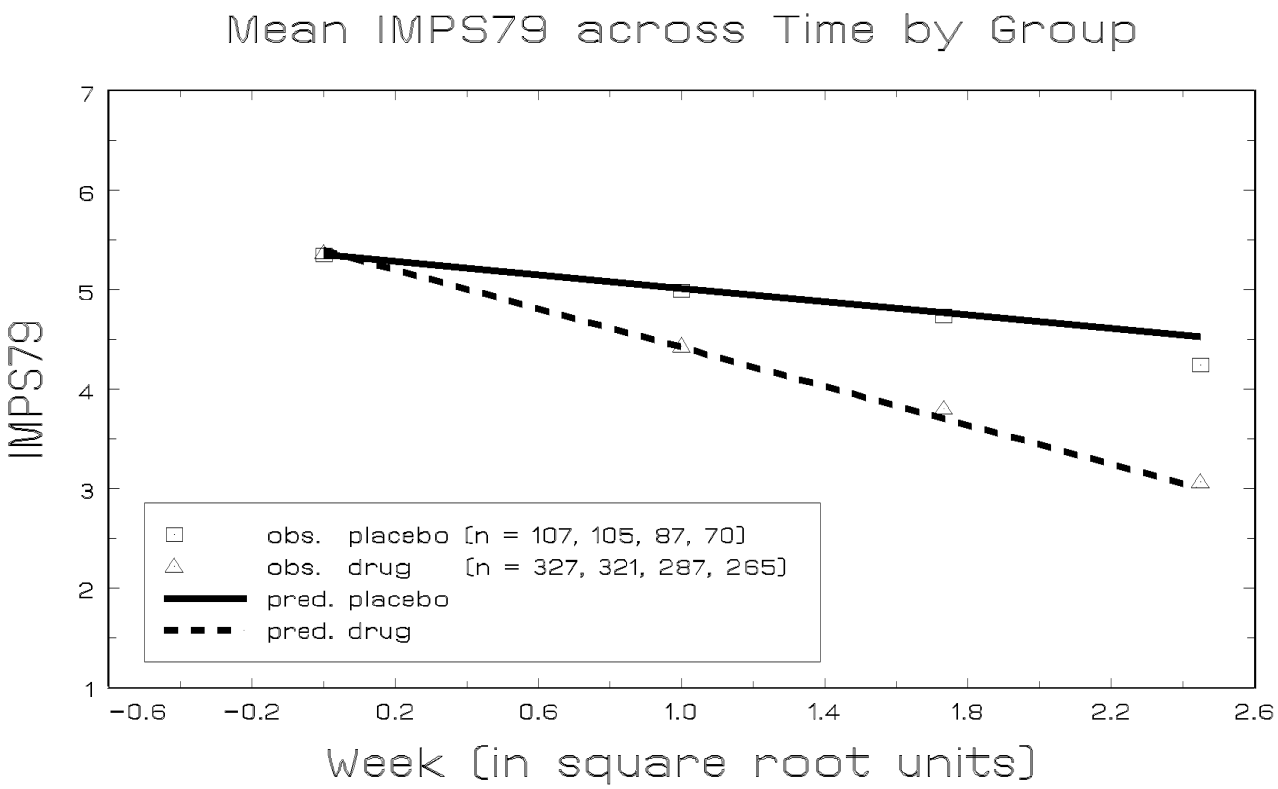
$\texttt{Drug} = 0$ for placebo, 1 for drug

$\texttt{SWeek} = 0, \sqrt{1} = 1, \sqrt{2} = 1.41, \sqrt{3} = 1.73, \sqrt{4} = 2, \sqrt{5} = 2.24, \sqrt{6} = 2.45$

NIMH Schizophrenia Study - IMPS79 across Time: ML Estimates (se)

	Completers $N = 335$			*All Subjects* $N = 437$		
	est.	se	$p <$	est.	se	$p <$
intercept	5.221	0.109	.001	5.348	0.088	.001
Drug (0 = plc; 1 = drug)	0.202	0.123	.101	0.046	0.101	.65
Time (sqrt week)	-0.393	0.073	.001	-0.336	0.068	.001
Drug by Time	-0.539	0.083	.001	-0.641	0.078	.001
Intercept variance	0.398	0.068		0.369	0.060	
	sd = .63			*sd =.61*		
Int-Time covariance	-0.011	0.035		0.021	0.034	
	r = -.04			*r =.07*		
Time variance	0.205	0.031		0.242	0.032	
	sd = .45			*sd =.49*		

Fitted and Obs. Means across Time by Condition



$$I\hat{M}PS_{ij} = 5.35 + .05\,Drug_i - .34\,Time_j - .64(D_i \times T_j)$$

Missing Data and Incomplete Data Models

$$\boldsymbol{y} \left\langle \begin{array}{ll} \boldsymbol{y}^{(O)} & R = 0 \text{ (observed)} \\ \boldsymbol{y}^{(M)} & R = 1 \text{ (missing)} \end{array} \right.$$

- GEE assumes "Missing Completely at Random" (MCAR)

$$P(\boldsymbol{R} \mid \boldsymbol{y}, \boldsymbol{X}) = P(\boldsymbol{R} \mid \boldsymbol{X}) \text{ for all } \boldsymbol{y}$$

  conditional on covariates, $\boldsymbol{R}$ is independent of $\boldsymbol{y}^{(O)}$ and $\boldsymbol{y}^{(M)}$

  $\Rightarrow$ "covariate-dependent missingness"

- Likelihood-based MRM assumes "Missing at Random" (MAR)

$$P(\boldsymbol{R} \mid \boldsymbol{y}, \boldsymbol{X}) = P(\boldsymbol{R} \mid \boldsymbol{X}, \boldsymbol{y}^{(O)}) \text{ for all } \boldsymbol{y}^{(M)}$$

  conditional on covariates *and* observed values of the dependent variable, $\boldsymbol{R}$ is independent of $\boldsymbol{y}^{(M)}$

  $\Rightarrow$ "ignorable non-response"

Missing Not At Random (MNAR) Models

- When the data are nonignorable (*i.e.*, MNAR), standard statistical models can yield badly biased results
- The observed data provide no information to either confirm or refute ignorability

$\Rightarrow$ **cannot test MAR versus MNAR**

Two general classes of MNAR models

- Pattern mixture models - use missing data pattern information in the longitudinal modeling
- Selection models - modeling of both the longitudinal and missingness processes

$\Rightarrow$ will be illustrated in terms of MRMs, however they can be more broadly defined and utilized

Comments on MNAR models

- Ordinary MRM (and other full-likelihood models) assume MAR, these extended models do not
- Use of nonignorable models can be helpful in conducting a sensitivity analysis; to see how the conclusions might vary as a function of what is assumed about the missing data
- Not necessarily a good idea to rely on a single MNAR model, because the assumptions about the missing data are impossible to assess with the observed data
- One should use MNAR models sensibly, possibly examining several types of such models for a given dataset

Pattern-mixture models for missing data

Little (1993, 1994, 1995); Hedeker & Gibbons (1997)

- divide subjects into groups depending on their missing data pattern
- the missing data pattern is a between-subjects variable to be used in longitudinal data analysis

For 3 timepoints, there are eight (2^3) possible missing data patterns:

pattern group	time1	time2	time3
1	O	O	O
2	O	O	M
3	O	M	O
4	M	O	O
5	M	M	O
6	O	M	M
7	M	O	M
8	M	M	M

where, O=observed and M=missing

Since MMM provides no data, it is ignored in the analysis

Representing patterns with dummy-coded variables

pattern	*D1*	*D2*	*D3*	*D4*	*D5*	*D6*
OOO	0	0	0	0	0	0
OOM	1	0	0	0	0	0
OMO	0	1	0	0	0	0
MOO	0	0	1	0	0	0
MMO	0	0	0	1	0	0
OMM	0	0	0	0	1	0
MOM	0	0	0	0	0	1

- these dummy-codes represent deviations from pattern OOO
- Other coding schemes can be used ("effect" or "sequential" coding)
- these variables are used as main effects and interactions

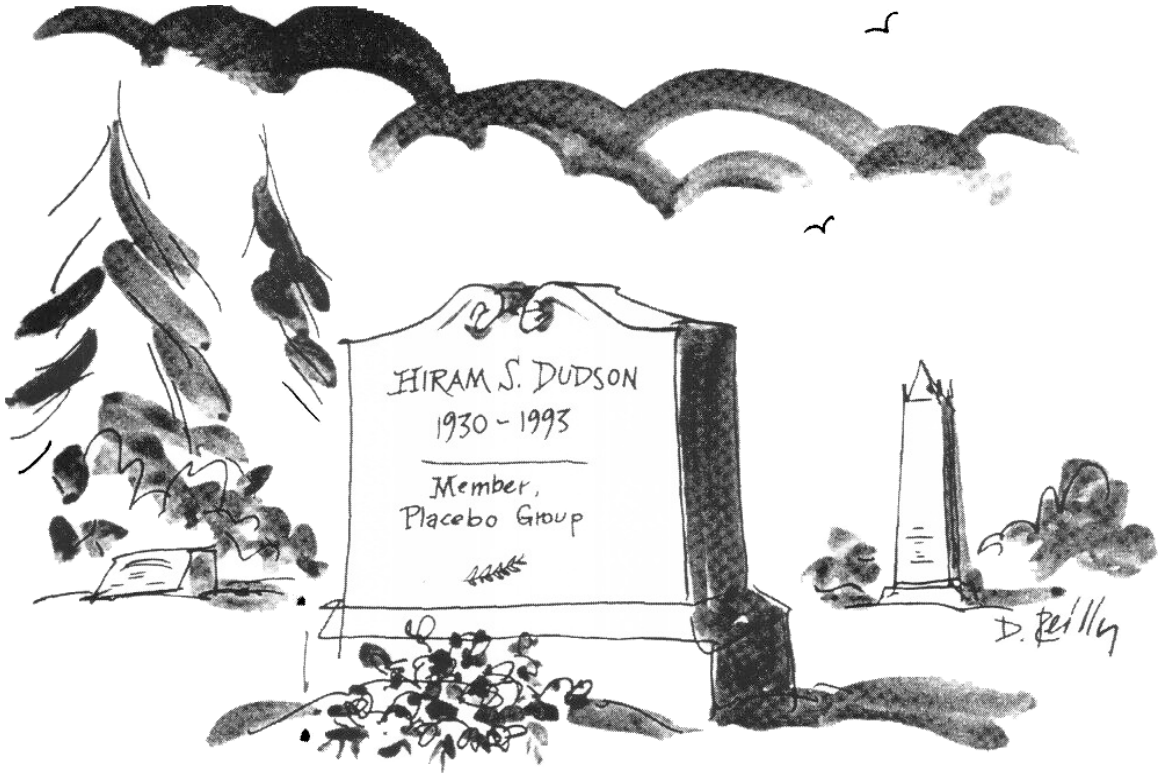
Classification of Subjects based on missing-data

$$\texttt{Drop}_i = \begin{cases} 0 & \text{subject measured at week 6 (last timepoint)} \\ 1 & \text{subject missing at week 6 (last timepoint)} \end{cases}$$

Drug group	Drop group completer	Drop group dropout	total
placebo	70 (.65)	38 (.35)	108
drug	265 (.81)	64 (.19)	329
total	335	102	437

- Dropout not independent of Drug $\chi^2_1 = 11.25, p < .001$
- Is dropout related to severity of illness?
- Does dropout moderate the influence of other variables' effects on severity of illness?

Where did the placebo patients go?



Mixed-effects pattern mixture model: Schiz data

augment the basic MRM of `IMPS79` over time:

$$\texttt{IMPS79}_{ij} = \beta_0 + \beta_1 \texttt{Drug}_i + \beta_2 \texttt{SWeek}_j + \beta_3 (\texttt{Drug}_i \times \texttt{SWeek}_j) + \upsilon_{0i} + \upsilon_{1i} \texttt{SWeek}_j + \varepsilon_{ij} \ ,$$

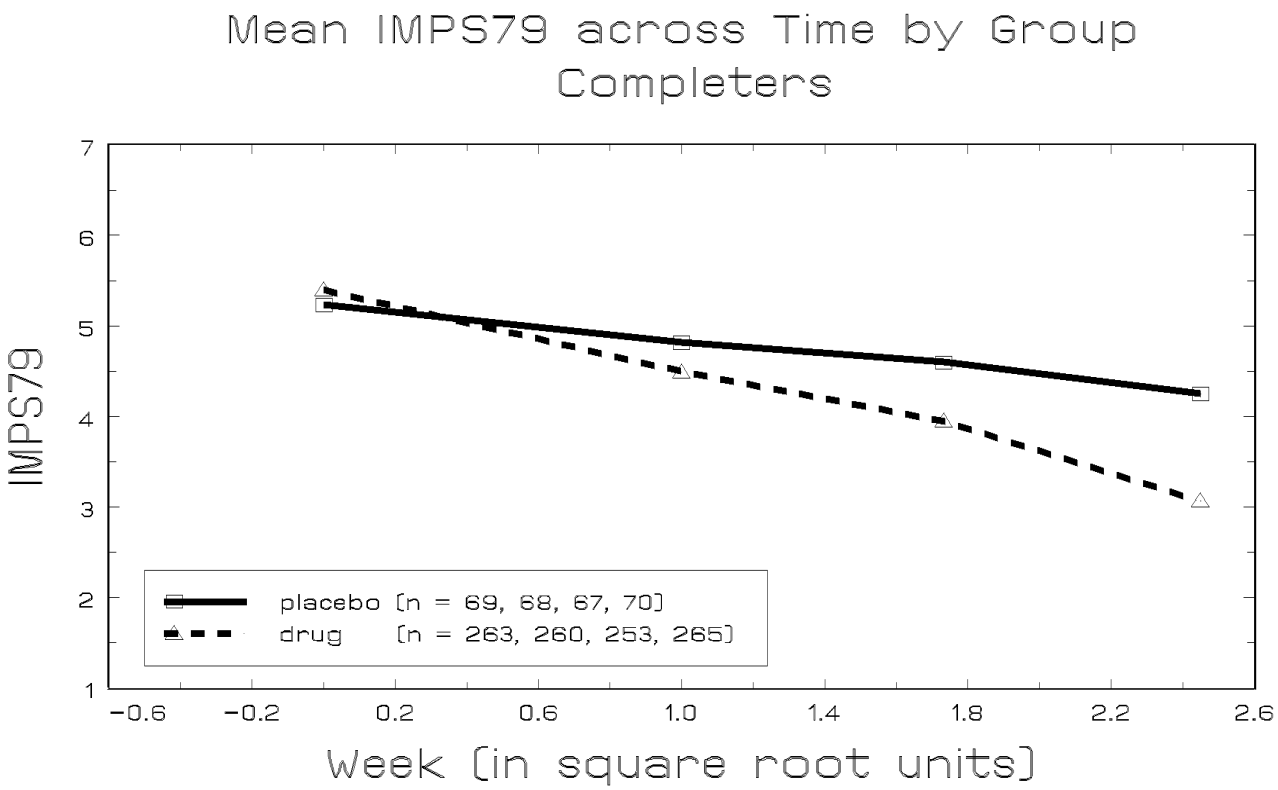
with variables based on the missing data patterns

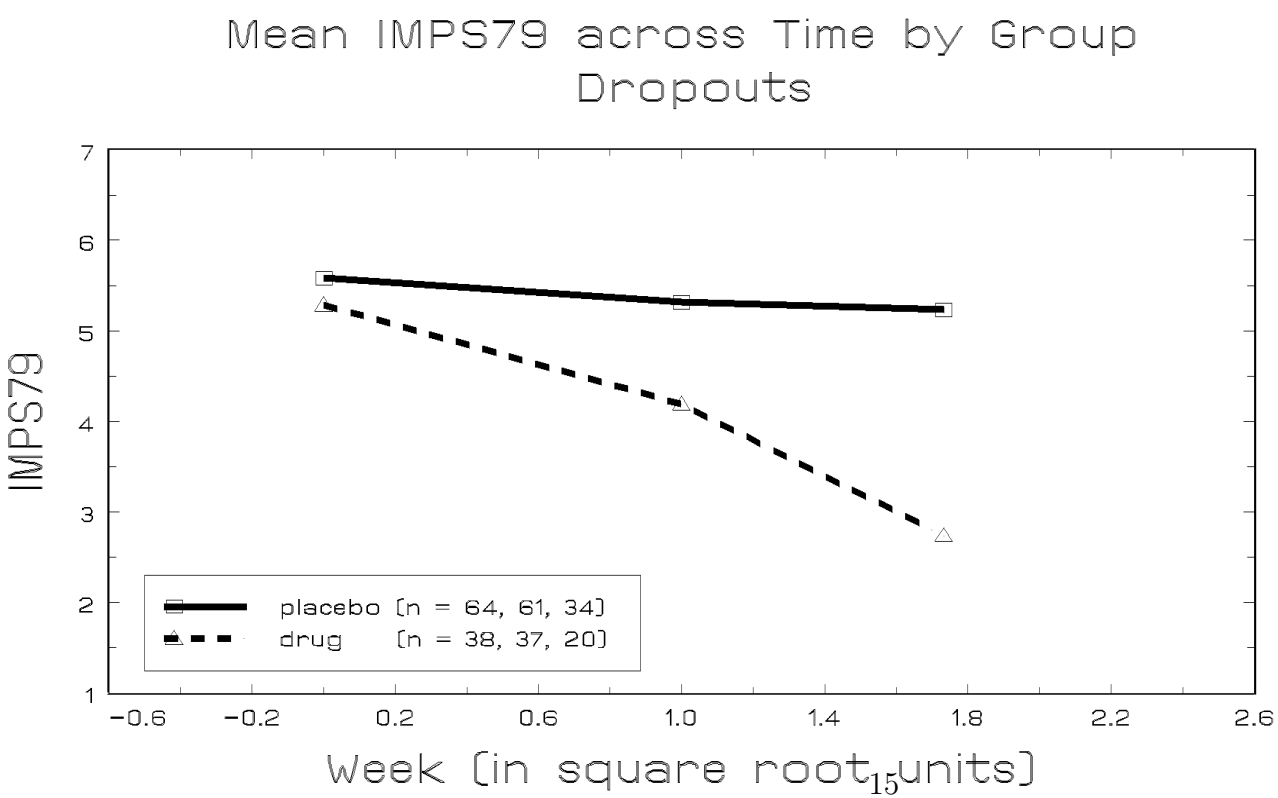
e.g., completers (N = 335) vs non-completers (N = 102)

`Drop` = 0 or 1 for those that did not or did dropout from the trial (*i.e.*, were not measured at the final study timepoint)

$$\begin{aligned}\texttt{IMPS79}_{ij} = \ & \beta_0 + \beta_1 \texttt{Drug}_i + \beta_2 \texttt{SWeek}_j + \beta_3 (\texttt{Drug}_i \times \texttt{SWeek}_j) \\ & + \beta_0^D \texttt{Drop}_i + \beta_1^D (\texttt{Drop}_i \times \texttt{Drug}_i) + \beta_2^D (\texttt{Drop}_i \times \texttt{Sweek}_j) \\ & + \beta_3^D (\texttt{Drop}_i \times \texttt{Drug}_i \times \texttt{Sweek}_j) + \upsilon_{0i} + \upsilon_{1i} \texttt{SWeek}_j + \varepsilon_{ij}\end{aligned}$$

- β_0, β_1, β_2, and β_3 are for the completer subsample
- β_0^D, β_1^D, β_2^D, and β_3^D how dropouts differ from completers
- three-way interaction is of particular interest - indicates how the drug by time interaction varies with study completion


Mean IMPS79 across Time by Group
Completers
IMPS79
7
6
5
4
3
2
1
−0.6
−0.2
0.2
0.6
1.0
1.4
1.8
2.2
2.6
Week (in square root units)
placebo (n = 69, 68, 67, 70)
drug (n = 263, 260, 253, 265)


Mean IMPS79 across Time by Group
Dropouts
IMPS79
7
6
5
4
3
2
1
−0.6
−0.2
0.2
0.6
1.0
1.4
1.8
2.2
2.6
Week (in square root units)
placebo (n = 64, 61, 34)
drug (n = 38, 37, 20)

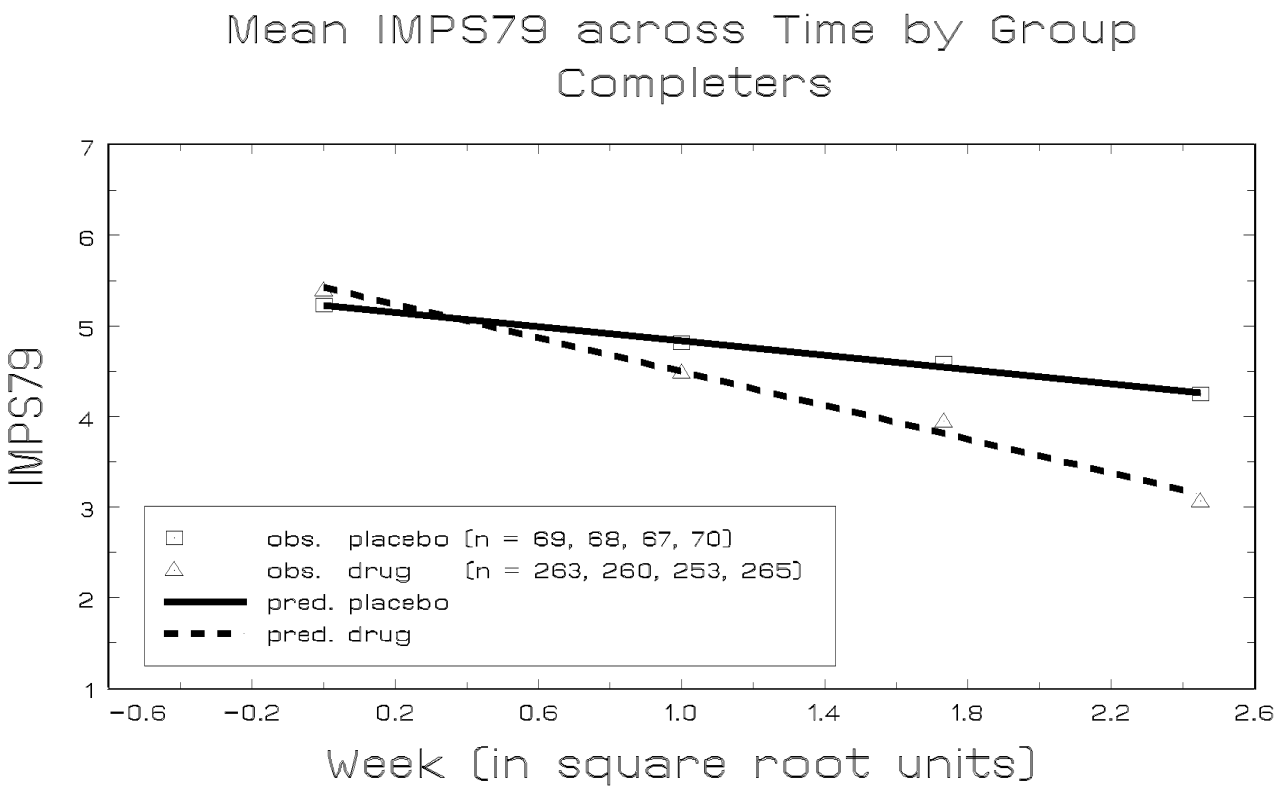
Less Restrictive Pattern Mixture Model

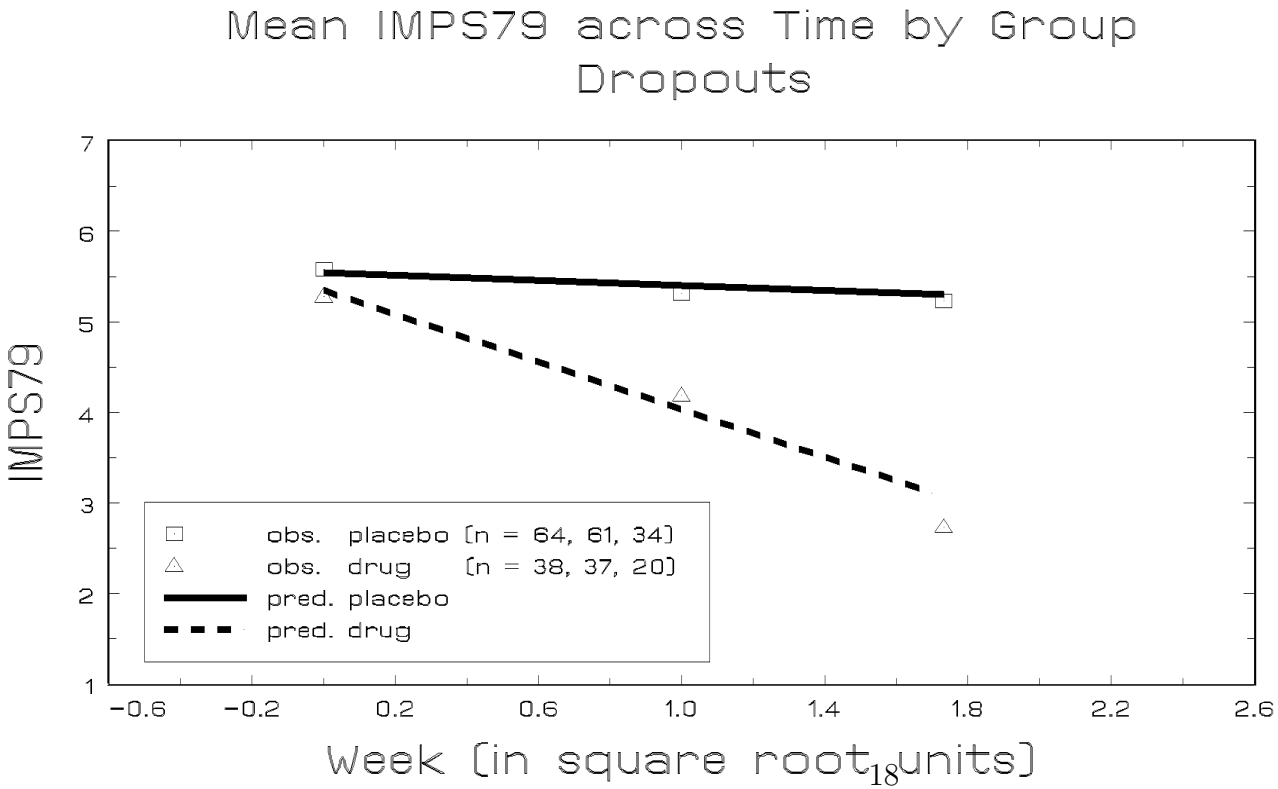
- use week of dropout variable $\mathtt{D}_i$ in forming missing data patterns
- six missing data patterns: five dropout weeks and completers
- Let $\mathtt{D}_m = \mathtt{D}_1, \ldots, \mathtt{D}_5$ denote dummy-variables which contrast each dropout pattern to the completers

$$
\begin{aligned}
\mathtt{IMPS79}_{ij} \;=\; & \beta_0 + \beta_1 \mathtt{Drug}_i + \beta_2 \mathtt{SWeek}_j + \beta_3 (\mathtt{Drug}_i \times \mathtt{SWeek}_j) \\
& + \sum_{m=1}^{5} \beta_0^m \mathtt{D}_m \;+\; \beta_1^m (\mathtt{D}_m \times \mathtt{Drug}_i) \;+\; \beta_2^m (\mathtt{D}_m \times \mathtt{Sweek}_j) \\
& + \beta_3^m (\mathtt{D}_m \times \mathtt{Drug}_i \times \mathtt{Sweek}_j) \\
& + \upsilon_{0i} + \upsilon_{1i} \mathtt{SWeek}_j + \varepsilon_{ij}
\end{aligned}
$$

- β_0, β_1, β_2, β_3 are for completers
- $\beta_0^m, \beta_1^m, \beta_2^m$, β_3^m indicate how dropout group m differs from completers
- the β_3^m parameters are of great interest

parameter	est	se	$p <$	est	se	$p <$	est	se	$p <$
`Int` β_0	5.348	.088	.0001	5.221	.108	.0001	5.221	.107	.0001
`Drug` β_1	.046	.101	.65	.202	.121	.096	.202	.120	.094
`SWeek` β_2	-.336	.068	.0001	-.393	.076	.0001	-.393	.075	.0001
`Drug` $\times$ `SWeek` β_3	-.641	.078	.0001	-.539	.086	.0001	-.539	.085	.0001
Dropout				`Drop` $= 1$ $(N = 102)$			`D` $= 1$ $(N = 37)$		
`Int` β_0^1				.320	.186	.086	.471	.288	.102
`Drug` β_1^1				-.399	.227	.079	-.456	.353	.20
`SWeek` β_2^1				.252	.159	.115	.240	.334	.47
`Drug` $\times$ `SWeek` β_3^1				-.635	.196	.002	-.412	.412	.32
							`D` $= 2$ $(N = 10)$		
`Int` β_0^2							.524	.437	.23
`Drug` β_1^2							-.703	.613	.25
`SWeek` β_2^2							.338	.398	.40
`Drug` $\times$ `SWeek` β_3^2							-.735	.562	.19
							`D` $= 3$ $(N = 42)$		
`Int` β_0^3							.047	.256	.85
`Drug` β_1^3							-.198	.318	.53
`SWeek` β_2^3							.377	.208	.07
`Drug` $\times$ `SWeek` β_3^3							-.835	.261	.002
							`D` $= 4$ $(N = 5)$		
`Int` β_0^4							.801	.653	.22
`Drug` β_1^4							-.237	.841	.78
`SWeek` β_2^4							-.101	.485	.84
`Drug` $\times$ `SWeek` β_3^4							-1.210	.625	.054
							`D` $= 5$ $(N = 8)$		
`Int` β_0^5							.337	.645	.60
`Drug` β_1^5							-.842	.746	.26
`SWeek` β_2^5							-.157	.466	.74
`Drug` $\times$ `SWeek` β_3^5							.231	.538	.67
Deviance		4649.0			4623.3			4607.8	


Mean IMPS79 across Time by Group
Completers
IMPS79
Week (in square root units)
obs. placebo (n = 69, 68, 67, 70)
obs. drug (n = 263, 260, 253, 265)
pred. placebo
pred. drug
7
6
5
4
3
2
1
−0.6
−0.2
0.2
0.6
1.0
1.4
1.8
2.2
2.6


Mean IMPS79 across Time by Group
Dropouts
IMPS79
Week (in square root units)
obs. placebo (n = 64, 61, 34)
obs. drug (n = 38, 37, 20)
pred. placebo
pred. drug
7
6
5
4
3
2
1
−0.6
−0.2
0.2
0.6
1.0
1.4
1.8
2.2
2.6

Pattern-mixture averaged results (Little, 1995)

- Obtained averaging over missing-data patterns
  - *e.g.*, completers and dropouts
- Uses sample proportions as estimates of missing-data pattern proportions
- Depends on "model" for missing-data patterns
  - *e.g.*, completer versus dropout status varies by tx

Completer		**Dropout**	
placebo	*70/108*	*placebo*	*38/108*
drug	*265/329*	*drug*	*64/329*
	335/437		**102/437**

Pattern-mixture averaged results

$$\hat{\bar{\boldsymbol{\beta}}} \;=\; \hat{\pi}_c \hat{\boldsymbol{\beta}}_c \;+\; \hat{\pi}_d \hat{\boldsymbol{\beta}}_d \;=\; \hat{\boldsymbol{\beta}}_c + \hat{\pi}_d \hat{\boldsymbol{\beta}}^D$$

- $\hat{\boldsymbol{\beta}}_c$ correspond to the coefficients in the current model formulation not involving dropout (*i.e.*, intercept, drug, time, drug by time)
- $(\hat{\boldsymbol{\beta}}_d - \hat{\boldsymbol{\beta}}_c) = \hat{\boldsymbol{\beta}}^D$ correspond to the dropout-related coefficients in the current model formulation (*i.e.*, dropout, dropout by drug, dropout by time, dropout by drug by time)
- $\hat{\pi}_d$ is the sample proportion of dropouts

$\Rightarrow$ averaged estimates are linear combinations of model estimates (obtained by simple arithmetic or via `ESTIMATE` statement in SAS)

Placebo Intercept

$$\underset{Completers}{\frac{335}{437}(5.22)} + \underset{Dropouts}{\frac{102}{437}(5.22+0.32)} = 5.22 + \frac{102}{437}(0.32) = 5.30$$

Placebo Time effect

$$\underset{Completers}{\frac{335}{437}(-0.39)} + \underset{Dropouts}{\frac{102}{437}(-0.39+0.25)} = -0.39 + \frac{102}{437}(0.25) = -0.33$$

Drug Intercept difference

$$\underset{Completers}{\frac{335}{437}(0.20)} + \underset{Dropouts}{\frac{102}{437}(0.20-0.40)} = 0.20 + \frac{102}{437}(-0.40) = 0.11$$

Drug Time difference

$$\underset{Completers}{\frac{335}{437}(-0.54)} + \underset{Dropouts}{\frac{102}{437}(-0.54-0.64)} = -0.54 + \frac{102}{437}(-0.64) = -0.69$$

SAS example using ESTIMATE

```
/* pattern-mixture random intercept and trend model
/* using marginal dropout proportion to estimate averaged results */

PROC MIXED METHOD=ML COVTEST;
CLASS id;
MODEL imps79 = sweek drug sweek*drug dropout dropout*sweek
         dropout*drug dropout*drug*sweek / SOLUTION;
RANDOM INTERCEPT sweek /SUB=id TYPE=UN G GCORR;

ESTIMATE 'avg int' INTERCEPT 1 sweek 0 drug 0 sweek*drug 0 dropout .2334
         dropout*sweek 0 dropout*drug 0 dropout*drug*sweek 0;
ESTIMATE 'avg sweek' INTERCEPT 0 sweek 1 drug 0 sweek*drug 0 dropout 0
         dropout*sweek .2334 dropout*drug 0 dropout*drug*sweek 0;
ESTIMATE 'avg drug' INTERCEPT 0 sweek 0 drug 1 sweek*drug 0 dropout 0
         dropout*sweek 0 dropout*drug .2334 dropout*drug*sweek 0;
ESTIMATE 'avg sweek*drug' INTERCEPT 0 sweek 0 drug 0 sweek*drug 1 dropout 0
         dropout*sweek 0 dropout*drug 0 dropout*drug*sweek .2334;
RUN;
```

where `dropout` =0 (completers) or =1 (dropouts) and 102/437 = .2334 (*i.e.*, dropout proportion)

Don't have (or like) SAS?
(*i.e.*, can I do pattern-mixture modeling with SPSS? .... YES!)

Weighted Effect Coding (Darlington, 1990, *Regression and Linear Models*, pp. 238-239): in ANOVA context

- yields comparisons of each cell mean, except the reference cell, with a weighted average of cell means

Effect coding

level	D
1	1
2	-1

becomes

Weighted effect coding

level	D^*
1	1
2	$-1 \times \frac{\text{weight of level 1}}{\text{weight of level 2}}$

$$Y = \beta_0 + \beta_1 D^* + e$$

β_0 = weighted average of Y means across the two levels
β_1 = difference between level 1 mean and the weighted average

SPSS example using weighted effect coding

Step 1 - do some data management to create the necessary variables

SCHIZREP.SAV

`ID`	subject's ID
`IMPS79`	severity of illness (dependent variable)
`Week`	study week (= 0, 1, 2, 3, 4, 5, 6)
`Drug`	=0 (placebo) or =1 (drug)
`SexM`	=0 (female) or =1 (male)
`SWeek`	sqrt of `Week`
`DrugSwk`	product of `Drug` by `Sweek`
`Week_max`	subject's maximum value of `Week`
`Dropout`	=0 (`Week_max` = 6) or =1 (`Week_max` < 6)
`DropW`	$= \frac{-\hat{\pi}_D}{\hat{\pi}_C} = \frac{-102}{335}$ (`Dropout` = 0) or =1 (`Dropout` = 1)
`DropWDrug`	product of `DropW` by `Drug`
`DropWSweek`	product of `DropW` by `SWeek`
`DropWDrugSwk`	product of `DropW` by `Drug` by `SWeek`

Model with weighted effect coding

$$
\begin{aligned}
\texttt{IMPS79}_{ij} = \; & \beta_0 + \beta_1 \texttt{Drug}_i + \beta_2 \texttt{SWeek}_j + \beta_3 (\texttt{Drug}_i \times \texttt{SWeek}_j) \\
& + \beta_0^{DW} \texttt{DropW}_i + \beta_1^{DW} (\texttt{DropW}_i \times \texttt{Drug}_i) \\
& + \beta_2^{DW} (\texttt{DropW}_i \times \texttt{Sweek}_j) \\
& + \beta_3^{DW} (\texttt{DropW}_i \times \texttt{Drug}_i \times \texttt{Sweek}_j) \\
& + \upsilon_{0i} + \upsilon_{1i} \texttt{SWeek}_j + \varepsilon_{ij}
\end{aligned}
$$

- β_0, β_1, β_2, and β_3 are weighted averages over completers and dropouts (*i.e.*, exactly what we want!)

- β_0^{DW}, β_1^{DW}, β_2^{DW}, and β_3^{DW} how dropouts differ from the weighted averages

SPSS syntax for model with weighted effect coding

Schizpm.sps

```
MIXED
  Imps79 WITH Drug Sweek DrugSwk
              DropW DropWDrug DropWSweek DropWDrugSwk
  /FIXED = Drug Sweek DrugSwk
           DropW DropWDrug DropWSweek DropWDrugSwk
  /METHOD = ML
  /PRINT = SOLUTION TESTCOV
  /RANDOM INTERCEPT Sweek | SUBJECT(ID) COVTYPE(UN) .
```

Pattern-mixture averaged results

using either approach (ESTIMATE in SAS or weighted effect coding in SPSS), we get:

parameter	estimate	std error	p-value
`Intercept`	5.2958	.0898	.0001
`Drug`	.1086	.1029	.29
`SWeek`	-.3346	.0670	.0001
`DrugSwk`	-.6868	.0776	.0001

Great! We're done, right?

I've got some good news, and some not-so-good news

averaged estimates are fine

standard errors are not exactly correct

Standard Errors for Averaged Estimates

$$\hat{V}(\hat{\bar{\boldsymbol{\beta}}}) \;=\; \hat{V}(\hat{\bar{\boldsymbol{\beta}}})_F \;+\; \frac{n_d\, n_c}{N^3}(\hat{\boldsymbol{\beta}}^D)^2$$

where, $\hat{V}(\hat{\bar{\boldsymbol{\beta}}})_F$ is the variance treating the sample proportions as known, *i.e.*, the square of the standard error one gets using

$$\hat{\bar{\boldsymbol{\beta}}} \;=\; \hat{\boldsymbol{\beta}}_c + \hat{\pi}_d \hat{\boldsymbol{\beta}}^D$$

and not taking into account the fact that π_d is estimated (*i.e.*, this is obtained using methods that yield linear combinations of estimates and their associated standard errors)

$\Rightarrow$ simple augmentation of $\hat{V}(\hat{\bar{\boldsymbol{\beta}}})_F$ to get correct standard errors

Calculation of $\hat{V}(\hat{\bar{\beta}}) = \hat{V}(\hat{\bar{\beta}})_F \; + \; \frac{n_d n_c}{N^3}(\hat{\beta}^D)^2$

parameter	$\hat{\bar{\beta}}$	$\hat{V}(\hat{\bar{\beta}})_F$	$\hat{\beta}^D$	Augment	$\hat{V}(\hat{\bar{\beta}})$	SE
intercept	5.2958	$(.0898)^2 = .00806$	.3203	.000042	.00810	.0900
time	-.3346	$(.0670)^2 = .00449$	.2517	.000026	.00452	.0672
drug	.1086	$(.1029)^2 = .01059$	-.3987	.000065	.01066	.1032
drug $\times$ time	-.6868	$(.0776)^2 = .00602$	-.6348	.000165	.00619	.0786

Augment $= \frac{n_d n_c}{N^3}(\hat{\beta}^D)^2$, here, $\frac{n_d n_c}{N^3} = \frac{102 \times 335}{(437)^3} = .00040945$

Pattern-mixture averaged results - using drug-stratified proportions

Placebo Intercept

$$\underset{Completers}{\frac{70}{108}(5.22)} + \underset{Dropouts}{\frac{38}{108}(5.22+0.32)} = 5.22 + \frac{38}{108}(0.32) = 5.33$$

Placebo Time effect

$$\underset{Completers}{\frac{70}{108}(-0.39)} + \underset{Dropouts}{\frac{38}{108}(-0.39+0.25)} = -0.39 + \frac{38}{108}(0.25) = -0.30$$

Drug Intercept difference

$$\underset{Completers}{\frac{265}{329}(0.20)} + \underset{Dropouts}{\frac{64}{329}(0.20-0.40)} = 0.20 + \frac{64}{329}(-0.40) = 0.12$$

Drug Time difference

$$\underset{Completers}{\frac{265}{329}(-0.54)} + \underset{Dropouts}{\frac{64}{329}(-0.54-0.64)} = -0.54 + \frac{64}{329}(-0.64) = -0.66$$

Calculation of $\hat{V}(\hat{\bar{\beta}}) = \hat{V}(\hat{\bar{\beta}})_F \; + \; \frac{n_d n_c}{N^3}(\hat{\beta}^D)^2$

parameter	$\hat{\bar{\beta}}$	$\hat{V}(\hat{\bar{\beta}})_F$	$\hat{\beta}^D$	Augment	$\hat{V}(\hat{\bar{\beta}})$	SE
intercept	5.3337	$(.0879)^2 = .00773$	.3203	.000217	.00795	.0891
time	-.3048	$(.0698)^2 = .00487$	.2517	.000134	.00500	.0707
drug	.1241	$(.1043)^2 = .01088$	-.3987	.000076	.01096	.1047
drug × time	-.6621	$(.0772)^2 = .00596$	-.6348	.000192	.00615	.0784

Augment $= \frac{n_d n_c}{N^3}(\hat{\beta}^D)^2$, where

$\frac{n_d n_c}{N^3} = \frac{38 \times 70}{(108)^3} = .00211159$ for placebo

$\frac{n_d n_c}{N^3} = \frac{64 \times 265}{(329)^3} = .00047625$ for drug

NIMH Schizophrenia Study - IMPS79 across Time: MRM models

	Ordinary			Pattern mixture			PM averaged		
parameter	est	se	$p <$	est	se	$p <$	est	se	$p <$
`Int` β_0	5.348	.088	.0001	5.221	.108	.0001	5.334	.089	.0001
`Drug` β_1	.046	.101	.65	.202	.121	.096	.124	.105	.24
`SWeek` β_2	-.336	.068	.0001	-.393	.076	.0001	-.305	.071	.0001
`Drug` $\times$ `SWeek` β_3	-.641	.078	.0001	-.539	.086	.0001	-.662	.078	.0001
`Int` β_0^D				.320	.186	.086			
`Drug` β_1^D				-.399	.227	.079			
`SWeek` β_2^D				.252	.159	.115			
`Drug` $\times$ `SWeek` β_3^D				-.635	.196	.002			
Deviance		4649.0			4623.3				

Mixed-effects selection models

These models have also been called

- random-coefficient selection models (Little, 95)
- random-effects-dependent models (Hogan & Laird, 97)
- shared parameter models (Wu & Carroll, 88; Ten Have *et al.*, 98)

- One specifies both a model for the longitudinal outcome and a model for the dropout (or missingness)
- Both models depend on random subject effects, most or all of which are shared by both models

Longitudinal model - ordinary MRM of $\boldsymbol{y}_i$

$$\boldsymbol{y}_i = \boldsymbol{X}_i\boldsymbol{\beta} + \boldsymbol{Z}_i\boldsymbol{v}_i + \boldsymbol{\varepsilon}_i$$

Dropout model - grouped/discrete time survival analysis of D_i

$$\log(-\log(1 - \mathrm{P}(D_i = j \mid D_i \geq j))) = \boldsymbol{W}_i\boldsymbol{\alpha} + \boldsymbol{v}_i\boldsymbol{\alpha}^*$$

$\boldsymbol{W}_i$ includes dropout predictors, some or all may be in $\boldsymbol{X}_i$

To the extent that $\boldsymbol{\alpha}^*$ are nonzero, this is a nonignorable model because missingness, here characterized simply as dropout time, is dependent on both $\boldsymbol{y}_i^O$ *and* $\boldsymbol{y}_i^M$ (via $\boldsymbol{v}_i$)

Treatment (denoted `Drug`) by last wave (denoted `Maxweek`)

	`Maxweek`						
`Drug`	1	2	3	4	5	6	Total
placebo	13	5	16	2	2	70	108
	(.12)	(.05)	(.15)	(.02)	(.02)	(.65)	
drug	24	5	26	3	6	265	329
	(.07)	(.02)	(.08)	(.01)	(.02)	(.81)	

$\Rightarrow$ dropout is more common among the placebo group

Pearson χ^2 test yields $p < .025$;

Mantel-Haenszel χ^2 test for trend yields $p < .0013$

Mixed-effects selection model - Schiz study

Longitudinal model:

$$\texttt{IMPS79}_{ij} = \beta_0 + \beta_1 \texttt{Drug}_i + \beta_2 \texttt{SWeek}_j + \beta_3 (\texttt{Drug}_i \times \texttt{SWeek}_j) + \upsilon_{0i} + \upsilon_{1i} \texttt{SWeek}_j + \varepsilon_{ij}$$

or, after orthogonalizing the random effects
($\boldsymbol{\upsilon}_i = \boldsymbol{S}\boldsymbol{\theta}_i$, where $\boldsymbol{\Sigma}_\upsilon = \boldsymbol{S}\boldsymbol{S}'$, Cholesky factorization)

$$\begin{aligned} \texttt{IMPS79}_{ij} \;=\; & \beta_0 + \beta_1 \texttt{Drug}_i + \beta_2 \texttt{SWeek}_j + \beta_3 (\texttt{Drug}_i \times \texttt{SWeek}_j) \\ & + (\sigma_{\upsilon_0} + \sigma^*_{\upsilon_{01}} \texttt{SWeek}_j)\, \theta_{0i} \;+\; \sigma^*_{\upsilon_1} \texttt{SWeek}_j\, \theta_{1i} \;+\; \varepsilon_{ij} \end{aligned}$$

with $\sigma^*_{\upsilon_{01}} = \sigma_{\upsilon_{01}} / \sigma_{\upsilon_0}$ and $\sigma^*_{\upsilon_1} = \sqrt{\sigma^2_{\upsilon_1} - \sigma^2_{\upsilon_{01}} / \sigma^2_{\upsilon_0}}$

Dropout model:

$$\begin{aligned}\log(-\log(1-\mathrm{P}(D_i = j \mid D_i \geq j))) \;=\; & \alpha_{0j} + \alpha_1 \texttt{Drug}_i + \alpha_2\theta_{0i} + \alpha_3\theta_{1i} \\ & + \alpha_4(\texttt{Drug}_i \times \theta_{0i}) \;+\; \alpha_5(\texttt{Drug}_i \times \theta_{1i})\end{aligned}$$

or as

$$\begin{aligned}\mathrm{P}(D_i \leq j) \;=\; & 1 - \exp(-\exp(\alpha_{0j} + \alpha_1 \texttt{Drug}_i + \alpha_2\theta_{0i} + \alpha_3\theta_{1i} \\ & + \alpha_4(\texttt{Drug}_i \times \theta_{0i}) + \alpha_5(\texttt{Drug}_i \times \theta_{1i})))\end{aligned}$$

- random effects are summaries of a person's observed *and unobserved* $\boldsymbol{y}$ data
- this shared parameter model is a nonignorable model if $\alpha_2 = \alpha_3 = \alpha_4 = \alpha_5 = 0$ is rejected
- test of whether *a particular model of ignorability is reasonable vs a particular model of nonignorability* (*i.e.*, not a general test of ignorability)

Separate and shared parameter models

	Separate (deviance = 5380.2)			Shared (deviance = 5350.1)		
parameter	ML est	std error	p-value	ML est	std error	p-value
Outcome						
intercept β_0	5.348	.088	.0001	5.320	.088	.0001
`Drug` β_1	.046	.101	.65	.088	.102	.87
`SWeek` β_2	-.336	.068	.0001	-.272	.073	.0002
`Drug` $\times$ `Sweek` β_3	-.641	.078	.0001	-.737	.083	.0001
Dropout						
`Drug` α_1	-.693	.205	.0008	-.703	.301	.02
Random intercept α_2				.447	.333	.18
Random slope α_3				.891	.467	.06
`Drug` $\times$ intercept α_4				-.592	.398	.14
`Drug` $\times$ slope α_5				-1.638	.536	.003

- separate parameter model yields identical results as running these two models, one for $\boldsymbol{y}_i$ and one for D_i, separately
- shared parameter model fits better, $\chi^2_4 = 30.1, p < .0001$
- for longitudinal component, conclusions are same as MAR model
- marginally significant slope: for the placebo group there is a tendency to dropout as the slope increases
- significant negative `Drug` $\times$ slope: the slope effect is opposite for the drug group; drug patients with more negative slopes (*i.e.*, greater improvement) are more likely to drop out

NIMH Schizophrenia Study: Severity across Time
ML Estimates (se) *random intercept and slope models*

	Completers *N = 335*	*All cases* *N = 437*	*Shared Parameter* *N = 437*	*Pattern Mixture* *N = 437*
intercept	5.221	5.348	5.320	5.334
	(.109)	(.088)	(.088)	(.089)
Drug (0=P; 1=D)	0.202	0.046	0.088	0.124
	(.123)	(.101)	(.102)	(.105)
Time (sqrt wk)	-0.393	-0.336	-0.272	-0.305
	(.073)	(.068)	(.073)	(.071)
Drug by Time	-0.539	-0.641	-0.737	-0.662
	(.083)	(.078)	(.083)	(.078)

Conclusions

- Mixed-effects regression models (MRMs) useful for incomplete longitudinal data
  - can handle subjects measured incompletely or at different timepoints
  - missing data assumed MAR
    - dependent on covariates *and*
    - available data on dependent variable

- Mixed-effects pattern-mixture and selection (*i.e.*, shared parameter) models augment MRM

  Pattern-mixture

  – adds missing-data pattern as between-subjects factor
  – assesses degree to which "missingness" influences outcomes
  – assesses degree to which "missingness" interacts with model terms (*i.e.*, intervention group, intervention group by time)

  Selection

  – missingness in terms of important covariates
  – missingness in terms of (shared) random subject effects

$\Rightarrow$ Does not invent data, attempts to maximize information obtained from *available* data

SAS MIXED code - SCHIZPM5b.SAS

```
DATA one; INFILE 'c:\mixdemo\schizrep.dat';
INPUT id imps79 week drug sex ;

/* the coding for the variables is as follows:
id = subject id number
imps79 = overall severity (1=normal, ..., 7=among the most extremely ill)
week = 0,1,2,3,4,5,6 (most of the obs.  are at weeks 0,1,3, and 6)
drug 0=placebo 1=drug (chlorpromazine, fluphenazine, or thioridazine)
sex 0=female 1=male */

/* compute the square root of week to linearize relationship */
sweek = SQRT(week);

/* calculate the maximum value of week for each subject
(suppress the printing of the output for this procedure) */
PROC MEANS NOPRINT; CLASS id; VAR week; OUTPUT OUT=two MAX=maxweek;
RUN;

/* determine if a subject has data at week 6
dropout = 0 (for completers) or = 1 (for dropouts) */
DATA three; SET two;
dropout=0;
IF maxweek LT 6 THEN dropout=1;
```

```
/* dataset with all subjects (adding the dropout variable) */
DATA four; MERGE one three; BY id; IF id NE .;

/* random intercept and trend model */
PROC MIXED DATA=four METHOD=ML COVTEST;
CLASS id;
MODEL imps79 = sweek drug sweek*drug / SOLUTION;
RANDOM INTERCEPT sweek /SUB=id TYPE=UN G GCORR;
RUN;

/* pattern-mixture random intercept and trend model
/* using marginal dropout proportion to estimate averaged results */
PROC MIXED DATA=four METHOD=ML COVTEST;
CLASS id;
MODEL imps79 = sweek drug sweek*drug dropout dropout*sweek
          dropout*drug dropout*drug*sweek / SOLUTION;
RANDOM INTERCEPT sweek /SUB=id TYPE=UN G GCORR;
ESTIMATE 'avg int' INTERCEPT 1 sweek 0 drug 0 sweek*drug 0 dropout .2334
          dropout*sweek 0 dropout*drug 0 dropout*drug*sweek 0;
ESTIMATE 'avg sweek' INTERCEPT 0 sweek 1 drug 0 sweek*drug 0 dropout 0
          dropout*sweek .2334 dropout*drug 0 dropout*drug*sweek 0;
ESTIMATE 'avg drug' INTERCEPT 0 sweek 0 drug 1 sweek*drug 0 dropout 0
          dropout*sweek 0 dropout*drug .2334 dropout*drug*sweek 0;
ESTIMATE 'avg sweek*drug' INTERCEPT 0 sweek 0 drug 0 sweek*drug 1 dropout 0
          dropout*sweek 0 dropout*drug 0 dropout*drug*sweek .2334;
RUN;
```

```
/* pattern-mixture random intercept and trend model
/* using drug-specific dropout proportions to estimate averaged results */

PROC MIXED DATA=four METHOD=ML COVTEST;
CLASS id;
MODEL imps79 = sweek drug sweek*drug dropout dropout*sweek
          dropout*drug dropout*drug*sweek / SOLUTION;
RANDOM INTERCEPT sweek /SUB=id TYPE=UN G GCORR;
ESTIMATE 'avg int' INTERCEPT 1 sweek 0 drug 0 sweek*drug 0 dropout .35185
          dropout*sweek 0 dropout*drug 0 dropout*drug*sweek 0;
ESTIMATE 'avg sweek' INTERCEPT 0 sweek 1 drug 0 sweek*drug 0 dropout 0
          dropout*sweek .35185 dropout*drug 0 dropout*drug*sweek 0;
ESTIMATE 'avg drug' INTERCEPT 0 sweek 0 drug 1 sweek*drug 0 dropout 0
          dropout*sweek 0 dropout*drug .19453 dropout*drug*sweek 0;
ESTIMATE 'avg sweek*drug' INTERCEPT 0 sweek 0 drug 0 sweek*drug 1 dropout 0
          dropout*sweek 0 dropout*drug 0 dropout*drug*sweek .19453;
RUN;
```

SAS code - SCHZ2MODS.SAS

```
TITLE1 'shared parameter model of time to dropout and imps79 across time';
DATA one; INFILE 'c:\mixdemo\schizrep.dat'; INPUT id imps79 week drug sex ;

/* The coding for the variables is as follows:
id = subject id number
imps79 = overall severity (1=normal, ..., 7=most extremely ill)
week = 0,1,2,3,4,5,6 (most of the obs. are at weeks 0,1,3, and 6)
drug 0=placebo 1=drug (chlorpromazine, fluphenazine, or thioridazine)
sex 0=female 1=male   */

/* compute the square root of week to linearize relationship */
sweek = SQRT(week);

/* calculate the maximum value of week for each subject
and get drug in this aggregated dataset too */
PROC MEANS NOPRINT; CLASS id; VAR week drug;
OUTPUT OUT=two MAX(week drug)=maxweek drug;

/* setting up imps79 across time and maxweek as one outcome vector */
DATA daty; SET one; outcome = imps79; ind = 0;
DATA datr; SET two; outcome = maxweek; ind = 1; IF id NE .;
DATA all; SET daty datr; BY id;
```

- uppercase represents specific SAS syntax; lowercase represents user-defined
- the SAS dataset `all` includes the $(n_i + 1) \times 1$ outcome vector $\boldsymbol{y}_i^*$, named `outcome`, which contains $\boldsymbol{y}_i$ as its first n_i elements and D_i as its final element
- `ind` with values of 0 or 1, is also defined; this variable will be used to distinguish between the $\boldsymbol{y}_i$ and D_i elements

```
/* random trend model for imps79 */
PROC MIXED DATA=daty METHOD=ML COVTEST;
CLASS id;
MODEL outcome = drug sweek sweek*drug / SOLUTION;
RANDOM INTERCEPT sweek /SUB=id TYPE=UN G GCORR;

/* model for time to dropout - grouped-time proportional hazards model */
PROC LOGISTIC DATA=datr;
MODEL outcome = drug / LINK = CLOGLOG;
```

```
/* separate modeling of imps79 and time to dropout */
PROC NLMIXED DATA=all;
PARMS b0=5.35 b1=.05 b2=-.34 b3=-.64 sde=.76 v0=.61 v01=.02 v1=.49
a1=-.69 i1=-1.95 i2=-1.70 i3=-.99 i4=-.84 i5=-.69;
IF (ind = 0) THEN
DO;
   z = (outcome - (b0 + b1*drug + b2*sweek + b3*drug*sweek
     + (v0 + v01*sweek/v0)*u1
     + SQRT(v1*v1 - (v01*v01)/(v0*v0))*sweek*u2));
   p = (1 / SQRT(2*3.14159*sde*sde)) * EXP(-.5 * (z*z) / (sde*sde));
END;
IF (ind = 1) THEN
DO;
   z = a1*drug;
   IF (outcome=1) THEN
     p = 1 - EXP(0 - EXP(i1+z));
   ELSE IF (outcome=2) THEN
     p = (1 - EXP(0 - EXP(i2+z))) - (1 - EXP(0 - EXP(i1+z)));
   ELSE IF (outcome=3) THEN
     p = (1 - EXP(0 - EXP(i3+z))) - (1 - EXP(0 - EXP(i2+z)));
   ELSE IF (outcome=4) THEN
     p = (1 - EXP(0 - EXP(i4+z))) - (1 - EXP(0 - EXP(i3+z)));
   ELSE IF (outcome=5) THEN
     p = (1 - EXP(0 - EXP(i5+z))) - (1 - EXP(0 - EXP(i4+z)));
   ELSE IF (outcome=6) THEN
     p = 1 - (1 - EXP(0 - EXP(i5+z)));
END;
IF (p > 1e-8) THEN ll = LOG(p); else ll = -1e100;
MODEL outcome ~ GENERAL(ll);
RANDOM u1 u2 ~ NORMAL([0,0], [1,0,1]) SUBJECT=id;
```

```
/* shared parameter model of imps79 and time to dropout */
PROC NLMIXED DATA=all;
PARMS b0=5.35 b1=.05 b2=-.34 b3=-.64 sde=.76 v0=.61 v01=.02 v1=.49
a1=-.69 a2=0 a3=0 a4=0 a5=0 i1=-1.95 i2=-1.70 i3=-.99 i4=-.84 i5=-.69;
IF (ind = 0) THEN
DO;
   z = (outcome - (b0 + b1*drug + b2*sweek + b3*drug*sweek
     + (v0 + v01*sweek/v0)*u1
     + SQRT(v1*v1 - (v01*v01)/(v0*v0))*sweek*u2));
   p = (1 / SQRT(2*3.14159*sde*sde)) * EXP(-.5 * (z*z) / (sde*sde));
END;
IF (ind = 1) THEN
DO;
   z = a1*drug + a2*u1 + a3*u2 + a4*u1*drug + a5*u2*drug;
   IF (outcome=1) THEN
     p = 1 - EXP(0 - EXP(i1+z));
   ELSE IF (outcome=2) THEN
     p = (1 - EXP(0 - EXP(i2+z))) - (1 - EXP(0 - EXP(i1+z)));
   ELSE IF (outcome=3) THEN
     p = (1 - EXP(0 - EXP(i3+z))) - (1 - EXP(0 - EXP(i2+z)));
   ELSE IF (outcome=4) THEN
     p = (1 - EXP(0 - EXP(i4+z))) - (1 - EXP(0 - EXP(i3+z)));
   ELSE IF (outcome=5) THEN
     p = (1 - EXP(0 - EXP(i5+z))) - (1 - EXP(0 - EXP(i4+z)));
   ELSE IF (outcome=6) THEN
     p = 1 - (1 - EXP(0 - EXP(i5+z)));
END;
IF (p > 1e-8) THEN ll = LOG(p); else ll = -1e100;
MODEL outcome ~ GENERAL(ll);
RANDOM u1 u2 ~ NORMAL([0,0], [1,0,1]) SUBJECT=id;
```