Missing Data and Dropout - part 2

BIOS6643

EJC

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1. Case study I: weight loss trial
2. Case study II: STEPPED Care trial
3. Case study III: Hormone therapy trial

Weight loss trial

- Randomized trial at the subject level to compare a toolboox intervention versus usual care in the primary care setting (reported in Saxon (2019 J Gen Intern Med))
- The toolbox consisted of: partial meal replacement program, Weight Watchers vouchers, recreation center membership, phentermine-topiramate ER, phentermine, or a group behavioral weight loss program (Colorado Weigh).
  - After 6 months of participation in the study, participants add a second tool, or add
  - A Diabetes Prevention Program-based weight loss maintenance program
- Study was conducted at 9 primary care clinics at Denver Health (DH)
- Participants were randomly selected from the DH registry

- The primary outcome was percentage of participants who achieved 5% weight loss at 12 months in those offered the toolbox of weight loss options compared with the usual care group.
- Secondary outcomes included weight loss tools chosen, weight loss tool utilization, and visit attendance.
- 305 individuals were randomly selected to be offered intervention, and 2640 were eligible comparators in the usual care group
- 119 individuals had a baseline visit (305-119=186 did not consent or did not attend baseline visit)

Demographic and baseline characteristics

Table 2 Baseline Characteristics of Intervention Group Versus Eligible Comparators

Characteristic*	Intervention ($n = 305$)	Eligible comparators ($n = 2640$)	p value
Sex—no. of patients (%)			
Female	200 (65.6%)	1877 (71.1%)	0.045
Male	105 (34.4%)	763 (28.9%)	
Race—no. of patients (%)†			
White/Caucasian	259 (84.9%)	2107 (79.8%)	0.10
Black/African American	43 (14.1%)	485 (18.4%)	
Asian	0 (0.0%)	8 (0.3%)	
Native Indian/Alaskan	0	0	
Other	0 (0.0%)	23 (0.9%)	
Unknown	3 (1.0%)	17 (0.6%)	
Ethnicity—no. of patients (%)†			
Hispanic or Latino	189 (62.0%)	1690 (64.0%)	0.48
Primary language—no. of patients (%)†			
English	219 (71.8%)	1836 (69.5%)	0.42
Spanish	86 (28.2%)	804 (30.5%)	
Insurance—no. of patients (%)‡			
Medicaid	112 (36.7%)	1091 (41.3%)	0.20
Medicare	95 (31.1%)	751 (28.4%)	
CICP/DFAP§	75 (24.6%)	670 (25.4%)	
Commercial	14 (4.6%)	77 (2.9%)	
Self-pay/other	9 (3.0%)	51 (1.9%)	
Age, mean (SD), year	53.0 (12.7)	51.1 (12.9)	0.015
Weight, mean (SD), kg	95.63 (16.69)	94.22 (15.97)	0.16
Height, mean (SD), cm	164.4 (10.74)	163.5 (9.90)	0.19
BMI, mean (SD), kg/m^2	35.22 (3.90)	35.17 (3.89)	0.83
BMI category			
Class I obesity (BMI 30–34.9 kg/m^2)	173 (56.7%)	1446 (54.8%)	0.74
Class II obesity (BMI 35–39.9 kg/m^2)	88 (28.9%)	818 (31.0%)	
Class III obesity (BMI 40–45 kg/m^2)	44 (14.4%)	376 (14.2%)	
Medical conditions—no. of patients (%)†			
Diabetes, hypertension, or dyslipidemia	251 (82.3%)	2158 (81.7%)	0.81
Diabetes	157 (51.5%)	1405 (53.2%)	0.56
Hypertension	213 (69.8%)	1880 (71.2%)	0.62
Dyslipidemia	179 (58.7%)	1461 (55.3%)	0.27

Exploring visits

Table 8 : Number of visits by Study Group

	Study Group					
	Tool		Control		Total	
	N	(%)	N	(%)	N	(%)
Total	119	(100.0%)	2930	(100.0%)	3049	(100.0%)
Number of visits						
1	11	(9.2%)	153	(5.2%)	164	(5.4%)
2	7	(5.9%)	384	(13.1%)	391	(12.8%)
3	11	(9.2%)	436	(14.9%)	447	(14.7%)
4	7	(5.9%)	462	(15.8%)	469	(15.4%)
5	10	(8.4%)	409	(14.0%)	419	(13.7%)
6	8	(6.7%)	341	(11.6%)	349	(11.4%)
7	8	(6.7%)	228	(7.8%)	236	(7.7%)
8	3	(2.5%)	157	(5.4%)	160	(5.2%)
9	7	(5.9%)	111	(3.8%)	118	(3.9%)
10	8	(6.7%)	83	(2.8%)	91	(3.0%)
11	11	(9.2%)	47	(1.6%)	58	(1.9%)
12	28	(23.5%)	27	(0.9%)	55	(1.8%)
13-19	0	(0%)	83	(2.8%)	83	(2.7%)
20-29	0	(0%)	9	(0.3%)	9	(0.3%)
Have final weight (1yr +/-6mo)						
No	6	(5.0%)	290	(9.9%)	296	(9.7%)
Yes	113	(95.0%)	2640	(90.1%)	2753	(90.3%)

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Table 9 : Total Follow-up Time (months) by Study Group

		Study Group		
		Tool	Control	Total
Total	**N**	119	2930	3049
Time between last-first visits, months	**Mean**	11.3	11.6	11.5
	Median	11.9	12.0	11.9
	Q1	11.4	10.7	10.7
	Q3	12.0	12.9	12.9

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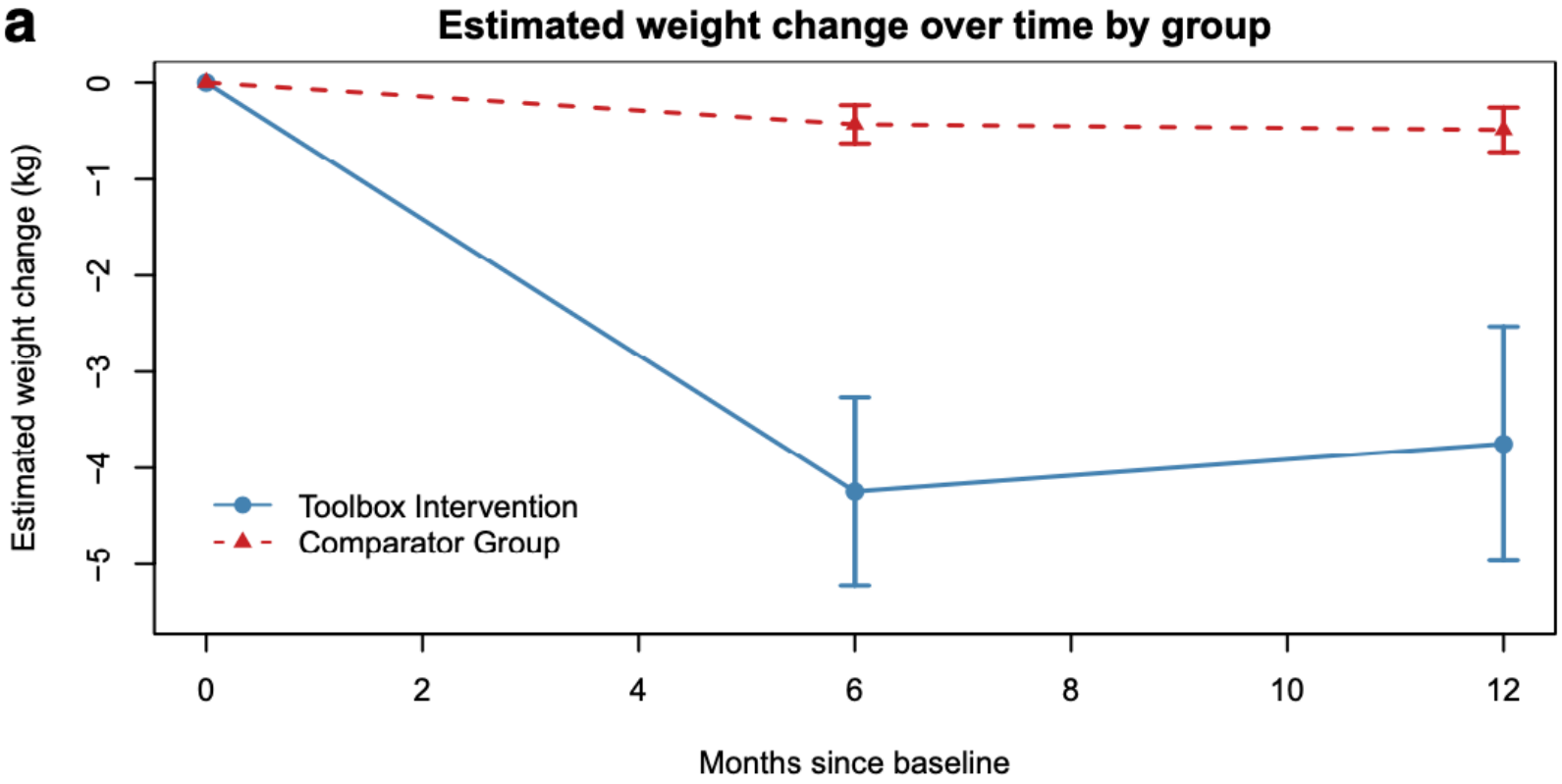
Main results of trial

Table 3 Percent with ≥5% Body Weight Loss, Mean Weight Loss, and Mean Percentage Weight Loss over 12 Months

Variable	Intervention group	Comparator group	*p* value*
Intervention-eligible population	*n* = 305	*n* = 2640	
Participants achieving ≥5% weight loss, no. (%)	71 (23.3)	415 (15.7)	< 0.001
Mean weight change, kg (SD)	−1.4 (6.4)	−0.4 (5.8)	0.007
Mean weight change, % (SD)	−1.4 (6.5)	−0.3 (6.1)	0.013
On-treatment population	*n* = 113	*n* = 2640	
Participants achieving ≥5% weight loss, no. (%)	39 (34.5)	415 (15.7)	< 0.001
Mean weight change, kg (SD)	−3.2 (6.7)	−0.4 (5.8)	< 0.001
Mean weight change, % (SD)	−3.2 (6.4)	−0.3 (6.1)	< 0.001
Per-protocol population (≥4 visits)	*n* = 89	*n* = 2640	
Participants achieving ≥5% weight loss, no. (%)	36 (40.4)	415 (15.7)	< 0.001
Mean weight change, kg (SD)	−3.8 (6.7)	−0.4 (5.8)	< 0.001
Mean weight change, % (SD)	−3.9 (6.4)	−0.3 (6.1)	< 0.001

**Chi-square test for categorical variables and t test with unequal variance for continuous variables*

Longitudinal model results



Model in SAS


```
ods rtf file='J:\Weight_Loss\rtf\longitudinal_weights_model_results.rtf' bodytitle nogtitle nogfoot style=Arial;
ods output estimates=ests;
proc mixed data =modelong noclprint covtest order=internal;
  class studygrp studyid ;
  model wtchgkg = timemo tminus6plus studygrp*timemo studygrp*tminus6plus/ noint chisq solution;
  random timemo tminus6plus / subject = studyid type = un gcorr;

  ESTIMATE 'wt chg for grp 1 at baseline'  timemo 0 studygrp*timemo 0 0  tminus6plus 0 studygrp*tminus6plus 0 0;
  ESTIMATE 'wt chg for grp 1 at 6 mo'  timemo 6 studygrp*timemo 6 0  tminus6plus 0 studygrp*tminus6plus 0 0 ;
  ESTIMATE 'wt chg for grp 1 at 12 mo'  timemo 12 studygrp*timemo 12 0  tminus6plus 6 studygrp*tminus6plus 6 0;

  ESTIMATE 'wt chg for grp 2 at baseline'    timemo 0 studygrp*timemo 0 0  tminus6plus 0 studygrp*tminus6plus 0 0;
  ESTIMATE 'wt chg for grp 2 at 6 mo'    timemo 6 studygrp*timemo 0 6  tminus6plus 0 studygrp*tminus6plus 0 0;
  ESTIMATE 'wt chg for grp 2 at 12 mo'    timemo 12 studygrp*timemo 0 12 tminus6plus 6 studygrp*tminus6plus 0 6  ;
  title 'Mixed model with knot at 6 months, random slopes, no group main effect';
  footnote "Created by: %pgmname";
run;
ods rtf close;
title;
footnote;
```

Sensitivity analyses to missing final weight

Table 11 : Primary Endpoint Sensitivity Analyses
Missing data for final weight handled three different ways

		Study Group			
Weight loss achieved		**Tool (119)**	**Control (2930)**	**Total (3049)**	**P-value***
(a) Lost >5% of initial body weight	No	80 (67.2%)	2,515 (85.8%)	2,595 (85.1%)	<0.001
	Yes	39 (32.8%)	415 (14.2%)	454 (14.9%)	
(b) Lost >5% of initial body weight	No	80 (67.2%)	2,495 (85.2%)	2,575 (84.5%)	<0.001
	Yes	39 (32.8%)	435 (14.8%)	474 (15.5%)	
(c) Lost >5% of initial body weight	No	65 (54.6%)	2,287 (78.1%)	2,352 (77.1%)	<0.001
	Yes	54 (45.4%)	643 (21.9%)	697 (22.9%)	

**Chi-square test*
Sensitivity analyses: (a) assumed missing weights meant unsuccessful weight loss, (b) used last obs carried forward, and (c) used nadir weight.
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Stepped care trial

STEPPED-CARE randomized trial. Results from real data included here.

- A behavioral intervention was tested versus usual care in 286 patients with lung or head and neck cancer.
- Population: low income patients in the Denver area across 5 hospitals
- Primary outcomes: anxiety, depression and coping skills scores
- Outcomes were measured at baseline, and at 6, 12 and 24 weeks

Demographic characteristics, death and lost to followup

Table 4.1: Baseline demographic characteristics of patients randomized to either condition

Variable	Overall N = 286[1]	Usual Care N = 139[1]	Intervention N = 147[1]	StdDiff[2]
Language preference				0.23
English	265 (93%)	133 (96%)	132 (90%)	
Spanish	21 (7.3%)	6 (4.3%)	15 (10%)	
Gender				0.11
Female	119 (42%)	54 (39%)	65 (44%)	
Male	167 (58%)	85 (61%)	82 (56%)	
Age	65 / 66 (58, 72)	65 / 67 (58, 73)	65 / 66 (58, 72)	0.001
Age Group				0.001
[18, 65]	134 (47%)	65 (47%)	69 (47%)	
> 65	152 (53%)	74 (53%)	78 (53%)	
Ethnicity				0.090
Hispanic	61 (21%)	27 (19%)	34 (23%)	
Non-Hispanic	225 (79%)	112 (81%)	113 (77%)	
Race[a]				0.090
Missing	16 (5.6%)	5 (3.6%)	11 (7.5%)	
Black	15 (5.2%)	6 (4.3%)	9 (6.1%)	
White	245 (86%)	123 (88%)	122 (83%)	
Other	10 (3.5%)	5 (3.6%)	5 (3.4%)	
Death	31 (11%)	13 (9.4%)	18 (12%)	0.090
Lost to follow up	54 (19%)	19 (14%)	35 (24%)	0.26

Longitudinal model results

Table 4.2: Analysis of primary outcome in the ITT populations

Outcome[1]	Time	Usual Care N = 139 [2]	Intervention N = 147 [2]	Difference[2]	p-value[3]
Anxiety	Baseline	15.62 (14.11, 17.13)	15.62 (13.9, 17.34)	0 (0, 0)	0.0243
	6 Weeks	15.92 (14.41, 17.43)	15.56 (13.84, 17.28)	0.37 (0.06, 0.68)	
	3 Months	16.22 (14.69, 17.75)	15.49 (13.75, 17.23)	0.73 (0.1, 1.36)	
	6 Months	16.83 (15.07, 18.59)	15.36 (13.46, 17.26)	1.46 (0.19, 2.73)	
Coping Skills	Baseline	201.58 (154.17, 248.99)	201.58 (191.94, 211.22)	0 (0, 0)	0.0061
	6 Weeks	197.42 (151.28, 243.56)	201.25 (191.69, 210.81)	-3.83 (-6.55, -1.11)	
	3 Months	193.26 (144.51, 242.01)	200.92 (190.98, 210.86)	-7.66 (-13.13, -2.19)	
	6 Months	184.94 (119.42, 250.46)	200.26 (188.5, 212.02)	-15.31 (-26.23, -4.39)	
Depression	Baseline	14.37 (13.14, 15.6)	14.37 (12.82, 15.92)	0 (0, 0)	0.0057
	6 Weeks	14.93 (13.71, 16.15)	14.49 (12.94, 16.04)	0.44 (0.13, 0.75)	
	3 Months	15.48 (14.23, 16.73)	14.61 (13.02, 16.2)	0.88 (0.25, 1.51)	
	6 Months	16.6 (15.13, 18.07)	14.85 (13.13, 16.57)	1.75 (0.52, 2.98)	

[1] The domains correspond to the following specific measures (see Table 1): Anxiety – PROMIS-Ca Short Form 8 (range: 8-40; higher values indicate worse outcome). Coping Skills – Coping Self Efficacy (range: 0-260; higher values indicate better outcome). Depression - PROMIS-Ca Short Form 8 (range: 8-40; higher values indicate worse outcome).

[2] A linear mixed model with random intercepts for both patients and clinics has been used, with adjustment for cancer type and cancer stage. The expected mean of the outcomes at the different times are displayed for lung cancer and late stage (3 or 4) patients in both the usual care and intervention arms.

[3]The p-value corresponds to the test of the interaction between time and intervention arm.

Missing

Table A.7: Demographic and baseline characteristics by missing category.

Characteristic	Overall, N = 286[1]	Completed, N = 184[1]	Missing, N = 102[1]	p-value[2]
Randomize				0.009
Control	139 (49%)	100 (54%)	39 (38%)	
Intervention	147 (51%)	84 (46%)	63 (62%)	
Language preference				0.009
English	265 (93%)	176 (96%)	89 (87%)	
Spanish	21 (7.3%)	8 (4.3%)	13 (13%)	
Gender				0.72
Female	119 (42%)	78 (42%)	41 (40%)	
Male	167 (58%)	106 (58%)	61 (60%)	
Age	65 / 66 (58, 72)	67 / 68 (61, 74)	61 / 62 (55, 70)	<0.001
Age Group				<0.001
[18, 65]	134 (47%)	71 (39%)	63 (62%)	
> 65	152 (53%)	113 (61%)	39 (38%)	
Ethnicity				0.013
Hispanic	61 (21%)	31 (17%)	30 (29%)	
Non-Hispanic	225 (79%)	153 (83%)	72 (71%)	
Race				0.093
*missing	16 (5.6%)	8 (4.3%)	8 (7.8%)	
Black	15 (5.2%)	7 (3.8%)	8 (7.8%)	
White	245 (86%)	160 (87%)	85 (83%)	
Other	10 (3.5%)	9 (4.9%)	1 (1.0%)	
Income				0.008
*missing	18 (6.3%)	6 (3.3%)	12 (12%)	
1. Less than $4,000	197 (69%)	127 (69%)	70 (69%)	
2. $4,000 - $5,400	25 (8.7%)	21 (11%)	4 (3.9%)	
3. More than $5,400	46 (16%)	30 (16%)	16 (16%)	
Education				0.053
*missing	1 (0.3%)	0 (0%)	1 (1.0%)	
1. High school or less	146 (51%)	87 (47%)	59 (58%)	
2. College or higher	139 (49%)	97 (53%)	42 (41%)	

Longitudinal model results adjusting for variables that are associated with missing

Table A.9: Analyses of primary outcomes adjusting for variables related to missing (age, ethnicity, education and income level). Table displays expected mean differences at different time points. These mean differences have been calculated based on model in Table A.8.

Outcome[a]	Time	Control	Intervention	Difference[b]	p-value[c]
Anxiety	Baseline	26.98 (13.06, 40.9)	26.98 (21.77, 32.19)	0 (0, 0)	0.032
	6 Weeks	27.22 (13.3, 41.14)	26.88 (21.67, 32.09)	0.35 (0.04, 0.66)	
	3 Months	27.46 (13.5, 41.42)	26.77 (21.54, 32)	0.69 (0.06, 1.32)	
	6 Months	27.95 (13.74, 42.16)	26.57 (21.3, 31.84)	1.38 (0.13, 2.63)	
Coping Skills	Baseline	184.6 (-721.35, 1090.55)	184.6 (142.46, 226.74)	0 (0, 0)	0.001
	6 Weeks	180.1 (-725.81, 1086.01)	184.61 (142.49, 226.73)	-4.51 (-7.2, -1.82)	
	3 Months	175.59 (-733.97, 1085.15)	184.61 (142.41, 226.81)	-9.02 (-14.37, -3.67)	
	6 Months	166.57 (-761.29, 1094.43)	184.62 (141.99, 227.25)	-18.04 (-28.74, -7.34)	
Depression	Baseline	21.62 (9.17, 34.07)	21.62 (16.68, 26.56)	0 (0, 0)	0.0048
	6 Weeks	22.14 (9.69, 34.59)	21.7 (16.76, 26.64)	0.44 (0.13, 0.75)	
	3 Months	22.66 (10.17, 35.15)	21.78 (16.84, 26.72)	0.88 (0.27, 1.49)	
	6 Months	23.7 (10.98, 36.42)	21.94 (16.94, 26.94)	1.76 (0.54, 2.98)	

[a] The domains correspond to the following specific measures (see Table 1): Anxiety – PROMIS-Ca Short Form 8 (range: 8-40; higher values indicate worse outcome). Coping Skills – Coping Self Efficacy (range: 0-260; higher values indicate better outcome). Depression - PROMIS-Ca Short Form 8 (range: 8-40; higher values indicate worse outcome).

[b] A linear mixed model with random intercepts for both patients and clinics has been used, with adjustment for cancer type, cancer stage, age (as continuous), ethnicity (Hispanic versus non-Hispanic), education level (college or more versus less than college) and income (less than $4,000, $4,000-$5,400, and More than $5,400). The expected mean of the outcomes at the different times are displayed for lung cancer, late stage (3 or 4), mean age, Hispanic ethnicity, less than college education level, and income level of $4, 000-$5,400 patients in both the usual care and intervention arms.

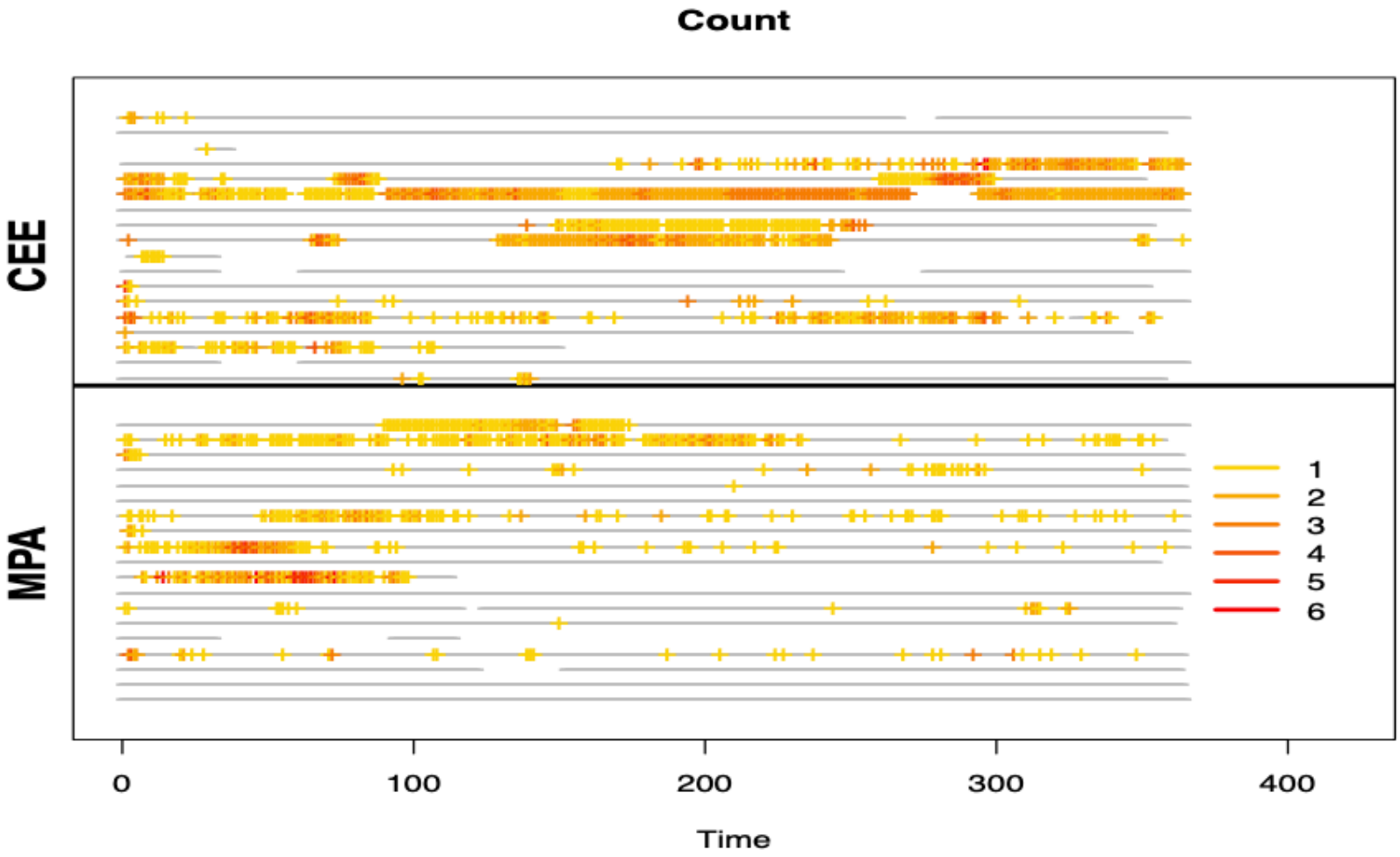
[c] The p-value corresponds to the test of the interaction between time and intervention arm.

[d] The sample size is 139 in the control and 147 in the intervention arms.

Hormone therapy trial to improve hot flushes/flashes

- Counts of the number of hot flushes per day over a period of one year, along with a daily severity level of the hot flushes, were recorded
- 38 healthy women were randomized to medroxyprogesterone acetate (MPA) versus conjugated equine oestrogen (CEE, gold standard)
  - 20 women were in the MPA group and 18 in the CEE group
- The objective was to investigate if MPA reduced the number of hot flushes (and the their severity)

Missing data might be NMAR



Joint model to address potentially informative visit process

- Joint model of
  - counts of hot flashes daily - Poisson with random effects over time
  - visit process (whether information was non-missing on a given day) - logistic longitudinal model
  - results reported in Juarez-Colunga (2017 Biometrics)
- Look at the results in the counts submodel. This sensitivity analysis only tests for informative missing of the type considered.