Title
The efficacy of a new drug against a disease

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Abstract
A randomized clinical trial was carried out with the purpose of testing the efficacy of a new drug against a disease. 1,554 male and female patients were randomly assigned to one of two treatments (*i.e.*, new drug and placebo). The outcome was severity of the disease determined at two follow-up visits, approximately six or twelve months after the beginning of treatment. To explore the treatment effects of this new drug, we mainly applied marginal modeling for repeated ordinal data with treatment (*i.e.*, new drug and placebo), gender (*i.e.*, male and female), occasion (*i.e.*, months 12 and months 6) and initial severity (*i.e.*, severity 2 or 3) as covariates. We fitted a saturated model with all potential interactions, obtained a reduced model using backward selection (p-value < 0.05), checked the proportionality and refitted this reduced model. We conclude that under most situations, significant differences exist between patients' response to these two treatments. Comparing patients at months 12 with those at months 6 after treatment, under most situations, we can observe a significantly increasing odds of getting less severe disease, which means a significantly overall improvement over time. The rate of improvement over time from months 6 to months 12 after treatment ranges from 1.69 to 5.17 per 6 months depending on initial severity (*i.e.*, severity 2 or 3), gender (*i.e.*, male and female) and cumulative proportional odds (*i.e.*, cumulative odds of severity equal to 2 and 1). The odds of getting this overall improvement over time for males is also significantly higher than that for females (odds ratio: 1.76, p-value: 0.0011, 95% CI: 1.25-2.46).

Introduction
Recently, a clinical trial has been designed to test the efficacy of a new drug against a disease. Male and female patients were randomly assigned to one of two treatments (*i.e.*, new drug and placebo). They were evaluated prior to treatment to determine the initial severity of the disease. Severity is measured on a three-point ordinal scale, 1 being the least severe. Only patients with initial severity 2 or 3 were included in the study. For each patient, severity of the disease was also determined at two follow-up visits, approximately 6 and 12 months after the beginning of treatment. The outcome was severity of the disease determined at two follow-up visits, approximately six or twelve months after the beginning of treatment.

The main question of interest here is whether differences exist between the patients' responses to the two treatments. Further questions pertain to the rate of improvement or worsening over time (*i.e.*, follow-up months 6 or 12) after treatment and differences in this improvement or worsening over time between males and females. We also explore whether differences exist between patients at months 12 and those at months 6, or between males and females, in term of difference in treatment effects (*i.e.*, new drug vs. placebo).

Methodology

Dataset

1,554 patients were recruited into our study, and based on the summary statistics at baseline (Table 1), we can observe an approximate equal proportion of each treatment in each gender group (*i.e.*, Female: 0.47 vs. 0.53, Male: 0.56 vs. 0.53), which implies that male and female patients are randomly assigned to one of two treatments (*i.e.*, new drug and placebo). We can also see an approximate equal proportion of each treatment in each initial severity group (*i.e.*, initial severity 2: 0.51 vs. 0.49, initial severity 3: 0.51 vs. 0.49).

Table 1. Summary statistics by treatment and gender at baseline

		Treatment		
		Drug	Placebo	Total
Gender	Female	393(0.47)	443(0.53)	836
	Male	401(0.56)	317(0.53)	718
Initial severity	2	361(0.51)	349(0.49)	710
	3	433(0.51)	411(0.49)	844

Based on summary statistics after six and twelve follow-up months (Table 2), we can observe an approximately unequal proportion of each treatment in each severity group. For the lower severity (*i.e.*, 1 or 2), we observe a higher proportion of this new drug group compared with placebo group, while for the higher severity (*i.e.*, 3), we see a higher proportion of placebo group.

Table 2. Summary statistics by treatment and gender after 6 follow-up months and 12 follow-up months

		Treatment		
		Drug	Placebo	Total
Months 6 severity	NA	36(0.58)	26(0.42)	62
	1	180(0.59)	127(0.41)	307
	2	370(0.56)	286(0.44)	656
	3	208(0.39)	321(0.61)	529
Months 12 severity	NA	36(0.58)	26(0.42)	62
	1	373(0.79)	102(0.21)	475
	2	259(0.51)	247(0.49)	506
	3	126(0.25)	385(0.75)	511

Overall, from initial, months 6 to months 12, we can see a general decreasing trend for proportion of this new drug (initial severity: 0.51, months 6 severity: 0.39, months 12 severity: 0.25) while a general increasing trend for proportion of placebo group (initial severity: 0.49, months 6 severity: 0.61, months 12 severity: 0.75) in severity equal to 3 or high severity group. We can also see a general increasing trend for proportion of this new drug (months 6 severity: 0.59, months 12 severity: 0.79) while a general decreasing trend for proportion of placebo group (months 6 severity: 0.41, months 12 severity: 0.21) in

severity equal to 1 or low severity group. Therefore, we can see the positive treatment effect of this new drug to this disease.

Marginal modeling for repeated ordinal data[1]

Let Y_t be the categorical variable with I categories at time t, and let $\mathbf{X}_t$ be the covariates at time t. With repeated ordinal responses, marginal cumulative logit model with or without proportional assumption or other logit models can be used for the marginal distributions:

$$\text{logit}P(Y_t \leq j) = \alpha_j + \boldsymbol{\beta}_j'\mathbf{X}_t, j = 1, \dots, I-1 \quad (1)$$

We can also write this formula (1) as follows:

$$\log\frac{P(Y_t \leq j)}{1-P(Y_t \leq j)} = \alpha_j + \boldsymbol{\beta}_j'\mathbf{X}_t, j = 1, \dots, I-1 \quad (2)$$

Since our outcome severity only has three categories (*i.e.,* 1 or 2 or 3), we have I equal to 3. Therefore, we are able to model both $\log\frac{P(Y_t \leq 2)}{1-P(Y_t \leq 2)} = \log\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$ and $\log\frac{P(Y_t \leq 1)}{1-P(Y_t \leq 1)} = \log\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$, equivalent to log cumulative proportional odds (*i.e.*, cumulative odds of severity equal to 2 and 1) for our analyses. Our final cumulative logit model should be based on weighted least squares (WLS) residuals of the observed and fitted marginal cumulative logits.

We mainly applied marginal modeling for repeated ordinal data with treatment (*i.e.*, new drug and placebo), gender (*i.e.*, male and female), occasion (*i.e.*, months 12 and months 6) and initial severity (*i.e.*, severity 2 or 3) as covariates. We first tried to fit the saturated model with all interactions, and then applied backward selection to eliminate those variables with no significance (p-value ≥ 0.05). If high-order interaction terms are significant (p-value < 0.05), we will keep low-order terms regardless of their significances.

If we have the proportionality for some covariates, we can use the same βs for those covariates for both $\log\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$ and $\log\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$ (*i.e.*, cumulative odds of severity equal to 2 and 1). Therefore, we need to check proportionality for each covariate after variable selection. After checking proportionality, we should refit this model based on WLS residuals and marginal cumulative logits.

Results

We first tried to fit the saturated model with all interactions (Appendix Table 1), and then applied backward selection to eliminate those variables with no significance (p-value ≥ 0.05) including four-way interaction, two three-way interaction and one two-way interaction. Since some high-order interaction terms were significant (p-value < 0.05), we kept low-order terms regardless of their significances including gender and the interaction between gender and occasion.

We then checked the proportionality for this reduce model (Appendix Table 2), and we observed three terms where proportionality did not hold including occasion, gender and the interaction between treatment and occasion (p-value < 0.05). For other terms, we have the proportionality for some covariates, so we can use the same βs for those covariates for both $\log\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$ and $\log\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$ (*i.e.*, cumulative odds of severity equal to 2 and 1).

We refitted our final model (Table 3), and we observed significant terms related to treatment including treatment (p-value: <0.0001), the interaction between treatment and occasion (p-value: <0.0001), the interaction between treatment and initial (p-value: 0.0008), the interaction between gender and treatment (p-value: 0.0003), the interaction among gender, treatment and occasion (p-value: 0.0007) and the interaction among treatment, initial and occasion (p-value: 0.0087). Therefore, we can conclude that there are significant differences between the patients' responses to the two treatments. Moreover, our final model fitted the observed very appropriately, based on the goodness of fit (statistic = 14.47, DF = 16, p-value = 0.5638).

Table 3. Final model analysis of weighted least squares estimates[1]

Parameter	Estimate	Standard Error	P-value
intercept	0.69	0.04	<.0001
	-1.19	0.05	<.0001
gender[2]	-0.01	0.04	0.8601
	-0.11	0.05	0.0195
treatment	0.62	0.04	<.0001
occasion[2]	0.05	0.04	0.1953
	0.19	0.04	<.0001
initial	-0.13	0.04	0.0006
gender*treatment	0.15	0.04	0.0003
gender*occasion	0.03	0.03	0.2771
treatment*occasion[2]	0.24	0.04	<.0001
	0.35	0.04	<.0001
treatment*initial	-0.13	0.04	0.0008
occasion*initial	0.06	0.03	0.0607
gender*treatment*occasion	0.11	0.03	0.0007
treatment*initial*occasion	0.08	0.03	0.0087

1 – goodness of fit statistic = 14.47, DF = 16, p-value = 0.5638
2 – terms with no proportional assumption

Comparing patients at months 12 with those at months 6 after treatment (Table 4), we used cumulative proportional odd ratio of months 12 vs. months 6 after treatment and 95% confidence interval. Except female patients with initial severity equal to 2 who do not have significant odds ratio (p-value: 0.9038, 95% CI: 0.74, 1.41), we can observe a significantly increasing odds of getting less severe disease, which means a significantly overall improvement over time from months 6 to months 12 (odds ratio > 1, p-value < 0.05, 95%CI limits > 1). The rate of improvement over time from months 6 to months 12 after treatment ranges from 1.69 to 5.17 per 6 months depending on initial severity (*i.e.*, severity 2 or 3), gender (*i.e.*, male and female) and cumulative proportional odds (*i.e.*, $\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$ and $\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$) (*i.e.*, cumulative odds of severity equal to 2 and 1).

Table 4. Occasion effects after treatment at each initial severity for each gender[1]

occasion effect after treatment[3] (months 12 vs. months 6)		gender			
		female		male	
		$\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$	$\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$	$\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$	$\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$
initial severity	2	1.02 (0.74, 1.41)[2]	1.69 (1.26, 2.26)	1.79 (1.24, 2.60)	2.97 (2.13, 4.14)
	3	1.77 (1.29, 2.44)	2.94 (2.12, 4.09)	3.12 (2.31, 4.21)	5.17 (3.83, 6.97)

1 – goodness of fit statistic = 14.47, DF = 16, p-value = 0.5638
2 – odds ratios that are not significant (p-value > 0.05)
3 – cumulative proportional odd ratio of months 12 vs. months 6 after treatment and 95% Confidence Interval

We also calculated the cumulative proportional odd ratio in terms of this overall improvement (*i.e.*, odd ratio of months 12 vs. months 6 after treatment) for male vs. female. The results showed the same odds ratio regardless of initial severity or cumulative proportional odds (*i.e.*, $\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$ and $\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$) (*i.e.*, cumulative odds of severity equal to 2 and 1). The odds of getting this overall improvement over time for males is also significantly 1.75 times higher than that for females (odds ratio: 1.76, p-value: 0.0011, 95% CI: 1.25-2.46).

Discussion

Besides, controlling for initial severities, follow-up time points and genders, under most situations, the odds of getting less severe disease significantly increases (*i.e.*, odds ratio > 1, p-value < 0.0001) comparing this new drug with placebo (Appendix Table 3). Furthermore, in term of difference in treatment effects, we can observe a significant difference between male and female patients at months 12 (odds ratio: 2.75, 95% CI: 1.81-4.19, p-value: <.0001) but not a significant difference at months 6 (odds ratio: 1.16, 95% CI: 0.79-1.71, p-value: 0.4395) regardless of initial severity. The odds ratio of getting less severe disease due to treatment effects (*i.e.*, new drug and placebo) increases significantly comparing male with female patients at months 12. We can also mostly see a significant difference between patients at months 12 and months 6 in term of difference in treatment effects. The odds ratio of getting less severe disease due to treatment effects (*i.e.*, new drug and placebo) increases significantly (*i.e.*, odds ratio > 1, p-value < 0.0001) comparing patients at months 12 with those at months 6 (Appendix Table 4).

We conclude that under most situations, significant differences exist between patients' response to these two treatments. Comparing patients at months 12 with those at months 6 after treatment, under most situations, we can observe a significantly increasing odds of getting less severe disease, which means a significantly overall improvement over time. The rate of improvement over time from months 6 to months 12 after treatment ranges from 1.69 to 5.17 per 6 months depending on initial severity (*i.e.*, severity 2 or 3), gender (*i.e.*, male and female) and cumulative proportional odds (*i.e.*, $\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$ and $\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$) (*i.e.*, cumulative odds of severity equal to 2 and 1). The odds of getting this overall improvement over time for males is also significantly higher than that for females (odds ratio: 1.76, p-value: 0.0011, 95% CI: 1.25-2.46).

References

[1] Lee K, Daniels MJ. A class of Markov models for longitudinal ordinal data. Biometrics. 2007;63(4):1060–1067. doi:10.1111/j.1541-0420.2007. 00800.x

Appendix

Table 1. Analysis of variance for this saturated model

Analysis of Variance			
	DF	Chi-Square	P-value
Intercept	2	1368.36	<.0001
gender[2]	2	4.89	**0.0866**
treatment	2	224.42	<.0001
occasion	2	23.09	<.0001
initial	2	13.16	0.0014
gender*treatment	2	12.37	0.0021
gender*occasion[2]	2	1.22	**0.5428**
gender*initial[1]	2	0.27	**0.873**
treatment*occasion	2	89.45	<.0001
treatment*initial	2	10.24	0.006
initial*occasion	2	6.63	0.0363
gender*treatment*occasion	2	11.33	0.0035
gender*treatment*initial[1]	2	0.35	**0.8413**
gender*initial*occasion[1]	2	0.8	**0.6712**
treatment*initial*occasion	2	8.32	0.0156
gender*treat*initial*occasion[1]	2	0.45	**0.7972**
Residual	0	.	.

1 - terms with p-value >= 0.05 will be eliminated from our model
2 - terms with p-value >= 0.05 will not be eliminated from our model, since high-order terms are significant

Table 2. Test for proportionality for this reduced model[3]

Analysis of Contrasts			
Contrast	DF	Chi-Square	P-value
test for proportionality in gender[1]	1	3.96	0.0467
test for proportionality in treatment	1	2.21	0.1372
test for proportionality in occasion[1]	1	7.89	0.0050
test for proportionality in initial	1	2.18	0.1395
test for proportionality in gender*treatment	1	0.05	0.8288
test for proportionality in gender*occasion	1	0.16	0.6912
test for proportionality in treatment*occasion[1]	1	6.34	0.0118
test for proportionality in treatment*initial	1	0.58	0.4470
test for proportionality in occasion*initial	1	3.76	0.0524
test for proportionality in gender*treatment*occasion	1	0.85	0.3573
test for proportionality in treatment*initial*occasion	1	2.97	0.0849
test for overall proportionality[2]	11	30.86	0.0012

1 – terms with no proportional assumption
2 – no overall proportional assumption
3- goodness of fit statistic = 2.16, DF = 8, p-value = 0.9756

Table 3. Treatment effects at each initial severity at each follow-up time point for each gender[1]

treatment effect[3] (drug vs. placebo)		occasion	gender			
			female		male	
			$\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$	$\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$	$\frac{P(Y_t=2)+P(Y_t=1)}{P(Y_t=3)}$	$\frac{P(Y_t=1)}{P(Y_t=3)+P(Y_t=2)}$
initial severity	2	months 6	3.01 (2.15, 4.22)	2.41 (1.72, 3.38)	3.51 (2.41, 5.10)	2.81 (1.92, 4.11)
	2	months 12	3.71 (2.62, 5.24)	4.63 (3.28, 6.54)	10.21 (6.79, 15.34)	12.75 (8.45, 19.23)
	3	months 6	1.30 (0.93, 1.80) [2]	1.04 (0.73, 1.48) [2]	1.51 (1.08, 2.10)	1.21 (0.85, 1.73)[2]
	3	months 12	3.04 (2.16, 4.28)	3.80 (2.68, 5.39)	8.38 (5.80, 12.12)	10.47 (7.17, 15.29)

1 – goodness of fit statistic = 14.47, DF = 16, p-value = 0.5638
2 – odds ratios that are not significant (p-value > 0.05)
3 – cumulative proportional odd ratio of drug vs. placebo and 95% Confidence Interval

Table 4. Occasion effects at each initial severity for each gender[1]

occasion effect [3] (months 12 vs. months 6) over treatment effect (drug vs. placebo)		gender			
		female		male	
		$\frac{P(Y_t = 2) + P(Y_t = 1)}{P(Y_t = 3)}$	$\frac{P(Y_t = 1)}{P(Y_t = 3) + P(Y_t = 2)}$	$\frac{P(Y_t = 2) + P(Y_t = 1)}{P(Y_t = 3)}$	$\frac{P(Y_t = 1)}{P(Y_t = 3) + P(Y_t = 2)}$
initial severity	2	1.23 (0.79, 1.92) [2]	1.92 (1.23, 3.01)	2.91 (1.75, 4.86)	4.54 (2.68, 7.69)
	3	2.35 (1.52, 3.64)	3.67 (2.27, 5.93)	5.56 (3.59, 8.61)	8.67 (5.30, 14.19)

1 – goodness of fit statistic = 14.47, DF = 16, p-value = 0.5638
2 – odds ratios that are not significant (p-value > 0.05)
3 – cumulative proportional odd ratio of months 12 vs. months 6 and 95% Confidence Interval over treatment effect (drug vs. placebo)

SAS code

```
LIBNAME final '/rhome/yl499/714/final';
FILENAME newdata '/rhome/yl499/714/final/final.dat';
run;

ODS RTF FILE="/rhome/yl499/714/final/final.rtf" STYLE=PearlJ;
ODS listing;
run;

*read in data;
DATA final.newdata;
INFILE newdata;
INPUT initial months6 months12 gender treatment count;
run;

proc format;
value severity
1 = 'least severe'
2 = 'initial severity 2'
3 = 'initial severity 3'
;
value gender
1 = 'Male'
0 = 'Female';
value trt
1 = 'Drug'
0 = 'Place';
run;

proc sort data=final.newdata;
by descending months12 descending months6 descending gender
descending treatment descending initial;
run;

*check proportional assumptions first;
proc catmod data=final.newdata order=data;
weight count;
population gender treatment initial;
response clogit;
model months12*months6 = gender treatment _response_ initial
gender*treatment gender*_response_ gender*initial treatment*_response_ treatment*initial initial*_response_
gender*treatment*_response_ gender*treatment*initial gender*initial*_response_
treatment*initial*_response_ gender*treatment*initial*_response_/design;
repeated occassion 2/_response_=occassion;
run;

*Marginal cumulative logit model with proportional assumption;

*variable selection;
*keep gender*treatment*occasion treatment*initial*occasion;
*keep gender*treatment gender*occasion treatment*occassion treatment*initial initial*occassion;
*check proportional assumptions first;
proc catmod data=final.newdata order=data;
weight count;
population gender treatment initial;
response clogit;
model months12*months6 = gender treatment _response_ initial
gender*treatment gender*_response_ treatment*_response_ treatment*initial initial*_response_
gender*treatment*_response_ treatment*initial*_response_ /design;
repeated occassion 2/_response_=occassion;
contrast 'test for porportionailty in sex' all_parms 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0;
contrast 'test for porportionailty in treatment' all_parms 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0;
contrast 'test for porportionailty in occasion' all_parms 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0;
contrast 'test for porportionailty in initial' all_parms 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0;
contrast 'test for porportionailty in sex*treatment' all_parms 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0;
contrast 'test for porportionailty in sex*occasion' all_parms 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0;
contrast 'test for porportionailty in treatment*occasion' all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0;
contrast 'test for porportionailty in treatment*initial' all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0;
contrast 'test for porportionailty in occasion*initial' all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0;
contrast 'test for porportionailty in gender*treatment*occassion' all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0;
contrast 'test for porportionailty in treatment*initial*occassion' all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1;
contrast 'test for overall proportionality'
all_parms 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
all_parms 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
all_parms 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0 0 0,
all_parms 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0 0 0,
all_parms 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0,
all_parms 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0 0 0,
all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0 0 0,
all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0 0 0,
all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0,
all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1 0 0,
all_parms 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 -1;
run;
```

```
*keep proportional assumption;
*not having proportional assumption, give more betas;
*sex occasion treatment*occasion;
*gender treatment _response_ initial
gender*treatment gender*_response_ treatment*_response_ treatment*initial initial*_response_
gender*treatment*_response_ treatment*initial*_response_;
proc catmod data=final.newdata order=data;
weight count;
population gender treatment initial;
response clogit;
model months12*months6 =
(
1 0 1 0 1 1 0 1 1 1 1 0 1 1 1 1,
0 1 0 1 1 0 1 1 1 1 0 1 1 1 1 1,
1 0 1 0 1 -1 0 1 1 -1 -1 0 1 -1 -1 -1,
0 1 0 1 1 0 -1 1 1 -1 0 -1 1 -1 -1 -1,

1 0 1 0 1 1 0 -1 1 1 1 0 -1 -1 1 -1,
0 1 0 1 1 0 1 -1 1 1 0 1 -1 -1 1 -1,
1 0 1 0 1 -1 0 -1 1 -1 -1 0 -1 1 -1 1,
0 1 0 1 1 0 -1 -1 1 -1 0 -1 -1 1 -1 1,

1 0 1 0 -1 1 0 1 -1 1 -1 0 -1 1 -1 -1,
0 1 0 1 -1 0 1 1 -1 1 1 0 -1 -1 1 -1,
1 0 1 0 -1 -1 0 1 -1 -1 1 0 -1 -1 1 1,
0 1 0 1 -1 0 -1 1 -1 -1 0 1 -1 -1 1 1,

1 0 1 0 -1 1 0 -1 -1 1 -1 0 1 -1 -1 1,
0 1 0 1 -1 0 1 -1 -1 1 0 -1 1 -1 -1 1,
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1 0 -1 0 1 1 0 1 -1 -1 1 0 1 1 -1 1,
0 1 0 -1 1 0 1 1 -1 -1 0 1 1 1 -1 1,
1 0 -1 0 1 -1 0 1 -1 1 -1 0 1 -1 1 -1,
0 1 0 -1 1 0 -1 1 -1 1 0 -1 1 -1 1 -1,

1 0 -1 0 1 1 0 -1 -1 -1 1 0 -1 -1 -1 -1,
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1 0 -1 0 1 -1 0 -1 -1 1 -1 0 -1 1 1 1,
0 1 0 -1 1 0 -1 -1 -1 1 0 -1 -1 1 1 1,

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1 0 -1 0 -1 -1 0 1 1 1 1 0 -1 -1 1 -1,
0 1 0 -1 -1 0 -1 1 1 1 0 1 -1 -1 1 -1,

1 0 -1 0 -1 1 0 -1 1 -1 -1 0 1 -1 1 1,
0 1 0 -1 -1 0 1 -1 1 -1 0 -1 1 -1 1 1,
1 0 -1 0 -1 -1 0 -1 1 1 1 0 1 1 -1 -1,
0 1 0 -1 -1 0 -1 -1 1 1 0 1 1 1 -1 -1
)
(1 2 ='cutpoints', 3 4 = 'sex', 5= 'treatment', 6 7 = 'occasion', 8 = 'initial',
9 = 'sex*treatment',10 = 'sex*occasion', 11 12 = 'treatment*occasion', 13 = 'treatment*initial',
14= 'occasion*initial', 15 = 'sex*treatment*occasion',16 = 'treatment*occasion*initial')/design oneway;

* treatment effects;
contrast '(1+2)/3 active vs placebo at months 6 at initial 2 for female'
all_parms 0 0 0 0 2 0 0 0 -2 0 -2 0 -2 0 2 2/est=exp;
contrast '1/(2+3) active vs placebo at months 6 at initial 2 for female'
all_parms 0 0 0 0 2 0 0 0 -2 0 0 -2 -2 0 2 2/est=exp;

contrast '(1+2)/3 active vs placebo at months 12 at initial 2 for female'
all_parms 0 0 0 0 2 0 0 0 -2 0 2 0 -2 0 -2 -2/est=exp;
contrast '1/(2+3) active vs placebo at months 12 at initial 2 for female'
all_parms 0 0 0 0 2 0 0 0 -2 0 0 2 -2 0 -2 -2/est=exp;

contrast '(1+2)/3 active vs placebo at months 6 at initial 3 for female'
all_parms 0 0 0 0 2 0 0 0 -2 0 -2 0 2 0 2 -2/est=exp;
contrast '1/(2+3) active vs placebo at months 6 at initial 3 for female'
all_parms 0 0 0 0 2 0 0 0 -2 0 0 -2 2 0 2 -2/est=exp;

contrast '(1+2)/3 active vs placebo at months 12 at initial 3 for female'
all_parms 0 0 0 0 2 0 0 0 -2 0 2 0 2 0 -2 2/est=exp;
contrast '1/(2+3) active vs placebo at months 12 at initial 3 for female'
all_parms 0 0 0 0 2 0 0 0 -2 0 0 2 2 0 -2 2/est=exp;

contrast '(1+2)/3 active vs placebo at months 6 at initial 2 for male'
all_parms 0 0 0 0 2 0 0 0 2 0 -2 0 -2 0 -2 2/est=exp;
contrast '1/(2+3) active vs placebo at months 6 at initial 2 for male'
all_parms 0 0 0 0 2 0 0 0 2 0 0 -2 -2 0 -2 2/est=exp;

contrast '(1+2)/3 active vs placebo at months 12 at initial 2 for male'
```

```
all_parms 0 0 0 0 2 0 0 0 2 0 2 0 -2 0 2 -2/est=exp;
contrast '1/(2+3) active vs placebo at months 12 at initial 2 for male'
all_parms 0 0 0 0 2 0 0 0 2 0 0 2 -2 0 2 -2/est=exp;

contrast '(1+2)/3 active vs placebo at months 6 at initial 3 for male'
all_parms 0 0 0 0 2 0 0 0 2 0 -2 0 2 0 -2 -2/est=exp;
contrast '1/(2+3) active vs placebo at months 6 at initial 3 for male'
all_parms 0 0 0 0 2 0 0 0 2 0 0 -2 2 0 -2 -2/est=exp;

contrast '(1+2)/3 active vs placebo at months 12 at initial 3 for male'
all_parms 0 0 0 0 2 0 0 0 2 0 2 0 2 0 2 2/est=exp;
contrast '1/(2+3) active vs placebo at months 12 at initial 3 for male'
all_parms 0 0 0 0 2 0 0 0 2 0 0 2 2 0 2 2/est=exp;


*after treatment months 12 vs. months 6;
contrast '(1+2)/3 months 12 vs months 6 trt = 1 for female at initial 2'
all_parms 0 0 0 0 0 2 0 0 0 -2 2 0 0 -2 -2 -2/est=exp;
contrast '1/(2+3) months 12 vs months 6 trt = 1 for female at initial 2'
all_parms 0 0 0 0 0 0 2 0 0 -2 0 2 0 -2 -2 -2/est=exp;

contrast '(1+2)/3 months 12 vs months 6 trt = 1 for female at initial 3'
all_parms 0 0 0 0 0 2 0 0 0 -2 2 0 0 2 -2 2/est=exp;
contrast '1/(2+3) months 12 vs months 6 trt = 1 for female at initial 3'
all_parms 0 0 0 0 0 0 2 0 0 -2 0 2 0 2 -2 2/est=exp;

contrast '(1+2)/3 months 12 vs months 6 trt = 1 for male at initial 2'
all_parms 0 0 0 0 0 2 0 0 0 2 2 0 0 -2 2 -2/est=exp;
contrast '1/(2+3) months 12 vs months 6 trt = 1 for male at initial 2'
all_parms 0 0 0 0 0 0 2 0 0 2 0 2 0 -2 2 -2/est=exp;

contrast '(1+2)/3 months 12 vs months 6 trt = 1 for male at initial 3'
all_parms 0 0 0 0 0 2 0 0 0 2 2 0 0 2 2 2/est=exp;
contrast '1/(2+3) months 12 vs months 6 trt = 1 for male at initial 3'
all_parms 0 0 0 0 0 0 2 0 0 2 0 2 0 2 2 2/est=exp;

*sex effects after treatment months 12 vs. months 6;
contrast '(1+2)/3 months 12 vs months 6 trt = 1 for male vs female at initial 2'
all_parms 0 0 0 0 0 0 0 0 0 4 0 0 0 0 4 0/est=exp;
contrast '1/(2+3) months 12 vs months 6 trt = 1 for male vs female at initial 2'
all_parms 0 0 0 0 0 0 0 0 0 4 0 0 0 0 4 0/est=exp;

contrast '(1+2)/3 months 12 vs months 6 trt = 1 for male vs female at initial 3'
all_parms 0 0 0 0 0 0 0 0 0 4 0 0 0 0 4 0/est=exp;
contrast '1/(2+3) months 12 vs months 6 trt = 1 for male vs female at initial 3'
all_parms 0 0 0 0 0 0 0 0 0 4 0 0 0 0 4 0/est=exp;

*sex effects;
contrast '(1+2)/3 active vs placebo at months 6 at initial 2 for male vs female'
all_parms 0 0 0 0 0 0 0 0 4 0 0 0 0 0 -4 0/est=exp;
contrast '1/(2+3) active vs placebo at months 6 at initial 2 for male vs female'
all_parms 0 0 0 0 0 0 0 0 4 0 0 0 0 0 -4 0/est=exp;

contrast '(1+2)/3 active vs placebo at months 12 at initial 2 for male vs female'
all_parms 0 0 0 0 0 0 0 0 4 0 0 0 0 0 4 0/est=exp;
contrast '1/(2+3) active vs placebo at months 12 at initial 2 for male vs female'
all_parms 0 0 0 0 0 0 0 0 4 0 0 0 0 0 4 0/est=exp;

contrast '(1+2)/3 active vs placebo at months 6 at initial 3 for male vs female'
all_parms 0 0 0 0 0 0 0 0 4 0 0 0 0 0 -4 0/est=exp;
contrast '1/(2+3) active vs placebo at months 6 at initial 3 for male vs female'
all_parms 0 0 0 0 0 0 0 0 4 0 0 0 0 0 -4 0/est=exp;

contrast '(1+2)/3 active vs placebo at months 12 at initial 3 for male vs female'
all_parms 0 0 0 0 0 0 0 0 4 0 0 0 0 0 4 0/est=exp;
contrast '1/(2+3) active vs placebo at months 12 at initial 3 for male vs female'
all_parms 0 0 0 0 0 0 0 0 4 0 0 0 0 0 4 0/est=exp;

*occasion effects;
contrast '(1+2)/3 active vs placebo at initial 2 for female at months 12 vs months 6'
all_parms 0 0 0 0 0 0 0 0 0 0 4 0 0 0 -4 -4/est=exp;
contrast '1/(2+3) active vs placebo at initial 2 for female at months 12 vs months 6'
all_parms 0 0 0 0 0 0 0 0 0 0 4 0 0 0 -4 -4/est=exp;

contrast '(1+2)/3 active vs placebo at initial 3 for female at months 12 vs months 6'
all_parms 0 0 0 0 0 0 0 0 0 0 4 0 0 0 -4 4/est=exp;
contrast '1/(2+3) active vs placebo at initial 3 for female at months 12 vs months 6'
all_parms 0 0 0 0 0 0 0 0 0 0 0 4 0 0 -4 4/est=exp;

contrast '(1+2)/3 active vs placebo at initial 2 for male at months 12 vs months 6'
all_parms 0 0 0 0 0 0 0 0 0 0 4 0 0 0 4 -4/est=exp;
contrast '1/(2+3) active vs placebo at initial 2 for male at months 12 vs months 6'
all_parms 0 0 0 0 0 0 0 0 0 0 0 4 0 0 4 -4/est=exp;

contrast '(1+2)/3 active vs placebo at initial 3 for male at months 12 vs months 6'
```

```
all_parms 0 0 0 0 0 0 0 0 0 0 4 0 0 0 4 4/est=exp;
contrast '1/(2+3) active vs placebo at initial 3 for male at months 12 vs months 6'
all_parms 0 0 0 0 0 0 0 0 0 0 0 4 0 0 4 4/est=exp;

run;
```