Chapter 15 - Repeated Measures Designs

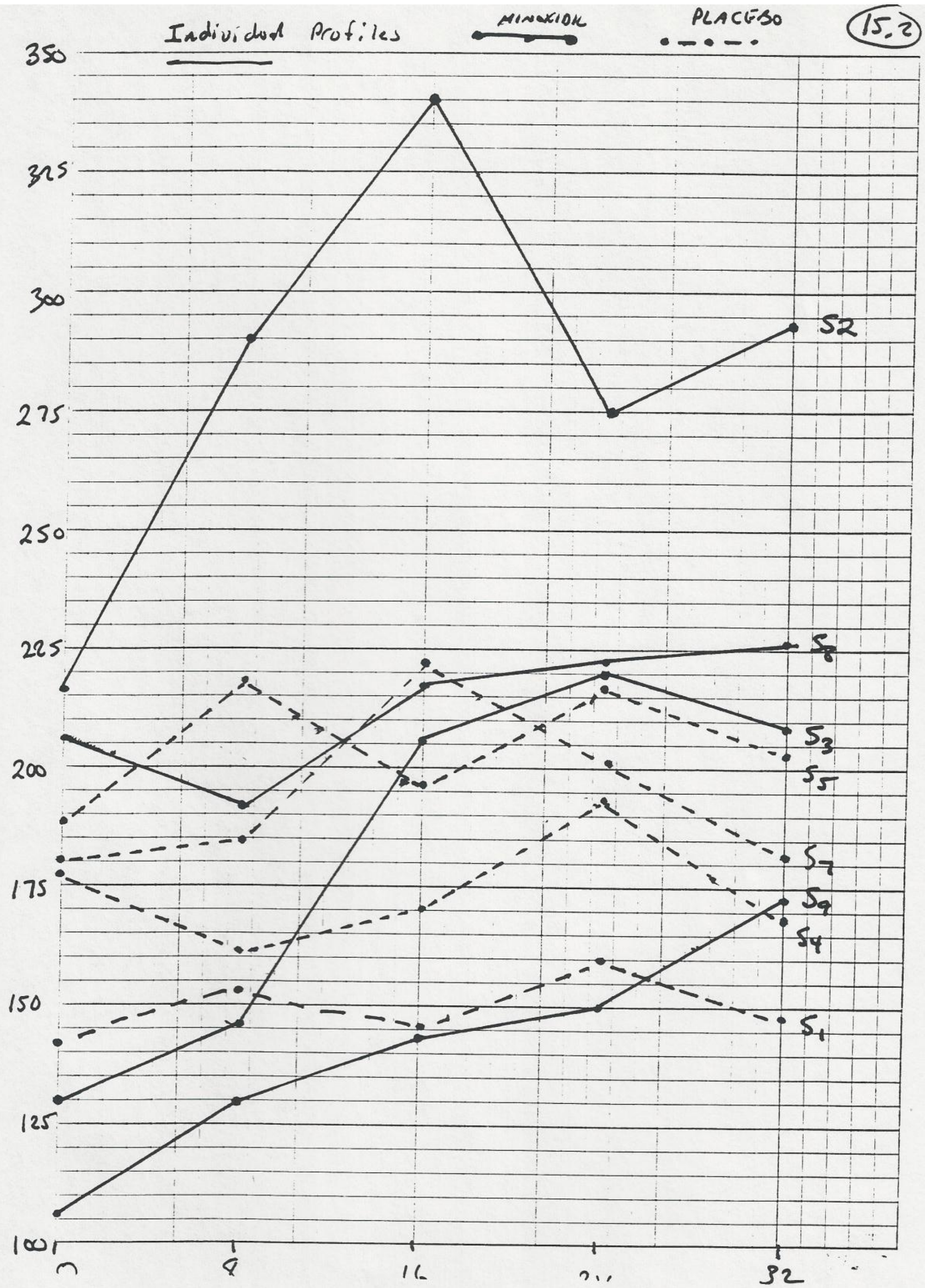
- Measurements under same treatment condition are followed across time periods for experimental units. Efficient use of resources.

EXAMPLE: "QUANTITATIVE ESTIMATION OF HAIR GROWTH I. ANDROGENETIC ALOPECIA IN WOMEN: EFFECT OF MINOXIDIL." Price & Menefee (1990) Journal of Investigative Dermatology 95:683-

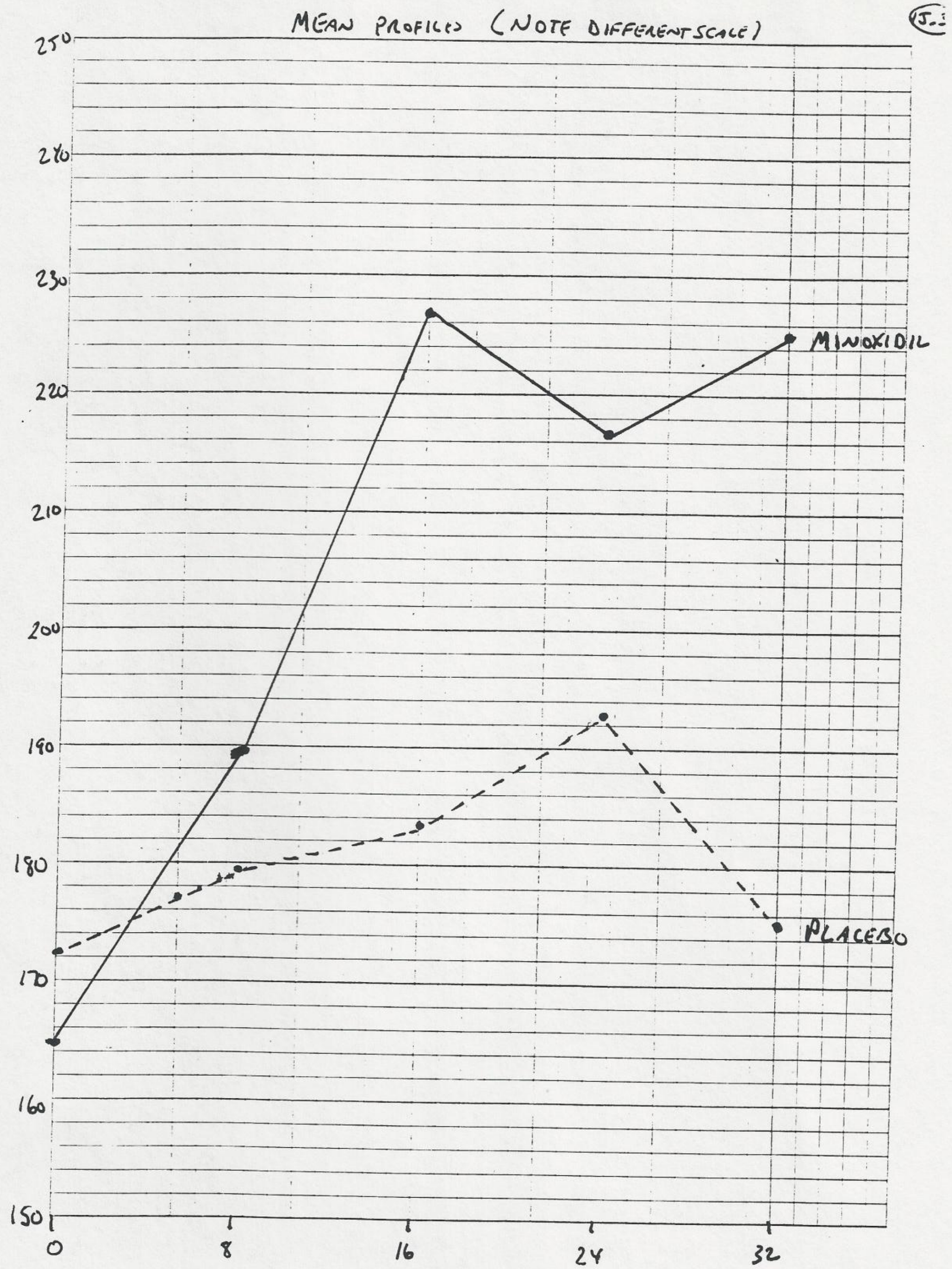
4 women Receive Placebo
4 " " 2% MINOXIDIL

ONE RESPONSE: TOTAL Daily weight HAIR ~~WEIGHT IN~~ OF HAIR GROWN IN TARGET REGION (x100 (mg @ 65% Relative Humidity)

TRT	Subject #	0 (NOT RELEVANT IN ANALYSIS)	WEEK 8	16	24	32	(NOT OF) MEANS
MINOXIDIL	2	216	290	340	275	294	29
	3	130	146	206	220	209	19
	8	206	193	218	223	226	21:
	9	106	130	144	150	173	149.
PLACEBO	1	142	154	145	160	148	15.
	4	178	161	170	194	169	17
	5	189	219	197	218	203	209.
	7	180	185	223	201	182	197.
Means	MINOXIDIL	164.50	189.75	227.00	217.00	225.50	
	PLACEBO	172.25	179.75	183.75	193.25	175.50	



Individual Profiles
MINOXIDIL
PLACEBO
15.2
350
325
300
275
250
225
200
175
150
125
100
0
8
16
32
S2
S8
S3
S5
S7
S9
S4
S1


MEAN PROFILES (NOTE DIFFERENT SCALE)
J-3
250
240
230
220
210
200
190
180
170
160
150
0
8
16
24
32
MINOXIDIL
PLACEBO

Relationships Among Repeated Measures

- Expect Measurements within subjects to be correlated.

$$\rho_{ij} = \frac{\sigma_{ij}}{\sigma_i \sigma_j}$$ where $\sigma_{ij} \equiv$ Covariance of measurements @ i and j.

$\sigma_i \equiv$ Standard deviation of measurements @ i

$$\sigma_{ij} = E[(Y_i - \mu_i)(Y_j - \mu_j)]$$

$$\sigma_i^2 = E[(Y_i - \mu_i)^2]$$

Matrix of Variances and Covariances for 4 repeated Meas.

$$\begin{array}{c|cccc|} & Y_1 & Y_2 & Y_3 & Y_4 \\ \hline Y_1 & \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ Y_2 & \sigma_{21} & \sigma_2^2 & \sigma_{23} & \sigma_{24} \\ Y_3 & \sigma_{31} & \sigma_{32} & \sigma_3^2 & \sigma_{34} \\ Y_4 & \sigma_{41} & \sigma_{42} & \sigma_{43} & \sigma_4^2 \\ \hline \end{array}$$

Sample Analogues (separate by group)

MINOXIDIL

1 = 8wks "S_1^2" $= \frac{1}{4} \sum_{subj} (Y_1 - \hat{\mu}_1)^2 = \frac{1}{4}\left[(290-190)^2 + (146-190)^2 + (193-190)^2 + (130-190)^2\right]$

$= 3886.3$

$S_2^2 = 5045$

$S_3^2 = 1975$

$S_4^2 = 1930$

$$\text{“}S_{12}\text{”} = \frac{1}{4}\sum_{Subj}(Y_1-\hat{\mu}_1)(Y_2-\hat{\mu}_2) =$$

$$\frac{1}{4}\left[(290-190)(340-227) + (146-190)(206-227) + (193-190)(218-227) + (130-190)(144-227)\right]$$

$$= 4294.25$$

“S_{13}” = 2462.5

“S_{14}” = 2681.9

“S_{23}” = 2999.5

“S_{24}” = 3110

“S_{34}” = 1861

Matrix of “Sample” Variances and Covariances.

3886	4294	2463	2682
4294	5045	3000	3110
2463	3000	1975	1861
2682	3110	1861	1930

Compound Symmetry Assumption (very Stringent)

- Variances @ Each time point are all =
- Correlation same among all pairs of time points (Assumes covariances at more distant time points same as at closer together time points)
- for our data, this seems “reasonable” (maybe) based on very small samples.

$$\sigma_1^2 = \sigma_2^2 = \sigma_3^2 = \sigma_4^2 = \sigma^2$$

$$\sigma_{12} = \sigma_{13} = \sigma_{14} = \sigma_{23} = \sigma_{24} = \sigma_{34} = \sigma_{ij} = \rho\sigma^2$$

Analogy to Split Plot Design

Subject ≡ Whole plot

Treatment (Between Subjects) ≡ Whole plot factor

Repeated Measures ≡ subplot

Treatments are randomized to subplots in split plot design, while no randomization occurs for repeated measures.

Huynh-Feldt Condition

$$V(Y_i - Y_j) = \sigma^2_{(Y_i - Y_j)} = 2\lambda \quad \forall\ i, j \quad (\text{some } \lambda > 0)$$

Note: $V(Y_i - Y_j) = \sigma^2_{Y_i} + \sigma^2_{Y_j} - 2\sigma_{ij}$

$$\Rightarrow \sigma^2_{Y_i} + \sigma^2_{Y_j} - 2\sigma_{ij} = 2\lambda$$

$$\Rightarrow \sigma_{ij} = \frac{1}{2}(\sigma^2_{Y_i} + \sigma^2_{Y_j}) - \lambda = \frac{1}{2}(\sigma_i^2 + \sigma_j^2) - \lambda \quad i \neq j$$

Variance - Covariance Matrix under this condition is called the Type H Matrix.

Mauchly W test for Huynh-Feldt condition. (Sphericity)

Ho: Huynh-Feldt Condition holds

Ha: ______ DOES NOT HOLD

Reject Ho for small p-values.

(See Example for Minoxidil that follows)

Univariate Analysis

$$y_{ijk} = \mu + \alpha_i + d_{ik} + \beta_j + (\alpha\beta)_{ij} + e_{ijk} \qquad \begin{array}{l} i=1,\dots,t \\ j=1,\dots,p \\ k=1,\dots,r \end{array}$$

Where: $y_{ijk} \equiv$ observation for trt i @ time j on subject k

$\alpha_i \equiv$ Effect for i^{th} trt $\quad (\sum \alpha_i = 0)$

$d_{ik} \equiv$ random effect of k^{th} subject w/in trt i $\quad d_{ik} \sim N(0$

$\beta_j \equiv$ Effect of j^{th} period

$(\alpha\beta)_{ij} \equiv$ Interaction between Trt i & Time j

$$\sum_i (\alpha\beta)_{ij} = \sum_j (\alpha\beta)_{ij} = 0$$

$e_{ijk} \equiv$ Random Error

Analysis of Variance

$$SS_{TOTAL} = \sum_i \sum_j \sum_k (y_{ijk} - \bar{y}_{\dots})^2 \qquad df_{TOTAL} = tpr - 1$$

$$SS_{TRTS} = pr \sum_i (\bar{y}_{i\dots} - \bar{y}_{\dots})^2 \qquad df_{TRTS} = t-1$$

$$SS_{SUBJ(TRTS)} = p \sum_i \sum_k (\bar{y}_{i\cdot k} - \bar{y}_{i\dots})^2 \qquad df_{SUBJ(TRTS)} = t(r-1)$$

$$SS_{TIME} = tr \sum_j (\bar{y}_{\cdot j \cdot} - \bar{y}_{\dots})^2 \qquad df_{TIME} = p-1$$

$$SS_{TRTS*TIME} = r \sum_i \sum_j (\bar{y}_{ij\cdot} - \bar{y}_{i\dots} - \bar{y}_{\cdot j\cdot} + \bar{y}_{\dots})^2 \qquad df_{TRTS*TIME} = (t-1)(\,$$

SS_{ERROR} - By subtraction

$$df_{ERROR} = (tpr-1) - [(t-1) + t(r-1) + (p-1) + (t-1)(p-$$

$$= (tpr-1) - [(t-1) + t[(p-1) + (r-1)]$$

$$= (tpr-1) - [\,t((p-1) + (r-1) + 1) - 1] \quad \rightarrow$$

$= tpr - t((p-1)+(r-1)+1)$

$= t[pr - p + 1 - r + 1 - 1] = t(pr - p - r + 1) = t(p-1)(r-1)$

Source	df	SS (from prev page)	MS	F_0
TRTS	$t-1$	SS_{TRTS}	$MS_{TRTS} = \frac{SS_{TRTS}}{t-1}$	$MS_{TRTS}/MSE(1)$
Error(1) $\equiv$ SUBJ(TRTS)	$t(r-1)$	$SS_{SUBJ(TRTS)}$	$MS_{Error(1)} = \frac{SS_{subj(TRTS)}}{t(r-1)}$	—
—	—	—	—	—
TIME	$p-1$	SS_{TIME}	$MS_{TIME} = \frac{SS_{TIME}}{p-1}$	$\frac{MS_{TIME}}{MSE(2)}$
TRTS*TIME	$(t-1)(p-1)$	$SS_{TRTS*TIME}$	$MS_{TRTS*TIME} = \frac{SS_{TRT}}{(t-1)(p-1)}$	$\frac{MS_{T*T}}{MSE(2)}$
Error(2)	$t(p-1)(r-1)$	SS_{ERROR}	$MSE(2) = \frac{SS_{ERROR}}{t(p-1)(r-1)}$	—
TOTAL	$tpr-1$	SS_{TOTAL}	—	—

$H_0: \alpha_i = 0 \quad \forall i$ (No TRT effects)

$H_A:$ Not all $\alpha_i = 0$ (TRT effects exist)

TS: $F_0^{TRTS} = \frac{MS_{TRTS}}{MSE(1)}$ RR: $F_0^{TRTS} \geq F_{\alpha, t-1, t(r-1)}$

$H_0: \beta_j = 0 \quad \forall j$ (No time effects)

$H_A:$ Not all $\beta_j = 0$ (Time effects exist)

T.S. $F_0^{TIME} = \frac{MS_{TIME}}{MSE(2)}$ RR: $F_0^{TIME} \geq F_{\alpha, p-1, t(p-1)(r-1)}$

$H_0: (\alpha\beta)_{ij} = 0 \quad \forall i,j$ $H_A:$ Not all $(\alpha\beta)_{ij} = 0$

T.S. $F_0^{TRT*TIME} = \frac{MS_{TRT*TIME}}{MSE(2)}$ RR: $F_0^{TRT*TIME} \geq F_{\alpha, (t-1)(p-1), t(p-1)(r-1)}$

MINOXIDIL EXAMPLE (NOT USING TIME 0 MEASUREMENTS)

$t = 2$ TRTS (MINOXODIL VS PLACEBO)

$p = 4$ PERIODS (WEEKS 8, 16, 24, 32)

$r = 4$ subjects per treatment

$\bar{y}_{...} = 198.9375$

$SS_{TOTAL} = 73045.875$

$\bar{y}_{1..} = 214.8125$ $\quad\quad$ $\bar{y}_{2..} = 183.0625$

$SS_{TRTS} = 16\left[(214.8125 - 198.9375)^2 + (183.0625 - 198.9375)^2\right]$

$= 16\left[252.02 + 252.02\right] = 8064.64$ $\quad\quad$ $df_{TRTS} = 1$

$\bar{y}_{.1.} = 184.750$ $\quad$ $\bar{y}_{.2.} = 205.375$ $\quad$ $\bar{y}_{.3.} = 205.125$ $\quad$ $\bar{y}_{.4.} = 200.500$

$SS_{TIME} = 8\left[201.29 + 41.44 + 38.29 + 2.44\right] = 2267.68$ $\quad$ $df_{TIME} = 3$

$\bar{y}_{11.} = 189.75$ $\quad$ $\bar{y}_{12.} = 227.00$ $\quad$ $\bar{y}_{13.} = 217.00$ $\quad$ $\bar{y}_{14.} = 225.50$

$\bar{y}_{21.} = 179.75$ $\quad$ $\bar{y}_{22.} = 183.75$ $\quad$ $\bar{y}_{23.} = 193.25$ $\quad$ $\bar{y}_{24.} = 175.50$

$i\ j$	$\bar{y}_{ij.} - \bar{y}_{i..} - \bar{y}_{.j.} + \bar{y}_{...}$
1 1	$189.75 - 214.8125 - 184.750 + 198.9375 = -10.875$
1 2	$227.00 - 214.8125 - 205.375 + 198.9375 = 5.750$
1 3	$217.00 - 214.8125 - 205.125 + 198.9375 = -4.00$
1 4	$-(-10.875 + 5.750 - 4.00) = 9.125$ $\quad$ $(\sum_j \widehat{(\alpha\beta)}_{ij} = 0)$
2 1	10.875 $\quad$ $(\sum_i \widehat{(\alpha\beta)}_{ij} = 0)$
2 2	-5.750
2 3	4.00
2 4	-9.125

$SS_{TRTS*TIME} = 4\left[(-10.875)^2 + (5.750)^2 + (-4)^2 + (9.125)^2 + (10.875)^2 + (-5.750)^2 + (4.00)^2 + (-9.125)^2\right] = 2004.75$

$df_{TRTS*TIME} = 3$

15.10

$\bar{y}_{1\cdot1} = 299.75$ $\bar{y}_{1\cdot2} = 195.25$ $\bar{y}_{1\cdot3} = 215.00$ $\bar{y}_{1\cdot4} = 149.25$

$\bar{y}_{2\cdot1} = 151.75$ $\bar{y}_{2\cdot2} = 173.50$ $\bar{y}_{2\cdot3} = 209.25$ $\bar{y}_{2\cdot4} = 197.75$

i	K	$\bar{y}_{i\cdot k\cdot} - \bar{y}_{i\cdots}$	$(\bar{y}_{i\cdot k\cdot} - \bar{y}_{i\cdots})^2$
1	1	299.75 − 214.8125 = 84.9375	7214.38
1	2	195.25 − 214.8125 = −19.5625	382.69
1	3	215.00 − 214.8125 = 0.1875	0.04
1	4	149.25 − 214.8125 = −65.5625	4298.44
2	1	151.75 − 183.0625 = −31.3125	980.47
2	2	173.50 − 183.0625 = −9.5625	91.44
2	3	209.25 − 183.0625 = 26.1875	685.79
2	4	197.75 − 183.0625 = 14.6875	215.72
			13868.97

$SS_{ERROR(1)} = SS_{SUBJ(TRTS)} = 4[13868.97] = 55475.88$

$SS_{ERROR(2)} = SS_{ERROR} = 73045.875 - 8064.64 - 2267.68 - 2004.75 - 55475.88$

$= 5232.93$ $df_{ERROR(2)} = 18$

ANOVA

SOURCE	df	SS	MS	F_0	$F_{.05}$
DRUG	1	8064.64	8064.64	0.87	5.99
SUBJ(DRUG) ERROR(1)	6	55475.88	9245.98	—	
PERIOD	3	2267.68	755.89	2.60	3.16
DRUG*PERIOD	3	2004.75	668.25	2.30	3.16
ERROR(2)	18	5232.93	290.72	—	
TOTAL	31	73045.875	—	—	

No Significant effects