AN ANALYSIS OF A SET OF MEDICAL DATA WITH MISSING OBSERVATIONS

BY

MARIA YAU-YING WAI

(B. Sc)

A PROJECT

Submitted to the School of Graduate Studies

in partial fulfilment of the Requirements

for the degree

Master of Science

McMaster University

(April) 1978

ABSTRACT

The efficacies of two tranquilizers and a placebo in reducing tension and related complaints were studied at three clinics over a period of six weeks. There was a considerable amount of missing data in this drug trial. The purposes of this project were:

(1) To estimate the missing values by the regression technique and

(2) to analyse the data by the multivariate analyses of variance method

A significant time trend in changes of severity during the six-week period was found in all three clinics. The predominant trend was linear. But quadratic and cubic trends were also found in some clinics.

As far as effectiveness of tranquilizers was concerned, there was no conclusive answer. In two clinics, the tranquilizers were not proved to be better than the placebo. In the third clinic, however the 2 active drugs were significantly different from the placebo. This inconsistant result of drug effects among the 3 clinics might be due to

(1) non-random allocation of subjects to the clinics and

(2) the fact that a large proportion of subjects failed to complete the study

CONTENTS

ACKNOWLEDGEMENT

I would like to express my sincere appreciation to my supervisor, Dr. C.W. Dunnett for his suggestion of this project,his patience, guidance and encouragement throughout the duration of this work.

Special thanks must go to Dr. C.H. Goldsmith for his valuable suggestions and assistance in completing this project.

AN ANALYSIS OF A SET OF MEDICAL DATA WITH MISSING OBSERVATIONS

I. INTRODUCTION

In order to assess the clinical efficacy of tranquilizers (psychotropic drugs) used in reducing tension,anxiety and related complaints,some psychopharmacological researchers employ a self-rating scale,such as the Hopkin Symptom Checklist (HSCL),the Hamilton Anxiety Scales, etc., to record the 'anxiety mood' of the patients over a treatment period. As in many other studies in which human subjects are involved,however, there are some common problems in obtaining complete data because of :

(i) some who drop-out and never complete the studies; or

(ii) some patients who missed their appointments or did not follow the recommended treatment procedures; or

(iii) some who refused to report their feelings by not answering certain parts of questions in the self-rating scale questionaires.

All of these will lead to incomplete data hence inducing difficulties in the analysis and interpretation of the effectiveness of the drugs.

How should the investigators handle the situation in which some subjects have one or more missing data items? One natural approach is to omit all subjects who have incomplete observations. If the number of subjects with missing data is small,if data are missing at random and if interest lies in statement regarding a population rather than individuals, the elimination of subjects with missing data is likely to lead to a satisfactory analysis. In practice, however, data may not be missing at random.Hence, elimination of subjects with missing values can result in a considerable loss of information.Also,it could introduce a bias.

A second standard approach is to estimate the missing values. Replacing missing values by variable means is perhaps the simplest method of estimating missing data.This approach has been used in many practical analyses and has given acceptable results.However,this method can also give very poor results if data are highly correlated.

Another method of estimation is by substituting the missing observations with the previous

values of the observations of the subject so long as the response variables are of the same type but only differ from each other in time or location.This method of estimation is plausible,but it also may significantly change the results if there is a lot of missing observations to be estimated in the samples.

A better estimate can be obtained through regression methods when the missing variables for each subject are highly correlated with one or more available variables.This method avoids much of the serious bias that can result from merely using the mean or previous values as substitutes.

There are still other ways of estimatiing missing values such as the estimation of missing observations through an iterative procedure (Beale and Little 1975). But it should be realized that no estimation procedure is completely satisfactory since any estimation will introduce some sort of bias into the analysis with the amount of bias being a function of the number of missing data items.The optimal choice of any method of estimation depends on the number of variables,the number of observations or observation

vectors, the correlation of the variables,and the amount of missing data etc. If the correlations of the variables are high,the regression method seems to be the better choice.

One purpose of this project is to explore the regression method in estimating missing observations in a drug trial study, where the response variables are highly correlated and the completion rate is relatively low.

Another purpose of the project is after estimation, to assess the clinical efficacy of the three drugs, namely test drug,placebo and standard drug in reducing tension, anxiety and related complaints of the non-pyschotherapy outpatients who had participated in this protocol.

II. DATA DESCRIPTION

1. Population

The patient population was made up of anxious psychoneurotic clinic outpatients frequenting three different clinics,A,B,C. These patients were randomly assigned to treatment within each clinic so that nearly one-third received test drug,one third received standard drug and one-third received a placebo. Neither the physicians nor the nurses were aware of which patients were receiving active drugs or placebo.

A total of 238 patients entered the study. Only 91 patients actually completed the study. In clinic A, 62 out of 90 patients completed the study, 12 dropped out after week 3's treatment,15 after week 4, and one failed to response at week 4's assessment. In clinic B, 12 out out of 62 patients completed the study, 2 dropped out after week 0's assessment, 10 after week 1 , 4 after week 2, 13 after week 3, 11 after week 4, 10 failed to show up in some of their visits. In clinic C , 17 out of 86 patients completed the entire study, 2 dropped out after week 1's treatment, 8 after week 2, 14 after week 3,15 after week 4 and 31 failed to appear in some of

their 6-week's visit. The distribution of patient status after 6 weeks' study can be seen in Table 1.

Table 2,3,4 list the sex,age and race distributions of the patients at each clinic elicited at the time of intake or at the first study visit.

2. EVALUATION METHOD

Patients were seen at 1-week intervals for a period of 6 weeks by the same physicians and nurses. Treatments began at the second week's visit. At each visit and before seeing the therapists, all patients were given a brief 35-item Hopkin Symptom Checklist (see Form 1), based upon a self-rating scale developed earlier by Parloff et al (1954) to record their 'anxiety mood' on a 4-point scale ranging from 'NOT AT ALL','A LITTLE', 'QUITE A BIT ', to 'EXTREMELY'.

Table 5,6,7,8,9,10 show the results of the mean, standard deviation and F-test at week 0,1,2,3,4,5 of the total raw score and the five factor raw scores (derived from a factor analysis on the 35 items,performed by LIPMAN et al on a sample of 1115 subjects) for the 3 drug groups in the 3 clinics A,B,C. The 5 factors spell out the diagnosis of general neurotic feeling,somatization,cognitive performance difficult,depression, fear/anxiety (see Appendix A). A lower mean score signifies improvement.

A complete list of the patient ID,race,sex,age,type of dosage taken and the total mean

score resulting from the 6-week assessment for each subject was shown in Table 11. The meaning of the codes were as follows :-

The first 3 digits of the patient ID signifies where the data are from,040 from Clinic A,006 from Clinic B, and 038 from Clinic C. Race was coded either 1 or 3. Sex was coded 0 for female, 1 for male. Dosage taken was coded 0 for Test drug, 1 for Placebo and 7 for Standard drug.

From the listing (Table 11), we realized a lot of the observations were missing in the later stages of the assessment period. Moreover the pattern of missing data tends to be nonrandom especially in the data coming from clinic B and C. The causes of the missing data could not be traced. The analysis on this data set was not expected to be very satisfactory because of the bias induced by the considerable amount of missing values.

III. ESTIMATION OF MISSING VALUES THROUGH REGRESSION APPROACH

There are several regression methods of estimation. (Frank,1976),(Dixon,1975). The first method uses a simple linear regression in which each missing variable is regressed on the available variable with which it has the highest absolute correlation. The amount of computation needed for this approach is quite small. A second method uses the two-step of a step-wise regression. That is each missing value for a variable is estimated by regressing that variable on up to two variables selected by stepwise regression. The variable that has the highest correlation with the dependent variable is chosen first,next is the one with highest correlation conditioned on the variable already in the equation. A third method employs stepwise regression in which the predictors continue to be selected as long as they satisfy the F-TO-ENTER criterion. This method is recommended from a theoretical point of view since it attempts to use the maximum amount of information in the available variables while without overfitting. However the method is more expensive as more computational time is needed. A fourth method computes (for each case) the regression of the missing variables on all available

variables. In this case,the F-TO-ENTER criterion is not used. This method runs the risk of overfitting if the sample size is small relative to the number of variables.

The correlation matrices of the treatment groups listed in Table 12 show that the response measurements that are adjacent in time are highly correlated. The same conclusion can be drawn by looking at the graphs which show definite trends of variations of mean scores against time (Graph 2,3,4). It appears that the first method of regression mentioned above is adequate for estimating the missing values in this data set, because this method is simple and economical .

Because some drug-week combinations have small numbers of completed data,we wonder if the responses of all 3 groups in the same clinic are parallel to each other,i.e.having equal slopes.If they do,we pool the data from the 3 groups together so as to have more data for a better estimation of the missing values.The theory behind this hypothesis for parallel slopes is summarized below :

Section III_). Following are the results of the three hypothesis test for trend analysis.

(4) Ho : There is no difference in treatments when averaged over time

CLINIC	S. OF VARIATION	S.S	D.F.	M.S.	F	P
A	DRUG	0.06359	2	0.03179	0.7533	0.4738
	WITHIN CELL	3.67205	87	0.04221		
B	DRUG	0.03753	2	0.01877	0.7101	0.4968
	WITHIN CELL	1.24219	47	0.02643		
C	DRUG	0.20101	2	0.10051	14.695	.00001
	WITHIN CELL	0.55402	81	0.00684		

For Clinic A and B, we accept the null hypothesis at alpha=.05. That is,there is no significant differences in the overall effect of the three drugs in Clinic A and B when averaged over time. The overall effectiveness of the active druga are not significantly better than the placebo in reducing anxiety,tension and other related complaints.

ANALYSIS OF VARIANCE FOR DIFFERENCES BETWEEN REGRESSION SLOPES

SOURCE	SUM OF SQUARES	D.F.	M.S.	F-RATIO
Due to pooled Regression (Common Slope)	$\frac{\{\Sigma(S_{xy})_i\}^2}{\Sigma(S_x^2)_i}$	1		
Difference between Slopes	$\frac{\Sigma(S_{xy})^2}{(S_x^2)_i} - \frac{\{\Sigma(S_{xy})_i\}^2}{\Sigma(S_x^2)_i}$	k-1	MSR	MSR/MSE
Residual about Separated lines	$\Sigma(S_y^2)_i - \Sigma\frac{(S_{xy})_i^2}{(S_x^2)_i}$	n-2k	MSE	
Within groups		n-k		

The correlation matrix in Table 12 indicated that the adjacent responses are more correlated than distant responses. By using complete cases and regressing week 5's mean scores on week 4 's mean scores of each patient in each of treatment groups for each clinic,we summarized the result in TABLE 13A which shows that there is no significance difference between the 3 slopes of the regression lines of the treatment groups in clinic A and B.In clinic C,because of the fact that there is not enough complete cases in the placebo group,we could only compare the slopes of regression lines of the two active drug groups which we found to be

statistically parallel. Similar results were obtained by regressing week 4's mean scores on week 3's mean scores of each patient and so forth, in each of the treatment groups for each clinic (TABLE 13B).So we can conclude that the regression lines of the treatment groups for each clinic are parallel to one another.The same conclusion can be drawn by looking at the Graph 2,3,4,where the lines joining the mean of the mean responses of the treatment groups when plotted against time of assessment are displayed.So it is feasible to pool the data within each clinic together to make a better estimation because of the increase in the sample size.

The missing data of the last week (week 5) were estimated by the first regression method.Using the complete set of data from each clinic and applying the reduction in sum of squares method suggested by Searle,it was found that (TABLE 14) week 4 is the best predictor for week 5.This is due to the fact that week 4's response observations are most correlated with those in week 5. By adding more variables like week 3's , week 2's etc. in the independent list for the regression does

not result in significant changes in the sum of squares or increases in R-squared values. However,in clinic C, a slightly significant result occurred after week 2's observation was added in the independent list of the equation. It is extremely likely however,that chance alone could induce such a significant result. Missing data in weeks 2 to 4 which are induced by patients not showing up in their appointment schedules,were estimated through the second method of regression,i.e. the Two-STEP stepwise regression approach.Subjects that had been dropped out even before the second visits (i.e. before the treatment began) were discarded.A complete list of the data with estimated values is shown in TABLE 15.

IV. METHOD OF ANALYSIS

Traditionally univariate analysis of variance for mixed models is used to analyse data of this type where components in observation vectors are similar in nature but made under conditions differing in time or location of measurements. This technique is more powerful and easier to handle than that of the multivariate analysis of variance. However, it has been observed (Greenhouse and Geisser 1959) that this approach is valid only when the variance-covariance matrix is of equal variance,equal covariance pattern (i.e.uniform),

$$\underset{\sim}{\Sigma}^{*} = \sigma^{2} \begin{vmatrix} 1 & \rho & \rho & \rho & \rho & \cdot & \cdot & \rho \\ \rho & 1 & \rho & \rho & \rho & \cdot & \cdot & \rho \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \rho & \cdot & \cdot & \cdot & \cdot & \cdot & 1 & \end{vmatrix}_{pxp}$$

where p= 6 in this study

So before commencing any hypothesis testing, we want to test if the common variance-covariance matrix of each clinic is of the uniform type $\underset{\sim}{\Sigma}^{*}$ (Table 16A). If they

analysis of variance of repeated measurement for mixed model nested design shown in the following table. Otherwise multivariate analysis would be appropriate.

TABLE D : UNIVARIATE ANALYSIS OF VARIANCE OF REPEATED MEASUREMENTS

SOURCE	D.F.	S.S.	F-RATIO
TIME	p-1	S1	F1=(N-g) S1/S5
GROUPS(TREATMENTS)	g-1	S2	F2=(N-g)S2/(g-1)S3
INDIVIDUAL WITHIN GROUP	N-g	S3	
GROUP X TIME	(p-1)(g-1)	S4	F3=(N-g)S4/(g-1)S5
INDIVIDUAL X TIME WITHIN GROUP	(p-1)(N-g)	S5	

Applying the likelihood ratio test on the original (untransformed) data for the hypothesis $\underset{\sim}{\Sigma} = \underset{\sim}{\Sigma}^{*}$ (BOX 1950) (Theory- see Appendix B), we obtained a value of the test statistics of 560.6978 for common matrix for 3 drug groups and 3 clinics, 228.36075 for clinic A,223.013887 for clinic B,240.20537 for clinic C . All these statistics are distributed approximately as Chi-square on 19 degree of freedom and all are highly significant ($p<.00001$).That means the var-covariance

matrix pooled together from the 3 drug groups and 3 clinics or pooled from 3 drug groups in each of the 3 clinic is not of the uniform type.By looking at Table 5, we found that the means are positively correlated with the variances in all clinics.The logarithmic transformation on the data is quite likely to remedy the situation and make the variance of a sample independent of its mean. So with the data transformed into log10 values, the same test statistics are now reduced to 446.4678 for 3 clinics and 3 drug groups, 191.821 for clinic A,158.766 for clinic B,242.952 for clinic C. Again they are highly significant. Thus a multivariate analysis of variance approach is more appropriate.

The usual multivariate analysis of variance procedure requires that the observation vectors have a common,but not necessarily uniform, var-covariance matrix.Applying Box's modified generalized likelihood ratio statistics (for theory, see Appendix B) for the hypothesis on the nine matrices (3 treatment groups in each of the 3 clinics).

we obtained a value of 510.8492 for the test statistics which is distributed approximately as a Chi-square on 168 degree of freedom. This value is highly significant ($p<.0001$),meaning that not all the nine clinic-drug combinations have a common var-covariance matrix. The test of homogeneity of var-covariance matrices among the three drug groups was then applied on the 3 clinics separately.

From TABLE A, we can see that the test statistics obtained for clinic A and C are highly significant at $p=.005$,where at clinic B,it is significant at $p=.02558$.Thus the assumption of common var-covariance matrices among the 3 drug groups is not valid even when the 3 clinics are treated separately.

TABLE A. TESTING OF HOMOGENEITY OF VARIANCE-COVARIANCE MATRICES

	CLINIC A	CLINIC B	CLINIC C	OVERALL
BOX M	91.21375	77.0726	87.3468	573.472
TEST STAT.	82.327	62.285	78.1971	510.849
D.F.	42	42	42	16
EXACT PROB. CHI-SQUARE	.00047	.02558	.00107	0.000

We repeated Box's modified generalized likelihood ratio test for homogeneity of var-covariance matrices (TABLE 16B) on the logarithmic transformed data expecting to get a better result as the variances have been stabilized. Table B shows that the nine drug-clinic combinations again do not have a common var-covariance matrices,thus we intend to analyse the data in 3 clinics separately. Table B also shows that the 3 drug groups in each of clinic A and B have a common var-covariance matrix, but not in C , all considered at 5% level of significance.

TABLE B. TESTING OF HOMOGENEITY OF VARIANCE-COVARIANCE MATRICES WITH DATA TRANSFORMED INTO LOG10 VALUES

	CLINIC A	CLINIC B	CLINIC C	OVERALL
BOX M	64.88985	69.29251	76.61151	529.69921
TEST STAT.	58.5678	55.9976	68.5863	471.8401
D.F.	42	42	42	168
EXACT PROB. CHI-SQUARE	.05049	.07821	.00742	.0000

V. RESULTS OF MULTIVARIATE ANALYSIS OF VARIANCE

With the help of a program MANOVA in STATISTICAL PACKAGE FOR SOCIAL SCIENCES (Norman H.Nie et. al,1977) we will be able to perform all the necessary multivariate hypothesis testings mentioned in appendix C.

We proceed with our analyses as follows:

(1) DRUG x TIME INTERACTION

The interaction effect between drugs and time in the three clinics is tested before the main effects are tested. The following results are obtained :

MULTIVARIATE TEST OF SIGNIFICANCE OF DRUG X TIME INTERACTION

	CLINIC A	CLINIC B	CLINIC C
EIGENVALUES	(1)0.164(69.5%) (2)0.072(30.5%)	(1)0.158(88.5%) (2)0.021(11.5%)	(1)1.149(94.3%) (2)0.070(5.68%)
PILLAIS	0.20738 F=1.9435 (p=.0426)	0.15658 F=0.7475 (p=.67810)	0.59920 F=6.67295 (p=.00001)
HOTELLINGS	.23515 F=1.92813 (p=.0447)	0.17855 F=0.75 (p=.67573)	1.21761 F=9.25385 (p=.00001)
WILKS	.80202 F=1.9360 (p=.0436)	0.84617 F=0.7491 (p=.67652)	0.43535 F=7.93991 (p=0.00001)
ROYS	.14049 (p>.05)	0.13645 (p <.01)	0.53456 (p<.01)

The F-statistics are not significant for Clinic B, and we thus conclude that there is no evidence to show the existence of interaction between treatment group and time of responses in Clinic B.

The interaction effect was barely significant (p=0.04) for Clinic A,and highly significant (p=0.00001) for Clinic C. To find out which drug causes the significant interaction in Clinic A and C, one drug is eliminated at a time and the interaction based on the remaining two drugs are tested. The results are as

follows.

MULTIVARIATE TEST OF SIGNIFICANCE FOR INTERACTION EFFECT FOR CLINIC A

TEST NAME	TEST - PLACEBO (1)	TEST-STANDARD (2)	PLACEBO-STANDARD (3)
HOTELLING	0.22411	0.13030	0.23206
T-SQUARE	F=2.42047	F=1.40720	F= 2.50629
	p=.04729	p=.23643	p=.04112

Column (2) indicated that there is no significant interaction between the test drug and the standard drug in both clinic A and C. But when test drug and placebo,standard drug and placebo are considered together,we find a highly significant interaction result (p=.00001) in Clinic C and a slighly significant interaction result in Clinic A if alpha = 0.05.

MULTIVARIATE TEST OF SIGNIFICANCE FOR INTERACTION EFFECT FOR CLINIC C

TEST NAME	TEST-PLACEBO (1)	TEST-STANDARD (2)	PLACEBO-STANDARD (3)
HOTELLING	1.56135	0.14377	1.32348
T-SQUARE	F= 15.9257	F=1.43769	F=12.9701
	p=.00001	p=.22716	p=.00001

(2) MAIN RESPONSE(TIME) EFFECT

Since the hypothesis of no treatment by response interaction is tenable in Clinic B at p=.05 and Clinic A at p=.04, we want to know if there is any difference due to main effect of time of measurements. By choosing C matrix as a summation matrix and M as a contrasting matrix (See Appendix B,Section III), the resulting joint hypothesis is :

$$H_o: \sum_{j=1}^{3} \xi_{j0} = \sum_{j=1}^{3} \xi_{j1} = \sum_{j=1}^{3} \xi_{j2} = \sum_{j=1}^{3} \xi_{j3} = \sum_{j=1}^{3} \xi_{j4} = \sum_{j=1}^{3} \xi_{j5}$$

and the following results are obtained :

MULTIVARIATE TEST OF SIGNIFICANCE ON THE MAIN TIME RESPONSE EFFECT FOR CLINIC A AND B

	CLINIC A	CLINIC B
EIGENVALUES	0.65661(100%)	12.40520(100%)
PILLAIS	0.39636 F(5,83)=10.8997 p=.00001	0.92540 F(5,43)=106.6847 p=.00001
HOTELLING T	0.65661 F(5,83)=10.8997 P=.00001	12.40520 F(5,43)=106.6847 P=.00001
WILKS	0.60364 F(5,83)=10.8997 P=.00001	0.0746 F(5,43)=106.6847 P=.00001
ROYS LARGEST ROOT	0.39636 S=1,M=1.5,N=40.5 P<.01	0.92540 S=1,M=1.5,N=20.5 P<.01

The results show that not all responses over the six weeks are equal. This is true for both clinic A and B.

Since the drug x time interaction is significant in Clinic C,the hypothesis of equal main effect of time measurement is tested by the following univariate tests.

UNIVARIATE F-TEST FOR MAIN EFFECT ON TIME RESPONSE MEASUREMENTS FOR CLINIC C (WITH DEGREE OF FREEDOM = 1,81)

VARIATE	HYP. SS	ERROR SS	HYP. MS	ERROR MS	F	P
WK0-WK1	6.90507	0.55402	6.90507	0.00684	1009.55	.00001
WK1-WK2	0.20561	0.26893	0.20561	0.00332	61.93	.00001
WK2-WK3	0.47105	0.45136	0.47105	0.00557	84.53	.00001
WK3-WK4	0.08820	0.43893	0.08820	0.00542	16.26	.00012
WK4-WK5	0.30593	0.23945	0.30593	0.00333	91.97	.00001
AVERAGE	7.97585	1.98268	1.59517	0.00490	325.84	.00001

All these univariate tests indicate there are significant week-to-week variations in the time responses. That is,the weekly total mean scores of the 3 drugs during the period of six weeks are not all equal.

(3) MAIN DRUG EFFECTS

Assuming the three drug-groups have a common variance-covariance matrix,we want to test :

Ho : The three groups of subjects who separately receive the three drugs,TEST,PLACEBO,and STANDARD DRUG have equal vectors of response means simultaneously during the six-week assessment period

$$H_o: \sum_{j=0}^{5} \zeta_{1j} = \sum_{j=0}^{5} \zeta_{2j} = \sum_{j=0}^{5} \zeta_{3j}$$

The analysis for the 3 clinics, which are analysed separately because of their unequal var-covariance matrices, are as follows :

	CLINIC A	CLINIC B
EIGENVALUES	1. 0.1635(61.02%) 2. 0.1045(38.98%)	1. 1.3085(93.83%) 2. 0.0861(6.17%)
PILLAIS	0.23509 F=1.8426 (p=.0452)	0.64604 F=3.4195 (p=.0004)
HOTELLINGS	0.26794 F=1.8086 (p=.0506)	1.3945 F=4.7645 (p=.00001)
WILKS	0.77820 F=1.8257 (p=.0478)	0.39887 F=4.0836 (p=.00005)
ROYS	0.14052 (p>.05)	0.56681 (p<.01)

The probabilities associated with the tests are approximately 0.05 in Clinic A, therefore there is no strong evidence against the null hypothesis that all three drugs have equal effects during the entire period of the study for Clinic A.

However in Clinic B,the probabilities associated with the F-statistics are very small,therefore we concluded that there is strong evidence that not all 3 drugs in Clinic B have equal effects during the six-week period.

Here again owing to the fact that drug x time interaction is highly significant in Clinic C, we have to analyse the hypothesis of equal drug effect through the following univariate tests.

UNIVARIATE F-TEST FOR MAIN EFFECT ON EQUAL TREATMENT FOR CLINIC C (WITH DEGREE OF FREEDOM = 1,81)

VARIATE	HYP.SS	ERROR SS	HYP.MS	ERROR MS	F	P
WEEK 0	0.0243	0.37001	.01217	0.00457	2.6652	0.07569
WEEK 1	0.0284	0.55188	.01423	0.00681	2.0890	0.13043
WEEK 2	0.2592	0.72110	.12964	0.00890	14.562	0.00001
WEEK 3	0.8175	1.01878	.16582	0.01258	32.499	0.00001
WEEK 4	0.3316	1.09246	.16582	0.01349	12.295	0.00002
WEEK 5	0.1516	1.04851	.07580	0.01294	5.8560	0.00421
AVERAGE	1.6128	4.80273	.13440	0.00988	13.6007	0.00001

The univariate tests show that the 3 drugs in Clinic C have different effects in weeks 2,3,4 and 5.To find out which drug caused the significant results,we

run the test again with two drugs at a time, and the following results are obtained.

UNIVARIATE F-TEST OF SIGNIFICANCE FOR EQUAL DRUG EFFECT FOR CLINIC C

VARIATE	TEST-PLACEBO (1)	TEST-STANDARD (2)	PLACEBO-STANDARD (3)
WEEK 0	F = 5.02103 p = 0.02910	F = 0.38367 p = 0.53825	F = 2.65014 p = 0.10947
WEEK 1	F = 3.40017 p = 0.07058	F = 0.59349 p = 0.44443	F = 1.74873 p = 0.19171
WEEK 2	F = 26.14361 p = 0.00001	F = 2.00746 p = 0.16227	F = 14.02274 p = 0.00045
WEEK 3	F = 57.81293 p = 0.00001	F = 1.25134 p = 0.26825	F = 41.0503 p = 0.00001
WEEK 4	F = 22.12929 P = 0.00002	F = 4.24960 p = 0.04409	F = 8.49929 p = 0.00520
WEEK 5	F = 9.88443 p = 0.00269	F = 0.76028 p = 0.38710	F = 5.93619 p = 0.01823
AVERAGE	F = 23.24291 p = 0.00001	F = 1.77224 p = 0.10414	F = 14.37352 p = .00001

From the above table we can see there is no significant F-tests caused by Test and standard drug all throughout the 6-week assessment period. But once again, the majority of the significant F-tests produced when Test-Placebo or Standard-Placebo are considered together.

TREND-ANALYSIS

Since the response measurements are ordered in time, there may be a significant time trend in the measurements.We therefore would also like to analyse the data by the technique for trend analysis of repeated measurement (Cramer,1966).

In a typical trend analysis of repeated measurements, the following questions are raised :

(A) Are there any difference between the 3 drugs in reducing tension, anxiety and related complaints of non-psychotherapy outpatients when averaged over time ?

(B) Does the difference among the 3 treatment groups change with time ?

(C) On the average, does the severity of symptoms change with time ?

Appropriate choice of C matrix and M matrix will help to answer the above questions. Here we try to use the M matrix to decompose the six time measurements into 6 components starting with the mean and ending with fifth degree orthogonal polynomials (See Appendix B

TREND ANALYSIS

Since the response measurements are ordered in time, there may be a significant time trend in the measurements.We therefore would also like to analyse the data by the technique for trend analysis of repeated measurement (Cramer,1966).

In a typical trend analysis of repeated measurements, the following questions are raised :

(A) Are there any difference between the 3 drugs in reducing tension, anxiety and related complaints of non-psychotherapy outpatients when averaged over time ?

(B) Does the difference among the 3 treatment groups change with time ?

(C) On the average, does the severity of symptoms change with time ?

Appropriate choice of C matrix and M matrix will help to answer the above questions. Here we try to use the M matrix to decompose the six time measurements

For Clinic C,there is strong evidence that not all of the three drugs,have equal overall effects. The following results of the tests show that there is no significant differences between the Test drug and the Standard drug,but the placebo definitely differs from the two active drugs.

Ho : There is no difference in treatments when averaged over time for Clinic C only

SOURCE OF VARIATION	S.S	DF	M.S.	F	P
DRUG(TEST+PLACEBO)	0.18860		0.1886	23.467	0.00001
WITHIN CELL	0.44202	5	0.0080		
DRUG(TEST+STANDARD)	0.01299		0.0130	2.1665	0.14685
WITHIN CELL	0.32389	4	0.0060		
DRUG(PLACEBO+STANDARD)	0.09832		0.0983	15.231	0.00027
WITHIN CELL	0.34213	3	0.0065		

(5) Ho : The difference among the 3 drug groups do not change with time

MULTIVARIATE TEST OF SIGNIFICANCE ON DIFFERENCES AMONG THE THREE DRUG GROUPS DOES NOT CHANGE WITH TIME

	CLINIC A	CLINIC B	CLINIC C
EIGENVALUES	(1) .1635(69.5%)	(1) .8466(94.3%)	(1) 1.4135(94.5%)
	(2) .0717(30.5%)	(2) .0512(5.7%)	(2) .08292(5.54%)
PILLAIS	0.20738 F=1.9435 (p=.0426)	0.50718 F=2.98978 (p=.00273)	0.66224 F=7.72256 (p=.00001)
HOTELLINGS	0.23515 F=1.92813 (p=.0447)	0.89783 F=3.77 (p=.00032)	1.49646 F=11.3731 (p=.00001)
WILKS	0.80202 F=1.9360 (p=.0436)	0.51515 F=3.38205 (p=.00092)	0.38260 F=9.49693 (p=.00001)
ROYS	0.14049 (p>.05)	0.45847 (p<.01)	0.58567 (p<.01)

From the above table,it seems that the differences between the 3 drugs change significantly at alpha=0.05 from week to week. The Hotelling T-test to each pair of the drugs so as to find out which drug induces the significant changes. The following results are obtained.

MULTIVARIATE TEST OF SIGNIFICANCE ON TESTING THE DIFFERENCE BETWEEN DRUGS OVER TIME

CLINIC	TEST NAME	TEST-PLACEBO	TEST-STANDARD	PLACEBO-STANDARD
A	HOTELLING	0.22411	0.13030	0.23206
	T-SQUARE	F= 2.42037	F=1.40720	F=2.50629
		p=.04729	p=.23643	p=.04112
B	HOTELLING	1.00585	0.09028	1.10059
	T-SQUARE	F=5.23045	F=0.43335	F=7.04379
		p=0.00187	p=.82080	p=.00015
C	HOTELLING	2.19843	0.17238	1.45290
	T-SQUARE	F=22.42398	F=1.72384	F=14.23849
		p=0.00001	p=0.14635	p=0.00001

Clearly, from above table, we can see there is no significant result obtained in all three clinics between Test drug and standard drug. However,significant results obtained in all three clinics between Test drug and placebo ,Standard drug and Placebo.

To see how the differences among the 3 drug groups change with time,we apply the test using the individual column of the orthogonal M matrix, and the following results are obtained:

TABLE SHOWING THE RESULTS OF F-TEST OF HOW THE DIFFERENCES AMONG THE 3 DRUG GROUPS CHANGE WITH TIME

VARIATE	CLINIC A	CLINIC B	CLINIC C
LINEAR	F = 2.94608	F = 0.71009	F = 14.69460
	p = 0.05781	p = 0.49680	p = 0.00001
QUADRATIC	F = 1.11482	F = 3.69776	F = 5.41234
	p = 0.33261	p = 0.03225	p = 0.00622
CUBIC	F = 1.52542	F = 1.17660	F = 26.1831
	p = 0.22329	p = 0.31724	p = 0.00001
FOURTH	F = 1.51250	F = 0.68938	F = 15.38326
	p = 0.22610	p = 0.50689	p = 0.00001
FIFTH	F = 2.45207	F = 0.45879	F = 16.06930
	p = 0.09205	p = 0.63485	p = 0.00001

(6) Ho: On the average,the severity of the symptoms does not change with time

MULTIVARIATE TEST OF SIGNIFICANCE ON THE SEVERITY OF SYMPTOM DOES NOT CHANGE OVER TIME

	CLINIC A	CLINIC B	CLINIC C
EIGENVALUES	0.6429(100%)	11.49407(100%)	40.36858(100%)
PILLAIS	0.39132 F=10.929 (p=.00001)	0.91996 F=103.45 (p=.00001)	0.97583 F=637.823 (p=.00001)
HOTELLINGS	0.64290 F=10.9294 (p=.00001)	11.4941 F=103.45 (p=.00001)	40.3686 F=637.824 (p=.00001)
WILKS	0.60868 F=10.9294 (p=.00001)	0.08004 F=103.45 (p=.00001)	0.02417 F=637.824 (p=.00001)
ROYS	0.39132 (p<.01)	0.91996 (p<.01)	0.97583 (p<.01)

In all cases, there is a significant time trend (p=0.00001) of the severity of symptoms (average over three drugs) over the six-week period. In order to find out how the severity of symptoms changed over time,we apply the test using the individual column of the orthogonal M matrix. The following results are obtained:

TABLE SHOWING THE RESULTS OF F-TEST OF HOW THE SEVERITY OF SYMPTOMS CHANGED OVER TIME

VARIATE	CLINIC A	CLINIC B	CLINIC C
LINEAR	F = 40.7606	F = 99.1675	F = 759.069
	p = 0.00001	p = 0.00001	p = 0.00001
QUADRATIC	F = 5.07461	F = 180.26956	F = 361.8471
	p = 0.02674	p = 0.00001	p = 0.00001
CUBIC	F = 0.95906	F = 18.96496	F = 1.82919
	p = 0.33008	p = 0.00007	p = 0.17990
FOURTH	F = 3.90205	F = 18.96496	F = 0.00771
	p = 0.05132	p = 0.25862	p = 0.93022
FIFTH	F = 1.95373	F = 0.57318	F = 0.59374
	p = 0.16566	p = 0.45262	p = 0.44316

VI. DISCUSSION AND CONCLUSION

The allocations of patients to the 3 clinics are not randomized according to sex,age and race. For instance, all patients in Clinic B are males and Clinic C has more race-1 patients than the other two clinics. Also the average age of the patients in clinics C is slighly higher. The amount of missing data in the 3 clinics differ substantially too.

Significant F-tests (Table 5 through Table 10) at week 0, and week 1 at alpha=0.05 in the total mean scores and factor mean scores in Clinic C also reveals that subjects in that clinic are not randomized in the treatment groups because there should not be any difference in means among the three drug groups before treatments begin.

There are 40 missing values (7.41%) in the 6-week assessment period in Clinic A, 112 (30.12%) in Clinic B,and 126 (24.42%) in Clinic C. It is believed that for every estimate we make , we will lose one degree of freedom for the residual term. This should not be true in this case. However,since the regression equations we create are obtained from the set of

completed observation subjects and then the estimate is obtained by substituting the patient's own available information into the appropriate equation for finding the missing values,instead of using other patient's information.Thus we are only losing a fraction of the degree of freedom in the residual term for every missing value we estimated. Nevertheless, since there are so many missing observations in the data set, and patients with missing scores on the different measures are not randomly distributed over the treatment conditions,(this is especially true in Clinic C where all the missing values centre around the Placebo group) so no matter how carefully we preceed in making inferences on the data,the result of the analyses can never be satisfactory, as the large number of missing data is believed to have introduced a systematic source of bias into the analysis. Moreover all the statistical tests employed here work only on the complete sets of data. By replacing the missing data with an estimate,we definitely violate some of the basic assumptions like i.i.d.(independent and identically distributed) because the statistical tests may no longer converge even asymptotically. To attempt to verify that those test

statistics are still valid under the situation in which all missing data has been replaced by estimated values is beyond the scope of this project.

The data are multivariate in nature because observations in 6 successive weeks are taken on the same subjects. Data of this type can be analysed by the univariate analysis of variance of the mixed model design provided that the var-covariance matrix is uniform. Test results indicate that the var-covariance matrix is not uniform,not even after the original data have been transformed into log10 values,we therefore choose to analyse the data by the mulivariate analysis of variance technique.This technique requires that the observation vectors must have a common var-covariance matrix. Test results show that observation vectors of the 3 drug groups in Clinic A and B have common var-covariance matrices only after the data have been transformed into log10 values.

There is significant interaction between the types of drug and time measurements in Clinic C,meaning that the effects of the 3 drugs do not behave in a parallel manner from week to week.Actually, the two

active drugs (Test and Standard) do behave in parallel. It is the placebo that behaves differently causing the interaction effect to be significant.

The total responses of the three drugs measured in each of the six weeks are not all equal,indicating that the severity of symptoms are not constant during the entire six-week period. This is true for all three Clinics.

The main drug effects in Clinic B are not significantly different, indicating that the efficacies of the two active drugs are not different than the placebo. But in Clinic A and C, there are significant differences among the 3 drugs.

In the trend analysis in which the time trend is taken into consideration,the drug effects, when averaged over six-weeks,are not significant in Clinic A and B. That means the overall effectiveness of the test drug and standard drug are not better than the placebo. In Clinic C, the overall efficacies of the 2 active drugs are similar,but significantly different from that of the placebo.

In all three clinics, the differences among the 3 drugs, compared on a weekly basis, change significantly with time. A closer look at the situation reveals that the differences between the two active drugs remain constant during the six weeks. However, the differences between placebo and test drug, placebo and standard drug do change significantly with time.

The weekly averaged severities of symptoms definitely have a trend over time. For Clinic A, the linear trend is most significant, followed by a quadratic trend which is also significant. For Clinic B, the linear,the quadratic and the cubic trends are all highly significant. For Clinic C, both the linear and the quadratic trends are highly significant.

From this study,the following observations may be made:

(1) Over a period of six weeks : there is some evidence in Clinic A that the Test drug and standard drug did reduce anxiety and related complaints,there is strong evidence in Clinic B and C that the 2 drugs definitely perform better

than the Placebo.

(2) The 2 test drugs are equally effective in all 3 clinics.

(3) In all 3 clinics,the amount of improvement by the 2 active drugs over placebo changes from week to week. The trend of improvement is predominantly linear in Clinic A,mainly quadratic in Clinic B, but quite complex in Clinic C.

The following points are to be recommended for similar studies in the future:

(1) continue to use the two active drugs because there are evidence to indicate that they are both effective.

(2) There is probobly no need to replace the Standard drug by the Test drug because they appear to be equally effective - unless the Test drug is easier and more economical to use.

(3) It is advisable to do a thorough investigation to find out why a large proportion of the patients failed to complete the 6-week treatment,especially

in Clinics B and C,where drop-out rates were 80%. To find out whether the patients dropped out is because of :

(i) patients have no trust in doctors or nurses or the drugs?

(ii) test drugs produce undesirable side effects to scare off the patients?

(iii) nurses or administrative personnals fail to remind patients of the next appointment?

(iv) part of the self-rating questionaires are too difficult or too personnel to answer?

(4) Better planning of the drug trial is highly recommended in the area of randomized allocation of patients to the 3 drugs in the 3 clinics,according to age,sex, and race.

find out why a large proportion of the patients failed to complete the 6-week treatment,especially in Clinics B and C,where drop-out rates were 80%. To find out whether the patients dropped out is because of :

(i) patients have no trust in doctors or nurses or the drugs?

(ii) test drugs produce undesirable side effects to scare off the patients?

(iii) nurses or administrative personnals fail to remind patients of the next appointment?

(iv) part of the self-rating questionaires are too difficult or too personnel to answer?

(4) Better planning of the drug trial is highly recommended in the area of randomized allocation of patients to the 3 drugs in the 3 clinics,according to age,sex, and race.

TABLE 1. PATIENT POPULATION

CLINIC	STUDY-DRUG	COMPLETED CASES	MISSING CASES	DROP - OUT AT WEEK					TOTAL
				1	2	3	4	5	
A	TEST DRUG	20 (66.7%)	0	0	0	0	6 (20.0%)	4 (13.3%)	30
	STANDARD DRUG	20 (66.7%)	1 (3.3%)	0	0	0	3 (10.0%)	6 (20.0%)	30
	PLACEBO	22 (73.3%)	0	0	0	0	3 (10.0%)	5 (16.7%)	30
B	TEST DRUG	4 (21.1%)	1 (5.3%)	2 (10.5%)	5 (26.3%)	1 (5.3%)	2 (10.5%)	4 (21.1%)	19
	STANDARD DRUG	6 (31.6%)	4 (21.1%)	0	1 (5.3%)	0	5 (26.3%)	3 (15.8%)	19
	PLACEBO	2 (8.3%)	5 (20.8%)	0	4 (16.7%)	3 (12.5%)	6 (25.0%)	4 (16.7%)	24
C	TEST DRUG	9 (31.0%)	13 (44.8%)	0	0	1 (3.4%)	1 (3.4%)	5 (17.3%)	29
	STANDARD DRUG	6 (21.4%)	16 (57.1%)	0 (3.6%)	1 (3.6%)	1 (3.6%)	0	4 (14.3%)	28
	PLACEBO	1 (3.4%)	2 (6.9%)	0	1 (3.4%)	6 (20.9%)	13 (44.8%)	6 (20.7%)	29

TABLE 2. SEX DISTRIBUTION OF THE STUDY POPULATION

CLINIC	STUDY-DRUG	COMPLETED CASES		DROP-OUT & MISSINGS		TOTAL
		MALE	FEMALE	MALE	FEMALE	
A	TEST DRUG	13 (43.3%)	7 (23.3%)	7 (23.3%)	3 (10.0%)	30
	STANDARD DRUG	12 (40.0%)	8 (26.7%)	5 (16.7%)	5 (16.7%)	30
	PLACEBO	15 (50.0%)	7 (23.3%)	5 (16.7%)	3 (10.0%)	30
	OVERALL	40 (44.4%)	22 (24.4%)	17 (18.9%)	11 (12.2%)	90
B	TEST DRUG	4 (21.1%)	0	15 (79.0%)	0	19
	STANDARD DRUG	6 (31.6%)	0	13 (68.4%)	0	19
	PLACEBO	2 (8.3%)	0	22 (91.7%)	0	24
	OVERALL	12 (19.4%)	0	50 (80.6%)	0	62
C	TEST DRUG	3 (10.3%)	2 (6.9%)	17 (58.6%)	7 (24.1%)	29
	STANDARD DRUG	6 (21.4%)	0	14 (50.0%)	8 (28.6%)	28
	PLACEBO	1 (3.4%)	0	20 (69.0%)	8 (27.6%)	29
	OVERALL	10 (11.6%)	2 (2.3%)	51 (59.3%)	23 (26.7%)	86

TABLE 3. AGE DISTRIBUTION OF THE STUDY POPULATION

CLINIC	STUDY-DRUG	COMPLETED CASES					DROP-OUTS & MISSINGS					T O T A L					F-TEST
		N	MEAN	S.D.	MIN	MAX.	N	MEAN	S.D.	MIN	MAX.	N	MEAN	S.D.	MIN	MAX.	
A	TEST DRUG	20	30.15	8.98	18	50	10	26.40	7.37	18	40	30	28.90	8.37	18	50	
	STANDARD	20	30.05	10.58	17	50	10	27.10	7.00	19	40	30	29.07	9.52	17	50	2.5376
	PLACEBO	22	35.36	10.59	23	58	8	29.50	8.55	19	42	30	33.73	10.31	19	58	p=.085
	OVERALL	62	32.00	10.26	17	58	28	27.46	7.40	18	42	90	30.57	9.60	17	58	
		F=1.9043 ; p=.1581					F=.3311 ; p=.7212										
B	TEST DRUG	5	31.00	9.25	25	47	14	28.57	6.54	20	42	19	29.21	7.15	20	47	
	STANDARD	8	30.00	5.58	23	36	11	34.27	7.85	22	47	19	32.47	7.14	22	47	0.8993
	PLACEBO	4	30.25	10.50	21	45	20	29.85	9.07	20	58	24	29.92	9.07	20	58	p=.4124
	OVERALL	17	30.35	7.47	21	47	45	30.53	8.19	20	58	62	30.48	7.94	20	58	
		F=0.0246 ; p=.9757					F=1.667 ; p=.2011										
C	TEST DRUG	9	34.89	9.24	19	45	20	33.35	6.72	24	50	29	33.83	7.46	19	50	
	STANDARD	6	36.17	10.87	26	57	22	32.82	11.50	20	62	28	33.54	11.25	20	62	0.2729
	PLACEBO	2	39.50	7.78	34	45	27	35.00	10.45	21	61	29	35.31	10.24	21	61	p=.7618
	OVERALL	17	36.00	9.54	19	57	69	33.83	9.81	20	62	86	34.23	9.69	19	62	
		F=0.3267 ; p=0.7275					F=0.18303 ; p=0.8349										

TABLE 4. RACE DISTRIBUTION OF THE STUDY POPULATION

CLINIC	STUDY-DRUG	RACE 1	RACE 2	TOTAL
A	TEST DRUG	1 (3.3%)	29 (96.7%)	30
	STANDARD DRUG	1 (3.3%)	29 (96.7%)	30
	PLACEBO	0 (0.0%)	30 (100.0%)	30
	TOTAL	2 (2.2%)	88 (97.8%)	90
B	TEST DRUG	3 (15.8%)	16 (84.2%)	19
	STANDARD DRUG	1 (5.3%)	18 (94.7%)	19
	PLACEBO	3 (12.5%)	21 (87.5%)	24
	TOTAL	7 (11.3%)	55 (88.7%)	62
C	TEST DRUG	12 (41.4%)	17 (58.6%)	29
	STANDARD DRUG	12 (42.9%)	16 (57.1%)	28
	PLACEBO	8 (27.6%)	21 (72.4%)	29
	TOTAL	32 (37.2%)	54 (62.8%)	86

TABLE 5 TOTAL MEAN SCORES AND F-TESTS AT WEEK 0,1,2,3,4,5 FOR DIFFERENT DRUG GROUPS FOR STUDY POPULATION

CLINIC	WEEK	TEST - DRUG			STANDARD-DRUG			PLACEBO			OVERALL			F	P
		N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	RATIO	
A	0	30	2.417	1.105	30	2.205	1.029	30	2.344	1.404	90	2.262	1.189	0.9211	0.4019
	1	30	2.201	1.085	30	1.723	0.874	30	2.062	1.161	90	1.995	1.055	1.6546	0.1971
	2	30	1.967	1.004	30	1.768	0.969	30	1.884	1.133	90	1.873	1.029	0.2763	0.7593
	3	30	1.773	0.959	30	1.714	0.884	30	2.035	1.198	90	1.841	1.021	0.8425	0.4341
	4	24	1.374	0.582	26	1.521	0.899	27	1.697	0.965	77	1.537	0.839	0.9474	0.3924
	5	20	1.338	0.645	21	1.357	0.777	22	1.922	1.025	63	1.548	0.869	3.3650	0.0412*
B	0	19	3.244	1.218	19	3.097	1.123	24	2.831	0.825	62	3.039	1.047	0.8623	0.4275
	1	17	2.770	1.123	18	2.479	1.232	24	2.223	0.883	59	2.459	1.074	1.3089	0.2783
	2	11	1.926	1.058	16	1.642	0.947	20	1.632	0.841	47	1.704	0.918	0.4103	0.6660
	3	10	2.261	0.953	16	1.791	0.920	15	1.693	0.878	41	1.870	0.919	1.2585	0.2957
	4	9	1.258	0.491	12	1.153	0.531	8	1.124	0.504	29	1.178	0.498	0.1678	0.8464
	5	5	1.404	0.553	10	1.131	0.500	7	1.598	0.627	22	1.342	0.567	1.5080	0.2467
C	0	29	2.570	0.449	28	2.631	0.414	29	2.777	0.456	86	2.660	0.444	1.6942	0.1900
	1	26	2.300	0.496	27	2.349	0.346	27	2.484	0.595	80	2.378	0.490	1.0094	0.3692
	2	28	1.796	0.403	25	1.929	0.434	28	2.420	0.552	81	2.053	0.538	13.673	0.0000*
	3	24	1.562	0.567	21	1.687	0.545	20	2.300	0.403	65	1.830	0.599	12.412	0.0000*
	4	17	1.385	0.602	16	1.584	0.441	7	2.049	0.427	40	1.581	0.555	4.1189	0.0243*
	5	22	1.352	0.490	22	1.351	0.269	3	1.420	0.348	47	1.356	0.385	0.0422	0.9587

TABLE 6 'GENERAL NEUROTIC FEELING' MEAN SCORES AND F-TEST AT WEEK 0,1,2,3,4,5 FOR THREE THREE DOSAGE GROUPS FOR THE STUDY POPULATION

CLINIC	WEEK	TEST - DRUG			STANDARD-DRUG			PLACEBO			OVERALL			F RATIO	P
		N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.		
A	0	30	2.996	1.645	30	2.332	1.447	30	2.630	1.959	90	2.652	1.700	1.1535	0.3203
	1	30	2.430	1.398	30	1.878	1.214	30	2.332	1.536	90	2.213	1.395	1.3467	0.2655
	2	30	2.035	1.354	30	1.837	1.202	30	1.846	1.445	90	1.906	1.326	0.2083	0.8124
	3	30	1.812	1.022	30	1.914	1.022	30	2.008	1.583	90	1.911	1.226	0.1883	0.8287
	4	24	1.323	0.669	26	1.640	1.329	27	1.683	1.349	78	1.556	1.168	0.7016	0.4991
	5	20	1.305	0.743	21	1.376	0.927	22	1.999	1.570	63	1.571	1.175	2.3047	0.1036
B	0	19	4.293	1.546	19	3.957	1.436	24	3.886	1.310	62	4.032	1.412	0.4715	0.6264
	1	16	3.375	1.110	18	3.098	1.509	24	2.875	1.464	58	3.083	1.382	0.6226	0.5403
	2	11	1.824	0.765	16	1.970	1.274	20	1.931	1.280	47	1.919	1.156	0.0511	0.9502
	3	10	2.596	1.313	16	2.401	1.371	15	1.948	1.444	41	2.283	1.377	0.7504	0.4791
	4	9	1.295	0.549	12	1.331	0.724	8	1.363	0.984	29	1.328	0.731	0.0169	0.9833
	5	5	1.420	0.530	10	1.369	0.764	7	1.851	1.000	22	1.534	0.802	0.7925	0.4671
C	0	29	2.625	0.849	28	2.599	0.657	29	2.835	0.827	86	2.687	0.782	0.7852	0.4594
	1	26	2.417	0.687	27	2.311	0.607	27	2.535	0.978	80	2.425	0.771	0.5626	0.5721
	2	28	1.878	0.458	25	1.839	0.392	28	2.608	0.741	81	2.118	0.656	16.577	0.0000*
	3	24	1.757	0.797	21	1.802	0.685	20	2.251	0.558	65	1.923	0.718	3.2296	0.0463*
	4	17	1.582	0.775	16	1.746	0.659	7	1.997	0.273	40	1.720	0.668	0.9699	0.3885
	5	22	1.534	0.733	22	1.429	0.357	3	1.863	0.147	47	1.506	0.562	0.8296	0.4429

TABLE 7. "SOMATIZATION" MEAN SCORES AND F-TESTS AT WEEK 0,1,2,3,4,5 FOR THREE DRUG GROUPS FOR THE STUDY POPULATION

CLINIC	WEEK	TEST - DRUG			STANDARD-DRUG			PLACEBO			OVERALL			F RATIO	P
		N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.		
A	0	30	1.922	0.937	30	1.692	0.996	30	1.782	1.184	90	1.799	1.037	0.3689	0.6926
	1	30	1.819	1.156	30	1.371	0.820	30	1.538	1.044	90	1.576	1.022	1.4895	0.2312
	2	30	1.671	0.920	30	1.462	1.048	30	1.476	0.957	90	1.536	0.970	0.4299	0.6520
	3	30	1.420	0.890	30	1.273	0.887	30	1.601	1.002	90	1.431	0.928	0.9373	0.3956
	4	24	1.211	0.588	26	1.087	0.682	27	1.336	0.810	77	1.218	0.702	0.8317	0.4393
	5	20	1.159	0.589	21	1.187	0.676	22	1.403	0.835	63	1.220	0.713	1.1660	0.3186
B	0	19	2.394	1.081	19	2.647	1.207	24	2.065	0.853	62	2.344	1.053	1.6901	0.1933
	1	17	2.271	1.411	18	2.103	1.374	24	1.650	0.727	59	1.967	1.177	1.5886	0.2133
	2	11	1.867	1.548	16	1.349	0.791	20	1.322	0.754	47	1.459	1.006	1.1953	0.3123
	3	10	2.110	1.282	16	1.389	0.795	15	1.336	0.911	41	1.545	1.002	2.2425	0.1201
	4	9	1.064	0.503	12	1.011	0.569	8	0.996	0.315	29	1.023	0.474	0.0477	0.9535
	5	5	1.182	0.730	10	0.960	0.573	7	1.217	0.481	22	1.092	0.569	0.4747	0.6293
C	0	29	2.201	0.602	28	2.367	0.744	29	2.194	0.633	86	2.253	0.659	0.6195	0.5407
	1	26	1.803	0.568	27	1.964	0.651	27	1.941	0.604	80	1.904	0.606	0.5369	0.5867
	2	28	1.456	0.478	25	1.629	0.619	28	1.837	0.535	81	1.641	0.560	3.4412	0.0370*
	3	24	1.153	0.411	21	1.350	0.531	20	1.880	0.523	65	1.440	0.569	12.670	0.0000*
	4	17	1.004	0.385	16	1.192	0.402	7	1.695	0.711	40	1.200	0.511	5.5975	0.0075*
	5	22	1.054	0.396	22	1.032	0.369	3	1.057	0.435	47	1.044	0.377	0.0195	0.9807

TABLE 8. 'COGNITIVE PERFORMANCE DIFFICULTY' MEAN SCORES AND F-TESTS AT WEEK 0,1,2,3,4, 5 FOR THREE DOSAGE GROUPS FOR THE STUDY POPULATION

CLINIC	WEEK	TEST - DRUG			STANDARD-DRUG			PLACEBO			OVERALL			F RATIO	P
		N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.		
A	0	30	2.506	1.433	30	2.008	0.949	30	2.634	1.766	90	2.383	1.433	1.6215	0.2035
	1	30	2.429	1.415	30	1.842	1.040	30	2.263	1.698	90	2.178	1.416	1.3849	0.2558
	2	30	2.391	1.546	30	1.842	1.059	30	2.225	1.588	90	2.153	1.421	1.1840	0.3109
	3	30	2.123	1.319	30	1.854	1.035	30	2.442	1.592	90	2.140	1.342	1.4581	0.2383
	4	24	1.624	0.764	26	1.886	1.153	27	1.934	1.506	77	1.821	1.186	0.4840	0.6183
	5	20	1.592	0.933	21	1.559	0.930	22	2.138	1.440	63	1.772	1.150	1.7622	0.1804
B	0	19	3.062	1.942	19	2.578	1.753	24	2.043	1.015	62	2.519	1.610	2.2311	0.1164
	1	17	2.913	1.729	18	2.055	1.413	24	1.647	1.205	59	2.136	1.505	3.9178	0.0256*
	2	11	2.173	1.638	16	1.386	1.082	20	1.267	0.806	47	1.519	1.170	2.4255	0.1002
	3	10	2.263	1.402	16	1.410	1.074	15	1.369	1.216	41	1.603	1.240	1.9692	0.1536
	4	9	1.394	0.977	12	0.883	0.817	8	0.836	0.478	29	1.029	0.809	1.3763	0.2703
	5	5	1.803	0.923	10	0.883	0.723	7	1.212	0.975	22	1.197	0.890	1.9414	0.1709
C	0	29	2.390	0.998	28	2.170	0.645	29	2.602	0.707	86	2.390	0.810	2.0726	0.1323
	1	26	2.225	0.971	27	2.076	0.632	27	2.431	0.930	80	2.244	0.858	1.1702	0.3157
	2	28	1.623	0.684	25	1.819	0.674	28	2.252	0.906	81	1.901	0.802	4.8988	0.0095*
	3	24	1.458	0.815	21	1.486	0.589	20	2.263	0.719	65	1.715	0.798	8.4201	0.0006*
	4	17	1.447	0.930	16	1.434	0.484	7	1.978	0.516	40	1.535	0.707	1.6289	0.2099
	5	22	1.354	0.784	22	1.179	0.457	3	1.139	0.798	47	1.256	0.642	0.4502	0.6404

TABLE 9. 'DEPRESSION' MEAN SCORES AND F-TESTS FOR WEEK 0,1,2,3,4,5 FOR THE 3 DRUG GROUPS FOR THE STUDY POPULATION

CLINIC	WEEK	TEST - DRUG			STANDARD-DRUG			PLACEBO			OVERALL			F RATIO	P
		N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.		
A	0	30	2.059	1.566	30	1.573	1.299	30	1.931	1.781	90	1.854	1.559	0.7778	0.4626
	1	30	1.982	1.684	30	1.394	1.122	30	1.624	1.331	90	1.667	1.404	1.3459	0.2657
	2	30	1.548	1.343	30	1.497	1.227	30	1.548	1.312	90	1.531	1.281	0.0156	0.9845
	3	30	1.752	1.312	30	1.497	1.338	30	1.399	1.142	90	1.551	1.263	0.6136	0.5438
	4	24	1.139	0.950	26	1.503	1.483	27	1.409	1.329	77	1.356	1.274	0.5369	0.5868
	5	20	1.228	0.913	21	1.413	1.363	22	1.546	1.391	63	1.401	1.236	0.3393	0.7137
B	0	18	3.567	1.556	19	2.760	1.522	24	3.663	1.571	61	3.353	1.578	2.0376	0.1396
	1	16	2.704	1.216	18	2.502	1.370	24	2.992	1.618	58	2.760	1.432	0.6102	0.5469
	2	11	1.476	0.774	16	1.746	1.150	20	1.957	1.241	47	1.772	1.111	0.6622	0.5208
	3	10	1.727	1.262	16	2.033	1.084	15	2.033	1.613	41	1.959	1.315	0.1973	0.8218
	4	9	1.267	0.542	12	1.395	0.854	8	1.554	1.292	29	1.399	0.895	0.2063	0.8149
	5	5	1.267	0.542	10	1.573	0.900	7	1.814	0.853	22	1.580	0.808	0.6481	0.5342
C	0	29	2.324	0.992	28	2.608	1.056	29	3.091	0.805	86	2.675	0.997	4.7704	0.0109*
	1	26	2.299	1.167	27	2.488	0.883	27	2.800	0.927	80	2.532	1.007	1.7119	0.1873
	2	28	1.705	0.819	25	2.095	0.910	28	2.691	1.016	81	2.166	0.998	8.1602	0.0006*
	3	24	1.746	1.149	21	1.741	1.013	20	2.493	0.944	65	1.974	1.081	3.5577	0.0345*
	4	17	1.177	0.934	16	1.602	0.790	7	2.471	1.071	40	1.573	0.994	5.1035	0.0110*
	5	22	1.127	0.772	22	1.441	0.666	3	1.011	0.443	47	1.267	0.715	1.2785	0.2886

TABLE 10. 'FEAR/ANXIETY' MEAN SCORES AND F-TESTS AT WEEK 0,1,2,3,4,5,FOR 3 DRUG GROUPS FOR THE STUDY POPULATION

CLINIC	WEEK	TEST - DRUG			STANDARD-DRUG			PLACEBO			OVERALL			F RATIO	P
		N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.		
A	0	30	2.781	1.594	30	2.513	1.639	30	3.821	1.553	90	2.702	1.584	0.3250	0.7234
	1	30	2.704	1.662	30	2.302	1.523	30	2.661	1.511	90	2.554	1.560	0.5944	0.5542
	2	30	2.129	1.360	30	2.086	1.372	30	2.423	1.606	90	2.212	1.440	0.4664	0.6289
	3	30	1.690	1.160	30	2.263	1.367	30	2.602	1.547	90	2.186	1.402	3.3016	0.0416*
	4	24	1.514	1.086	26	1.735	1.124	27	2.395	1.167	77	1.914	1.342	3.0849	0.0517
	5	20	1.506	1.037	21	1.623	1.185	22	2.957	1.539	63	2.052	1.426	8.5035	0.0006*
B	0	19	3.476	1.508	19	3.254	1.599	24	2.736	1.277	62	3.122	1.464	1.4892	0.2339
	1	17	2.868	1.316	18	2.512	1.439	24	2.081	1.062	59	2.439	1.281	1.9827	0.1472
	2	11	2.016	1.005	16	1.722	1.611	20	1.736	1.009	47	1.797	1.225	0.2224	0.8015
	3	10	2.052	0.769	16	1.770	1.493	15	1.995	1.104	41	1.921	1.188	0.2114	0.8104
	4	9	1.394	0.868	12	1.075	0.813	8	1.003	0.570	29	1.154	0.764	0.6489	0.5309
	5	5	1.535	0.945	10	1.018	0.740	7	1.896	1.094	22	1.415	0.950	1.9844	0.1650
C	0	29	3.712	0.791	28	4.073	0.723	29	4.267	0.955	86	4.017	0.852	3.3398	0.0403*
	1	26	3.441	0.881	27	3.652	0.665	27	3.673	0.962	80	3.591	0.840	0.6059	0.5482
	2	28	2.718	0.794	25	2.869	0.835	28	3.539	1.083	81	3.048	0.975	6.3284	0.0028*
	3	24	2.177	0.896	21	2.417	0.664	20	3.375	0.933	65	2.623	0.975	12.013	0.0000*
	4	17	1.887	0.645	16	2.333	0.734	7	2.718	0.905	40	2.211	0.776	3.6004	0.0373*
	5	22	1.781	0.559	22	2.042	0.625	3	2.033	0.332	47	1.919	0.586	1.1651	0.3213

TABLE 11. A COMPLETE LIST OF THE PATIENT ID,RACE,SEX,AGE,TYPE OF DOSAGE TAKEN AND THE TOTAL MEAN SCORE FOR THE 6 CONSECUTIVE WEEKS

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
04001	3	1	23	0	3.786	3.457	3.326	1.289	1.420	1.026
04002	3	1	26	1	3.917	3.851	2.866	4.180	3.983	4.180
04003	3	1	24	7	3.326	3.720	3.851	4.180	4.443	3.917
04004	3	1	37	1	.960	.829	.894	1.026	.829	1.026
04005	3	1	34	7	4.771	2.866	4.903	3.983	2.997	2.800
04006	3	1	26	0	2.077	3.260	2.603	2.866	2.866	2.669
04007	3	0	17	7	1.683	1.814	1.749	1.683	1.289	1.157
04008	3	0	32	0	1.289	.974	1.026	.829	1.091	1.091
04009	3	1	35	1	3.194	3.063	.960	1.354	.631	.631
04010	3	0	18	0	2.274	1.946	1.551	1.683	1.486	
04011	3	1	17	7	3.523	3.260	3.391	2.340	1.814	1.814
04012	3	1	39	1	2.011	1.946	2.011	2.471	2.274	2.209
04013	3	1	44	7	1.091	1.091	.960	1.026	.829	.829
04014	3	1	25	1	4.903	3.194	2.274	2.471	2.143	3.391
04015	3	1	26	0	3.917	4.049	1.749	2.340	1.683	1.683
04016	3	0	22	7	3.129	2.471	2.209	2.800		
04017	3	0	52	1	2.274	1.880	1.946	3.260	2.471	2.406
04018	3	1	32	0	3.851	2.734	2.406	2.209	1.683	2.209
04019	3	1	30	0	2.077	1.880	1.289	1.617	1.354	2.406
04020	3	1	26	1	4.443	2.406	1.814	1.223	1.091	1.091
04021	3	0	20	7	1.354	1.683	1.486	2.209	1.814	1.551
04022	3	1	34	0	1.880	4.311	1.683	1.749	2.011	
04023	3	0	37	7	3.129	1.157	1.026	1.486	1.486	1.354
04024	3	0	26	1	2.011	1.880	1.157	1.223	1.420	.960
04025	3	1	26	1	5.166	5.166	5.100	5.034		
04026	3	0	23	7	.960	.829	1.157	.763	.829	
04027	3	1	47	0	4.837	3.194	2.209	2.077	2.603	1.946
04028	3	1	30	1	3.720	2.931	2.537	2.669	1.420	1.551
04029	3	1	24	7	3.589	1.749	2.209	2.866	1.354	1.289
04030	3	1	26	0	2.997	2.866	3.457	2.931		
04031	1	0	28	7	1.814	1.749	1.814	1.814	1.683	
04032	3	1	37	0	1.486	1.447	.894	.829	.631	.566
04033	3	0	27	1	1.223	1.223	1.091	1.091	1.289	1.289
04034	3	0	24	7	.829	.697	.697	.763	.829	.697
04035	1	0	23	1	1.091	.960	.697	.763	.631	.631
04036	3	0	24	0	1.551	1.157	1.289	.763	.763	.763
04037	3	1	27	0	2.537	2.340	3.786	2.669		
04038	3	1	31	1	1.223	1.617	1.749	1.551		
04039	3	0	19	7	2.077	1.379	1.157	.960		.763
04040	3	1	58	1	1.749	1.880	2.406	2.997	3.260	3.129
04041	3	1	24	7	2.997	3.720	1.880	1.683		
04042	3	0	41	0	1.354	1.354	1.289	1.223	1.181	1.026

TABLE 11 (cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
04085	3	1	32	0	1.420	1.749	1.551	1.091	.960	.894
04086	3	1	20	1	.894	.960	.829	.631	.631	
04087	3	1	50	7	1.289	1.551	1.486	1.486	1.026	.960
04088	3	0	23	7	1.683	1.814	1.880	1.617	1.420	1.289
04089	3	0	21	0	1.551	.960	1.091	1.223	1.486	
04090	3	0	19	1	2.143	1.420	1.157	1.026	.894	
00601	3	1	23	0	2.997	2.143	1.486	3.391	1.157	
00602	3	1	24	1	3.786	2.997	2.011	1.551		
00603	3	1	33	7	3.063	3.851	1.026	1.157	1.880	1.880
00604	3	1	31	1	2.866	2.866	1.289	1.223	1.157	
00605	3	1	42	7	1.880	1.420	1.814	1.683	1.091	
00606	3	1	27	0	3.129					
00607	3	1	36	7	3.194	1.486	1.223	1.551	.974	.960
00609	3	1	22	1	3.326	2.603	1.814	2.471	2.077	
00610	3	1	26	0	2.669	2.209	1.157	1.551	1.223	1.223
00611	3	1	37	7	4.762	4.246		3.063		
00612	3	1	33	1	2.340	1.486	1.486			
00614	3	1	21	1	3.003	2.529	1.880	1.683		1.683
00615	3	1	28	7	1.354	1.354	1.946	1.946		
00617	3	1	32	1	3.129	.763	.906	.894		
00618	3	1	26	0	3.654	3.523	1.880	1.551	1.406	1.406
00619	3	1	28	0	2.406	2.406				
00620	3	1	25	1	3.260	2.340	1.157	.829		1.223
00621	3	1	23	7	3.851	3.260	1.354	1.354	1.091	
00622	3	1	42	0	1.420	1.420	.697		.566	
00623	3	1	30	7	2.011	1.814	.763		.894	1.157
00624	3	1	29	1	2.209	2.143				
00625	3	1	32	1	3.589	2.077	3.194	1.946		
00626	3	1	30	7	2.669	1.157	1.551	1.026	.631	.566
00628	3	1	24	1	4.049	3.747				
00631	3	1	36	7	3.917	3.917	3.786	3.391		
00633	3	1	37	1	1.617	.697	.500	.500	.500	
00635	3	1	47	1	1.946	1.946	1.683	2.077		2.931
00636	3	1	25	0	2.340	2.011	2.011	1.946	1.946	1.617
00637	3	1	26	0	5.363	5.231	4.640	3.720		
00638	1	1	24	1	1.683	1.157	1.109	.829	.697	
00639	3	1	24	7	3.129	2.077	1.091	1.880	1.157	.894
00640	1	1	24	1	3.063	2.997	2.603			
00641	3	1	24	7	3.720	3.786	3.129	3.544	2.406	2.077
00642	1	1	42	0	4.626	5.034				
00643	3	1	20	1	3.720	3.720	4.049	4.049		
00645	3	1	47	0	3.260	3.523	2.259	2.406	2.077	2.143

TABLE 11 (cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
00645	3	1	47	7	2.143	2.077	1.157	1.683		
00647	3	1	32	0	3.917	3.654	1.814			
00648	3	1	45	1	1.354	1.091	.960	1.244	1.026	1.289
00650	3	1	30	1	3.326	2.800	1.683	1.880	1.486	1.486
00654	3	1	31	0	1.946	1.946		2.866	.894	.631
00655	1	1	32	7	3.194	2.537		1.617	1.486	1.354
00656	3	1	25	1	3.427	2.866				
00657	1	1	22	0	3.589	2.866	1.420	1.091	1.157	
00658	3	1	27	1	1.814	1.354	.829			
00659	3	1	36	7	2.209	1.617	1.157		.697	.697
00660	3	1	27	0	4.574	2.225				
00663	3	1	45	7	3.523		1.157	.631		.829
00666	3	1	58	1	4.288	3.589				
00667	3	1	34	7	1.749	1.551	1.157	.697	.763	.894
00669	1	1	28	1	3.194	2.209	1.683		1.289	1.551
00670	3	1	26	0	3.129	2.471	2.669	2.997		
00671	3	1	29	7	2.997	2.800	3.326	2.603		
00672	3	1	24	1	1.946	1.617	1.354	1.946		
00673	3	1	30	0	3.523	2.209	1.157	1.091	.894	
00674	3	1	32	1	2.471	1.946	1.289	2.274		
00675	3	1	22	7	6.020	4.903				
00676	3	1	30	0	1.683	1.223				
00679	3	1	25	0	5.691	2.997				
00680	3	1	24	1	2.537	1.814	1.157		.763	1.026
00681	3	1	29	7	3.457	.763	.631	.829	.763	
00682	1	1	20	0	1.718					
03801	1	1	27	0	2.340	2.931	1.880		1.420	1.354
03802	1	1	50	1	2.537	2.537	2.669	2.603		
03803	1	1	26	7	2.077	2.011	1.289	1.354	1.223	1.289
03804	1	1	30	1	2.340	1.814	1.486	1.814		1.289
03805	1	1	30	7	2.274	1.814	2.603	2.011	1.683	1.420
03806	3	0	26	0	2.537	2.011	1.486	1.486		1.157
03807	1	0	45	7	2.800	2.669	3.129			
03808	1	1	32	0	1.946		1.880			
03809	3	0	31	1	2.669	1.814	1.880	2.143		
03810	3	1	36	0	2.800	2.603	2.734	2.800		
03811	1	1	34	7	3.326	3.260	2.274	1.551	1.683	1.289
03812	1	0	26	1	1.814	1.223				
03813	1	1	37	7	2.340	1.749	1.551	1.289	1.289	1.026
03814	3	1	49	1	3.260	3.326	2.866			
03815	1	1	41	0	2.800		2.077	1.551	1.223	1.157
03816	3	0	24	7	2.406	2.406	2.471	3.129	2.537	

TABLE 11 (cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
03817	3	1	39	1	3.391	3.457	3.786			
03818	3	0	35	0	1.814	1.683	1.157	1.157	1.091	
03819	3	1	43	0	2.537	1.683	1.354	1.157	1.223	1.091
03820	3	1	37	1	2.866	3.063	2.866			
03821	3	0	22	7	2.866	2.537		1.582	1.223	1.091
03822	3	1	36	0	3.129	2.143	1.551		1.289	1.157
03823	3	1	20	7	2.931	2.931	1.749	3.129	2.669	
03824	3	1	34	1	2.274	1.946	1.420	2.011	1.354	1.157
03825	3	1	54	1	2.603	1.880	1.946	1.880		
03826	1	1	32	7	2.274	2.077		1.551	1.354	1.157
03827	3	1	34	0	4.180	3.917	2.669	3.457	3.654	3.391
03828	3	1	29	1	3.786	3.194	2.997			
03829	3	1	45	7	2.734	2.406	1.814		1.617	1.289
03830	1	1	37	0	2.011	1.946		1.420	1.354	.894
03831	3	1	41	7	3.720	2.406	1.289	1.157		1.091
03832	1	0	19	0	2.471	2.603	2.406	2.011	1.289	1.223
03833	1	1	38	1	2.866	2.669	2.209			1.814
03834	3	1	36	7	3.523	2.997	1.749		1.420	
03835	3	1	27	1	2.603	3.063	2.603	2.603		
03836	3	1	36	0	2.931	2.471	1.880	1.354	1.354	
03837	1	0	28	0	2.274	2.406	1.749	1.289	1.091	
03838	3	1	54	1	2.997	2.734	2.734	2.866		
03839	3	1	25	7	2.931	2.340	1.880	1.289		1.223
03840	3	1	36	1	2.800	2.340	2.603	2.011		
03841	3	1	33	7	2.274	2.209	1.683	1.354	1.289	1.223
03842	3	1	29	0	2.734	2.931	1.880	1.289	1.157	
03843	3	0	21	1	2.340	2.209	2.274			
03844	3	1	24	7	2.406	2.143	1.486		1.223	1.223
03845	1	0	44	0	2.143	1.749	1.223	1.026	.894	.960
03846	3	1	34	7	2.866	2.471	1.749	1.354	1.354	
03847	3	0	35	0	2.669	1.749	1.486	1.354		1.157
03848	3	0	34	1	2.866	2.274	1.946	2.011		
03849	3	0	31	0	2.537	2.734	1.551	1.157		1.091
03850	1	1	35	1	2.537	2.406	1.946	1.946		
03851	1	0	25	7	2.537	2.191				
03852	3	1	20	7	2.537	2.340	1.814	1.551		1.486
03853	1	0	45	1	2.471	1.749	1.946	2.209	1.946	
03854	1	1	34	0	2.800	2.537	2.143	1.683		1.420
03855	1	1	62	7	2.406	2.406	1.880	1.420		1.289
03856	1	1	32	1	2.209	2.209	2.077	2.274	2.537	
03857	3	1	45	0	2.800	2.406	1.420	1.354	1.223	1.354
03858	1	1	35	1	3.129	3.326	3.194	3.194		

TABLE 11 (cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
03859	1	0	38	7	2.537	2.143	2.077	2.340		2.209
03860	3	0	44	0	2.274	1.880	1.486	1.157	1.223	
03861	3	1	61	1	3.063	2.406	2.537	2.931	2.603	
03862	1	1	34	0	2.537	2.406	1.551	1.486		1.617
03863	3	1	37	7	2.011	1.946	1.617	1.617		1.749
03864	1	0	22	7	2.734	2.209	2.011		1.617	1.814
03865	1	1	28	0	2.340	1.946	1.551	1.157		1.223
03866	3	0	26	1	2.274	1.880	2.011	2.077		
03867	3	1	57	7	2.800	2.406	2.340	1.814	1.354	1.289
03868	1	1	25	0	2.209	1.946	1.880	1.223		1.289
03869	3	0	25	1	3.260		2.603	2.734		
03870	3	1	32	0	2.406	1.880	1.683		1.223	1.091
03871	1	1	25	7	2.471	2.471	1.749	1.486		1.157
03872	3	1	28	1	2.866	2.603	2.406	2.077		
03873	1	1	26	0	2.669	2.340	1.683	1.486		1.551
03874	3	1	27	1	2.603	2.340	2.143	2.340		
03875	3	0	23	7	2.537	1.946	1.749	1.420		1.354
03876	3	1	24	0	3.063	2.406	1.749		1.289	1.354
03877	1	1	31	7	2.011	2.406	2.124	1.551		1.354
03878	3	1	35	1	3.589	3.326	3.391			
03879	3	1	50	0	2.245	2.143	1.683	1.551		1.354
03880	3	1	38	1	2.537	2.143	2.209		2.011	
03881	3	0	36	7	2.800	2.537	1.617		1.814	1.354
03882	3	1	27	0	2.866		2.471	2.274	1.551	1.486
03883	3	1	27	1	2.537		2.143	1.814	1.814	
03884	3	1	55	7	2.537		2.537	1.486		1.354
03885	3	0	43	0	2.471	2.340	2.011	1.617		1.379
03886	3	0	21	1	3.457	3.129	2.866	2.471	2.077	

TABLE 12.Sample Correlation of vector of mean observations made at WEEK 0,1,2,3,4,5

For Clinic A

1.00000	.85927	.79218	.78263	.69935	.67354
.85927	1.00000	.81521	.80163	.72125	.68600
.79263	.81521	1.00000	.90177	.84079	.80630
.78263	.80163	.90177	1.00000	.91994	.89921
.69935	.72105	.84079	.91994	1.00000	.96527
.67354	.68600	.80630	.89921	.96527	1.00000

For Clinic B

1.0000	.64784	.49442	.41558	.47097	.43765
.64784	1.00000	.69270	.64635	.75169	.73210
.49442	.69270	1.00000	.84228	.77341	.67534
.41558	.64635	.84228	1.00000	.84395	.72938
.47097	.75210	.77341	.84395	1.00000	.96547
.43765	.73210	.67534	.72938	.96547	1.00000

For Clinic C

1.000	.72249	.44719	.40063	.39727	.38580
.72249	1.00000	.65121	.55652	.54160	.53161
.44719	.65121	1.00000	.75892	.66199	.63811
.40063	.55652	.75892	1.00000	.87290	.85416
.39727	.54160	.66199	.87290	1.00000	.95770
.38580	.53161	.63811	.85416	.95770	1.00000

TABLE 13A. ANALYSIS OF VARIANCE FOR COMMON SLOPE FOR 3 TREATMENT GROUPS OBTAINED BY REGRESSING WEEK 5 TOTAL MEAN SCORES ON WEEK 4 TOTAL MEAN SCORES.

FOR CLINIC A

SOURCE	DF	S.S.	M.S.	F	F ON PE-MS
Due to pooled regression	1	36.94	36.94	448.19	410.44
Difference between slopes	2	0.13	0.06	0.78	0.70
Due to separate regression	3	37.07	12.36	149.92	134.15
Residual	56	4.62	0.08		
Lack of fit	38	2.96	0.08		0.84
Pure Error	18	1.66	0.09		
TOTAL	59				

FOR CLINIC B

SOURCE	DF	S.S	M.S.	F	F ON PE-MS
Due to pooled regression	1	3.16	3.16	117.64	
Difference between slopes	2	0.05	0.02	0.93	
Due to pooled regression	3	3.21	1.07	39.83	
Residual	12	0.32	0.03		
Lack of fit	12	0.32	0.03		
Pure error	0				
Total	15				

FOR CLINIC C

SOURCE	DF	S.S.	M.S.	F	F ON PE-MS
Due to pooled regression	1	4.55	4.55	159.33	148.61
Difference between slopes	1	0.07	0.07	2.59	2.42
Due to separate regression	2	4.62	2.31	80.96	75.51
Residual	20	0.57	0.03		
Lack of fit	8	0.20	0.03		0.83
Pure error	12	0.37	0.03		
Total	22				

TABLE 13B. UNIVARIATE F-TESTS FOR COMMON SLOPE FOR 3 DRUG GROUPS

Difference between Slopes by regressing	CLINIC A F-STATISTIC	CLINIC B F-STATISTIC	CLINIC C F-STATISTIC
WEEK 1 on WEEK 0	F = 0.45 D.F= 2,84 p = .645	F = 0.45 D.F= 2,53 p = .646	F = 3.50 D.F= 2,74 p = .0342
WEEK 2 on WEEK 1	F = 0.86 D.F= 2,84 p = .570	F = 0.68 D.F= 2,40 p = .517	F = 5.12 D.F= 2,69 p = .009
WEEK 3 on WEEK 2	F = 1.70 D.F= 2,84 p = .187	F = 0.31 D.F= 2,32 p = .740	F = 1.99 D.F= 2,56 p = .144
WEEK 4 on WEEK 3	F = 0.27 D.F= 2,71 p = .768	F = 4.04 D.F= 2,18 p = .035	F = 0.85 D.F= 2,24 p = .557
WEEK 5 on WEEK 4	F = 0.78 D.F= 2,56 p = .533	F = 0.93 D.F= 2,12 p = .576	F = 2.59 D.F= 2,20 p = .190

TABLE 14 : USING REDUCTION SUM OF SQUARES METHOD TO FIND THE BEST REGRESSION MODEL FOR ESTIMATION

FOR CLINIC A

WK4,D1,D2	S.S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	41.401	3	13.800	168.71	.000	.8972
Residual	4.744	58	.082			

WK4,WK3,D1,D2	S.S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	41.580	4	10.395	129.805	.000	.9011
Residual	4.565	57	0.080			

WK4,WK3,WK2, D1,D2	S.S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	41.649	5	8.330	103.748	.000	.9026
Residual	4.496	56	.080			

WK4,WK3,WK2, WK1,D1,D2	S. S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	41.680	6	6.947	85.573	.000	.9032
Residual	4.465	55	.081			

WK4,WK3,WK2, WK1,WK0,D1,D2	S. S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	41.726	7	5.961	72.835	.000	
Residual	4.419	54	0.082			

MODEL	S. S.	DF	M. S.	F-RATIO	P
WK4,D1,D2	41.401	3	13.80	168.297	.000
Adding WK3	0.179	1	0.179	2.183	n.s
Adding WK2	0.069	1	0.069	0.841	n.s.
Adding WK1	0.031	1	0.031	0.378	n.s.
Adding WK0	0.046	1	0.046	0.568	n.s.
Residuals	4.419	54	0.082		

TABLE 14 (Continued)

FOR CLINIC B

WK4,D1,D2	S. S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	2.523	3	0.841	32.592	.00008	.9244
Residual	0.206	8	0.026			

WK4,WK3,D1,D2	S. S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	2.570	4	.643	28.318	.00020	.9418
Residual	0.159	7	.023			

WK4,WK3,WK2, D1,D2	S. S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	2.571	5	0.514	19.471	.00120	.9419
Residual	0.158	6	0.026			

WK4,WK3,WK2, WK1,D1,D2	S. S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	2.589	6	0.432	15.453	.00433	.9488
Residual	0.140	5	0.028			

WK4,WK3,WK2, WK1,WK0,D1,D2	S. S.	DF	M. S.	F-RATIO	P	R-SQUARE
Regression	2.624	7	0.375	14.219	.01101	.9614
Residual	0.105	4	0.026			

MODEL	S. S.	DF	M. S.	F-RATIO	P
WK4,D1,D2	2.523	3	0.841	32.346	.00473
Adding WK3	0.047	1	0.047	1.808	.24962
Adding WK2	0.001	1	0.001	0.0385	.84709
Adding WK1	0.018	1	0.018	0.6923	.54434
Adding WK0	0.035	1	0.035	1.346	.31107
Residuals	0.105	4	0.026		

TABLE 14 (Continued)

FOR CLINIC C

WK4,D1,D2	S.S.	DF	M. S.	F-RATIO	P	R-SQUARES
Regression	4.4	3	1.467	76.346	.000	.9663
Residual	0.154	8	0.019			

WK4,WK3,D1,D2	S.S.	DF	M. S.	F-RATIO	P	R-SQUARES
Regression	4.404	4	1.101	51.686	.00003	.9673
Residual	0.149	7	0.021			

WK4,WK3,WK2 D1,D2	S.S.	DF	M. S.	F-RATIO	P	R-SQUARES
Regression	4.502	5	0.900	104.12	.00001	.9886
Residual	0.052	6	0.009			

WK4,WK3,WK2, WK1,D1,D2	S.S.	D.F.	M. S.	F-RATIO	P	R-SQUARES
Regression	4.511	6	0.752	87.534	.00007	.9906
Residual	0.043	5	0.009			

WK4,WK3,WK2, WK1,WK0,D1,D2	S.S.	DF	M. S.	F-RATIO	P	R-SQUARES
Regression	4.511	7	0.644	60.884	.00067	
Residuals	0.042	4	0.011			

MODEL	S.S.	DF	M. S.	F-RATIO	P
WK4,D1,D2	4.4	3	1.467	133.364	.001
Adding WK3	0.004	1	.004	0.3636	.5819
Adding WK2	0.098	1	.098	8.909	.04087
Adding WK1	0.009	1	.009	0.818	.58026
Adding WK0	0.000	1	.000	0.000	
Residuals	0.042	4	.011		

TABLE 15. LIST OF PATIENT ID, RACE, SEX, TYPE OF DOSAGE TAKEN AND THE TOTAL MEAN SCORE OF THE 6-WEEK ASSESSMENT PERIODS WITH ESTIMATES SUBSTITUTED FOR MISSING VALUES

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
04001	3	1	23	0	3.786	3.457	3.326	1.289	1.420	1.026
04002	3	1	26	1	3.917	3.851	2.866	4.180	3.983	4.180
04003	3	1	24	7	3.326	3.720	3.851	4.180	4.443	3.917
04004	3	1	37	1	.960	.829	.894	1.026	.829	1.026
04005	3	1	34	7	4.771	2.866	4.903	3.983	2.997	2.800
04006	3	1	26	0	2.077	3.260	2.603	2.866	2.866	2.669
04007	3	0	17	7	1.683	1.814	1.749	1.683	1.289	1.157
04008	3	0	32	0	1.289	.974	1.026	.829	1.091	1.091
04009	3	1	35	1	3.194	3.063	.960	1.354	.631	.631
04010	3	0	18	0	2.274	1.946	1.551	1.683	1.486	1.455
04011	3	1	17	7	3.523	3.260	3.391	2.340	1.814	1.814
04012	3	1	39	1	2.011	1.946	2.011	2.471	2.274	2.209
04013	3	1	44	7	1.091	1.091	.960	1.026	.829	.829
04014	3	1	25	1	4.903	3.194	2.274	2.471	2.143	3.391
04015	3	1	26	0	3.917	4.049	1.749	2.340	1.683	1.683
04016	3	0	22	7	3.129	2.471	2.209	2.800	2.385	2.280
04017	3	0	52	1	2.274	1.880	1.946	3.260	2.471	2.406
04018	3	1	32	0	3.851	2.734	2.406	2.209	1.683	2.209
04019	3	1	30	0	2.077	1.880	1.289	1.617	1.354	2.406
04020	3	1	26	1	4.443	2.406	1.814	1.223	1.091	1.091
04021	3	0	20	7	1.354	1.683	1.486	2.209	1.814	1.551
04022	3	1	34	0	1.880	4.311	1.683	1.749	2.011	1.945
04023	3	0	37	7	3.129	1.157	1.026	1.486	1.486	1.354
04024	3	0	26	1	2.011	1.880	1.157	1.223	1.420	.960
04025	3	1	26	1	5.166	5.166	5.100	5.034	4.442	4.395
04026	3	0	23	7	.960	.829	1.157	.763	.829	0.802
04027	3	1	47	0	4.837	3.194	2.209	2.077	2.603	1.946
04028	3	1	30	1	3.720	2.931	2.537	2.669	1.420	1.551
04029	3	1	24	7	3.589	1.749	2.209	2.866	1.354	1.289
04030	3	1	26	0	2.997	2.866	3.457	2.931	2.625	2.544
04031	1	0	28	7	1.814	1.749	1.814	1.814	1.683	1.60
04032	3	1	37	0	1.486	1.447	.894	.829	.631	.566
04033	3	0	27	1	1.223	1.223	1.091	1.091	1.289	1.289
04034	3	0	24	7	.829	.697	.697	.763	.829	.697
04035	1	0	23	1	1.091	.960	.697	.763	.631	.631
04036	3	0	24	0	1.551	1.157	1.289	.763	.763	.763
04037	3	1	27	0	2.537	2.340	3.786	2.669	2.391	2.326

TABLE 15 (Cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
04038	3	1	31	1	1.223	1.617	1.749	1.551	1.433	1.500
04039	3	0	19	7	2.077	1.379	1.157	.960	.803	.763
04040	3	1	58	1	1.749	1.880	2.406	2.997	3.260	3.129
04041	3	1	24	7	2.997	3.720	1.880	1.683	1.420	1.352
04042	3	0	41	0	1.354	1.354	1.289	1.223	1.181	1.026
04043	3	1	23	1	4.443	3.654	3.654	3.654	3.457	3.391
04044	3	1	24	7	.829	.697	.829	.829	.566	.763
04045	3	1	24	0	3.654	2.800	2.406	2.143	1.937	1.889
04046	3	1	23	7	1.354	1.157	1.157	1.157	1.091	1.026
04047	3	1	22	0	2.011	1.026	1.289	1.157	1.091	1.289
04048	3	1	37	1	.829	.829	.894	1.157	.960	1.075
04049	3	1	18	0	1.223	.763	.763	.697	.763	.763
04050	3	0	23	1	.960	.829	.697	.894	.894	1.013
04051	3	1	20	7	1.091	1.026	1.091	.631	.631	.631
04052	3	0	30	7	1.551	1.617	1.617	1.551	1.026	.894
04053	3	1	35	1	4.443	4.180	3.983	3.589	3.654	3.391
04054	3	0	18	0	1.683	1.486	1.551	1.420	1.223	1.157
04055	3	1	25	7	2.340	1.354	2.274	1.814	1.749	1.617
04056	3	1	50	1	3.194	3.194	2.997	2.734	2.603	2.603
04057	3	1	50	0	2.274	1.880	2.077	2.077	2.209	2.340
04058	3	0	25	1	2.143	1.420	1.617	2.406	1.617	1.814
04059	3	0	37	7	3.129	2.997	2.274	1.617	1.486	1.880
04060	3	1	33	0	4.377	2.209	2.143	1.880	1.354	1.026
04061	3	1	36	1	4.114	3.326	4.114	4.246	3.762	3.740
04062	3	1	20	0	3.523	3.391	2.603	2.209	2.002	1.944
04063	3	0	34	7	1.551	1.880	1.683	1.223	1.026	.960
04064	3	1	29	7	2.734	1.486	1.157	1.683	3.457	3.257
04065	3	1	40	0	4.311	4.903	5.166	5.429	4.776	4.620
04066	3	0	42	1	1.354	1.420	1.551	1.420	1.420	1.486
04067	3	1	50	7	1.354	1.223	1.091	1.289	1.354	1.420
04068	3	0	25	0	1.814	1.486	1.420	1.223	1.091	.894
04069	3	1	41	1	1.223	1.223	1.091	1.157	1.354	1.551
04070	3	0	25	0	2.340	1.814	1.617	1.486	1.420	1.420
04071	3	1	40	7	2.143	2.143	1.354	2.077	1.617	1.538
04072	3	1	52	1	1.354	1.091	1.223	1.354	1.486	1.420
04073	3	0	36	0	1.157	1.289	.894	.697	.631	.566
04074	3	1	42	1	1.157	1.091	1.157	1.091	1.091	1.091

TABLE 15 (Cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
04075	3	1	35	7	1.486	.697	2.866	2.143	1.818	1.734
04076	3	1	34	0	2.209	2.274	2.896	2.669	2.391	2.326
04077	3	1	44	7	.829	.763	.697	.763	.894	.894
04078	3	0	28	1	1.551	1.486	1.091	1.289	1.223	1.091
04079	3	1	26	0	2.143	2.011	2.077	1.814	1.223	1.026
04080	3	1	36	1	1.617	1.814	1.749	1.814	1.749	1.946
04081	3	0	19	7	.829	.829	.829	.697	.763	0.741
04082	3	0	20	0	.894	1.026	.894	.894	.763	0.780
04083	3	0	42	1	1.026	1.091	1.223	1.289	1.354	1.443
04084	3	1	32	7	2.274	2.274	2.274	2.274	2.077	1.968
04085	3	1	32	0	1.420	1.749	1.551	1.091	.960	.894
04086	3	1	20	1	.894	.960	.829	.631	.631	.767
04087	3	1	50	7	1.289	1.551	1.486	1.486	1.026	.960
04088	3	0	23	7	1.683	1.814	1.880	1.617	1.420	1.289
04089	3	0	21	0	1.551	.960	1.091	1.223	1.486	1.455
04090	3	0	19	1	2.143	1.420	1.157	1.026	.894	1.013
00601	3	1	23	0	2.997	2.143	1.486	3.391	1.157	1.170
00602	3	1	24	1	3.786	2.997	2.011	1.551	1.250	1.383
00603	3	1	33	7	3.063	3.851	1.026	1.157	1.880	1.880
00604	3	1	31	1	2.866	2.866	1.289	1.223	1.157	1.304
00605	3	1	42	7	1.880	1.420	1.814	1.683	1.091	1.034
00606	3	1	27	0	3.129					
00607	3	1	36	7	3.194	1.486	1.223	1.551	.974	.960
00609	3	1	22	1	3.326	2.603	1.814	2.471	2.077	2.080
00610	3	1	26	0	2.669	2.209	1.157	1.551	1.223	1.223
00611	3	1	37	7	4.762	4.246	2.581	3.063	2.111	1.816
00612	3	1	33	1	2.340	1.486	1.486	1.728	1.355	1.463
00614	3	1	21	1	3.003	2.529	1.880	1.683	1.538	1.683
00616	3	1	28	7	1.354	1.354	1.946	1.946	1.475	1.341
00617	3	1	32	1	3.129	.763	.906	.894	0.896	1.104
00618	3	1	26	0	3.654	3.523	1.880	1.551	1.406	1.406
00619	3	1	28	0	2.406	2.406				
00620	3	1	25	1	3.260	2.340	1.157	.829	0.968	1.223
00621	3	1	23	7	3.851	3.260	1.354	1.354	1.091	1.034
00622	3	1	42	0	1.420	1.420	.697	0.498	.566	0.671
00623	3	1	30	7	2.011	1.814	.763	0.893	.894	1.157
00624	3	1	29	1	2.209	2.143				

TABLE 15 (Cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
00625	3	1	32	1	3.589	2.077	3.194	1.946	1.474	1.551
00626	3	1	30	7	2.669	1.157	1.551	1.026	.631	.566
00628	3	1	24	1	4.049	3.747				
00631	3	1	36	7	3.917	3.917	3.786	3.391	2.297	1.955
00633	3	1	37	1	1.617	.697	.500	.500	.500	0.749
00635	3	1	47	1	1.946	1.946	1.683	2.077	2.706	2.931
00636	3	1	25	0	2.340	2.011	2.011	1.946	1.946	1.617
00637	3	1	26	0	5.363	5.231	4.640	3.720	2.720	2.386
00638	1	1	24	1	1.683	1.157	1.109	.829	.697	0.915
00639	3	1	24	7	3.129	2.077	1.091	1.880	1.157	.894
00640	1	1	24	1	3.063	2.997	2.603	2.858	2.025	1.976
00641	3	1	24	7	3.720	3.786	3.129	3.544	2.406	2.077
00642	1	1	42	0	4.626	5.034				
00643	3	1	20	1	3.720	3.720	4.049	4.049	2.671	2.445
00645	3	1	47	0	3.260	3.523	2.259	2.406	2.077	2.143
00646	3	1	47	7	2.143	2.077	1.157	1.683	1.326	1.229
00647	3	1	32	0	3.917	3.654	1.814	1.850	1.654	1.590
00648	3	1	45	1	1.354	1.091	.960	1.244	1.026	1.289
00650	3	1	30	1	3.326	2.800	1.683	1.880	1.486	1.486
00654	3	1	31	0	1.946	1.946	2.477	2.866	.894	.631
00655	1	1	32	7	3.194	2.537	1.519	1.617	1.486	1.354
00656	3	1	25	1	3.427	2.866				
00657	1	1	22	0	3.589	2.866	1.420	1.091	1.157	1.170
00658	3	1	27	1	1.814	1.354	.829	1.063	.960	1.160
00659	3	1	36	7	2.209	1.617	1.157	1.062	.697	.697
00660	3	1	27	0	4.574	2.225				
00663	3	1	45	7	3.523	1.244	1.157	.631	.769	.829
00666	3	1	58	1	4.288	3.589				
00667	3	1	34	7	1.749	1.551	1.157	.697	.763	.894
00669	1	1	28	1	3.194	2.209	1.683	1.830	1.289	1.551
00670	3	1	26	0	3.129	2.471	2.669	2.997	2.308	2.079
00671	3	1	29	7	2.997	2.800	3.326	2.603	1.849	1.620
00672	3	1	24	1	1.946	1.617	1.354	1.946	1.474	1.551
00673	3	1	30	0	3.523	2.209	1.157	1.091	.894	.948
00674	3	1	32	1	2.471	1.946	1.289	2.274	1.661	1.690
00675	3	1	22	7	6.020	4.903				
00676	3	1	30	0	1.683	1.223				

TABLE 15 (Cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
00679	3	1	25	0	5.691	2.997				
00680	3	1	24	1	2.537	1.814	1.157	1.186	.763	1.026
00681	3	1	29	7	3.457	.763	.631	.829	.763	0.757
00682	1	1	20	0	1.718					
03801	1	1	27	0	2.340	2.931	1.880	1.691	1.420	1.354
03802	1	1	50	1	2.537	2.537	2.669	2.603	1.957	1.686
03803	1	1	26	7	2.077	2.011	1.289	1.354	1.223	1.289
03804	1	1	30	1	2.340	1.814	1.486	1.814	1.447	1.289
03805	1	1	30	7	2.274	1.814	2.603	2.011	1.683	1.420
03806	3	0	26	0	2.537	2.011	1.486	1.486	1.180	1.157
03807	1	0	45	7	2.800	2.669	3.129	2.740	2.449	2.084
03808	1	1	32	0	1.946	1.643	1.880	1.867	1.715	1.649
03809	3	0	31	1	2.669	1.814	1.880	2.143	1.489	1.274
03810	3	1	36	0	2.800	2.603	2.734	2.800	2.673	2.497
03811	1	1	34	7	3.326	3.260	2.274	1.551	1.683	1.289
03812	1	0	26	1	1.814	1.223				
03813	1	1	37	7	2.340	1.749	1.551	1.289	1.289	1.026
03814	3	1	49	1	3.260	3.326	2.866	2.866	3.462	2.404
03815	1	1	41	0	2.800	2.492	2.077	1.551	1.223	1.157
03816	3	0	24	7	2.406	2.406	2.471	3.129	2.537	2.227
03817	3	1	39	1	3.391	3.457	3.786	4.386	3.211	2.830
03818	3	0	35	0	1.814	1.683	1.157	1.157	1.091	1.112
03819	3	1	43	0	2.537	1.683	1.354	1.157	1.223	1.091
03820	3	1	37	1	2.866	3.063	2.866	3.462	2.404	2.179
03821	3	0	22	7	2.866	2.537	1.981	1.582	1.223	1.091
03822	3	1	36	0	3.129	2.143	1.551	1.455	1.289	1.157
03823	3	1	20	7	2.931	2.931	1.749	3.129	2.669	2.342
03824	3	1	34	1	2.274	1.946	1.420	2.011	1.354	1.157
03825	3	1	54	1	2.603	1.880	1.946	1.880	1.222	1.039
03826	1	1	32	7	2.274	2.077	1.943	1.551	1.354	1.157
03827	3	1	34	0	4.180	3.917	2.669	3.457	3.654	3.391
03828	3	1	29	1	3.786	3.194	2.997	3.594	2.519	2.272
03829	3	1	45	7	2.734	2.406	1.814	1.611	1.617	1.289
03830	1	1	37	0	2.011	1.946	1.534	1.420	1.354	.894
03831	3	1	41	7	3.720	2.406	1.289	1.157	1.195	1.091
03832	1	0	19	0	2.471	2.603	2.406	2.011	1.289	1.223
03833	1	1	38	1	2.866	2.669	2.209	2.867	2.147	1.814

TABLE 15 (Cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
03834	3	1	36	7	3.523	2.997	1.749	1.462	1.420	1.255
03835	3	1	27	1	2.603	3.063	2.603	2.603	1.957	1.686
03836	3	1	36	0	2.931	2.471	1.880	1.354	1.354	1.341
03837	1	0	28	0	2.274	2.406	1.749	1.289	1.091	1.112
03838	3	1	54	1	2.997	2.734	2.734	2.866	2.224	1.920
03839	3	1	25	7	2.931	2.340	1.880	1.289	1.343	1.223
03840	3	1	36	1	2.800	2.340	2.603	2.011	1.355	1.156
03841	3	1	33	7	2.274	2.209	1.683	1.354	1.289	1.223
03842	3	1	29	0	2.734	2.931	1.880	1.289	1.157	1.170
03843	3	0	21	1	2.340	2.209	2.274	2.868	1.885	1.761
03844	3	1	24	7	2.406	2.143	1.486	1.218	1.223	1.223
03845	1	0	44	0	2.143	1.749	1.223	1.026	.894	.960
03846	3	1	34	7	2.866	2.471	1.749	1.354	1.354	1.198
03847	3	0	35	0	2.669	1.749	1.486	1.354	1.159	1.157
03848	3	0	34	1	2.866	2.274	1.946	2.011	1.355	1.156
03849	3	0	31	0	2.537	2.734	1.551	1.157	1.063	1.091
03850	1	1	35	1	2.537	2.406	1.946	1.946	1.289	1.098
03851	1	0	25	7	2.537	2.191				
03852	3	1	20	7	2.537	2.340	1.814	1.551	1.636	1.486
03853	1	0	45	1	2.471	1.749	1.946	2.209	1.946	1.672
03854	1	1	34	0	2.800	2.537	2.143	1.683	1.463	1.420
03855	1	1	62	7	2.406	2.406	1.880	1.420	1.427	1.289
03856	1	1	32	1	2.209	2.209	2.077	2.274	2.537	2.186
03857	3	1	45	0	2.800	2.406	1.420	1.354	1.223	1.354
03858	1	1	35	1	3.129	3.326	3.194	3.194	2.557	2.215
03859	1	0	38	7	2.537	2.143	2.077	2.340	2.453	2.209
03860	3	0	44	0	2.274	1.880	1.486	1.157	1.223	1.227
03861	3	1	61	1	3.063	2.406	2.537	2.931	2.603	2.244
03862	1	1	34	0	2.537	2.406	1.551	1.486	1.617	1.617
03863	3	1	37	7	2.011	1.946	1.617	1.617	1.896	1.749
03864	1	0	22	7	2.734	2.209	2.011	1.705	1.617	1.814
03865	1	1	28	0	2.340	1.946	1.551	1.157	1.189	1.223
03866	3	0	26	1	2.274	1.880	2.011	2.077	1.422	1.215
03867	3	1	57	7	2.800	2.406	2.340	1.814	1.354	1.289
03868	1	1	25	0	2.209	1.946	1.880	1.223	1.262	1.289
03869	3	0	25	1	3.260	3.097	2.603	2.734	2.090	1.803
03870	3	1	32	0	2.406	1.880	1.683	1.478	1.223	1.091

TABLE 15 (Cont'd)

PID	RACE	SEX	AGE	DRUG	WK0	WK1	WK2	WK3	WK4	WK5
03871	1	1	25	7	2.471	2.471	1.749	1.486	1.312	1.157
03872	3	1	28	1	2.866	2.603	2.406	2.077	1.422	1.215
03873	1	1	26	0	2.669	2.340	1.683	1.486	1.553	1.551
03874	3	1	27	1	2.603	2.340	2.143	2.340	1.689	1.450
03875	3	0	23	7	2.537	1.946	1.749	1.420	1.489	1.354
03876	3	1	24	0	3.063	2.406	1.749	1.549	1.289	1.354
03877	1	1	31	7	2.011	2.406	2.124	1.551	1.510	1.354
03878	3	1	35	1	3.589	3.326	3.391	3.990	2.865	2.550
03879	3	1	50	0	2.245	2.143	1.683	1.551	1.378	1.354
03880	3	1	38	1	2.537	2.143	2.209	2.783	2.011	1.729
03881	3	0	36	7	2.800	2.537	1.617	1.635	1.814	1.354
03882	3	1	27	0	2.866	2.626	2.471	2.274	1.551	1.486
03883	3	1	27	1	2.537	2.325	2.143	1.814	1.814	1.557
03884	3	1	55	7	2.537	2.366	2.537	1.486	1.499	1.354
03885	3	0	43	0	2.471	2.340	2.011	1.617	1.413	1.379
03886	3	0	21	1	3.457	3.129	2.866	2.471	2.077	1.786

TABLE 16 A (Continued)

FOR CLINIC B

VARIANCE-COVARIANCE MATRIX FOR TEST-DRUG

1.03980	.9758	.6582	.3954	.4191	.3873
.9758	1.064	.8006	.4479	.4873	.444
.6582	.8006	1.0429	.795	.5405	.417
.3954	.4479	.795	1.0051	.4108	.3109
.4191	.4873	.5405	.4108	.4204	.3576
.3873	.444	.417	.3109	.3576	.3207

VARIANCE-COVARIANCE MATRIX FOR PLACEBO

.5756	.465	.4202	.2869	.1576	.1082
.465	.6699	.5098	.4756	.3094	.2376
.4202	.5098	.7071	.5826	.3582	.2745
.2869	.4756	.5826	.6753	.4368	.3436
.1576	.3094	.3582	.4368	.3608	.3074
.1082	.2376	.2745	.3436	.3074	.2707

VARIANCE-COVARIANCE MATRIX FOR STANDARD DRUG

.8039	.62	.3045	.3753	.2436	.1677
.62	1.2183	.6194	.7099	.5488	.4434
.3045	.6194	.8419	.7424	.4193	.3048
.3753	.7099	.7424	.8171	.4632	.334
.2436	.5488	.4193	.4632	.3308	.2606
.1677	.4434	.3048	.334	.2606	.2164

COMMON VARIANCE-COVARIANCE MATRIX FOR 3 DRUG GROUPS

.766819	.640613	.434053	.344268	.249909	.195043
.640613	.960494	.617502	.553864	.437628	.360345
.434053	.617502	.834449	.690111	.422966	.318811
.344268	.553864	.690111	.803777	.440264	.332474
.249909	.437628	.422966	.440264	.363898	.302221
.195043	.360345	.318811	.332474	.302221	.262762

TABLE 16A (Continued)

FOR CLINIC C

VARIANCE-COVARIANCE MATRIX FOR TEST-DRUG

.2017	.162	.0954	.1471	.1535	.1451
.162	.24	.1339	.1693	.1635	.1547
.0954	.1339	.1593	.1765	.148	.1328
.1471	.1693	.1765	.2684	.2531	.2251
.1535	.1635	.148	.2531	.2812	.252
.1451	.1547	.1328	.2251	.252	.2356

VARIANCE-COVARIANCE MATRIX FOR PLACEBO

.1805	.1875	.186	.1961	.1555	.1297
.1875	.2925	.2666	.2751	.2368	.1952
.186	.2666	.3046	.3142	.2507	.2165
.1961	.2751	.3142	.4435	.3234	.2908
.1555	.2368	.2507	.3234	.3547	.2842
.1297	.1952	.2165	.2908	.2842	.2409

VARIANCE-COVARIANCE MATRIX FOR STANDARD DRUG

.1776	.0991	-.0057	-.005	-.0027	-.0134
.0991	.119	.0298	.0462	.037	.0186
-.0057	.0298	.1739	.124	.0849	.0651
-.005	.0462	.124	.2021	.2114	.1774
-.0027	.037	.0849	.2114	.1854	.1525
-.0134	.0186	.0651	.1774	.1525	.1396

COMMON VARIANCE-COVARIANCE MATRIX FOR 3 DRUG GROUPS

.18690	.15031	.09315	.11461	.10403	.08909
.15031	.21866	.14472	.16505	.14733	.12451
.09315	.14472	.21242	.20555	.16198	.13897
.11461	.16505	.20555	.33116	.26315	.23169
.10403	.14733	.16198	.26315	.27495	.23080
.08909	.12451	.13897	.23169	.23080	.20655

TABLE 16A (Continued)

COMMON VARIANCE-COVARIANCE MATRIX FOR ALL 3 CLINICS

.811541	.611734	.507141	.477444	.39309	.368616
.611734	.735872	.536904	.523707	.447539	.409627
.507141	.536904	.698292	.616658	.487365	.437043
.477444	.523707	.616658	.726342	.558706	.508413
.39309	.447539	.487365	.558706	.548387	.497214
.368616	.409627	.437043	.508413	.497214	.481761

TABLE 16B SAMPLE VARIANCE-COVARIANCE MATRIX OF MEAN OBSERVATIONS MADE AT WEEK 0,1,2,3,4,5 FOR 3 CLINICS AFTER TRANSFORMATION

FOR CLINIC A

VARIANCE - COVARIANCE MATRIX FOR TEST - DRUG

.03848	.03362	.03179	.03157	.02895	.02706
.03362	.04646	.03630	.03759	.03478	.03258
.03179	.03630	.04285	.03929	.03724	.03747
.03157	.03759	.03929	.04558	.04221	.04283
.02895	.03478	.03724	.04221	.04384	.04383
.02706	.03258	.03474	.04283	.04383	.04905

VARIANCE-COVARIANCE MATRIX FOR PLACEBO

.06637	.05728	.05032	.04901	.04179	.04054
.05728	.05471	.04903	.04799	.04294	.04069
.05032	.04903	.05695	.05502	.05444	.05282
.04901	.04799	.05502	.06039	.05713	.05542
.04179	.04294	.05444	.05713	.06191	.05908
.04054	.04069	.05282	.05542	.05908	.05973

VARIANCE-COVARIANCE MATRIX FOR STANDARD DRUG

.04894	.03886	.03640	.03944	.03586	.03482
.03886	.04710	.03442	.03514	.03020	.02916
.03640	.03442	.04571	.04021	.03298	.03169
.03944	.03514	.04021	.04696	.04049	.03810
.03586	.03020	.03298	.04049	.04533	.04258
.03482	.02916	.03169	.03810	.04258	.04157

COMMON VARIANCE-COVARIANCE MATRIX FOR CLINIC A

.05126	.04325	.03950	.04001	.03553	.03414
.04325	.04943	.03991	.04024	.03597	.03414
.03950	.03991	.04850	.04484	.04155	.03975
.04001	.04024	.04484	.05098	.04661	.04545
.03553	.03597	.04155	.04661	.05036	.04849
.03414	.03414	.03975	.04545	.04849	.05012

TABLE 16B (Continued)

FOR CLINIC B

VARIANCE-COVARIANCE MATRIX FOR TEST-DRUG

.02291	.02113	.01848	.01765	.02029	.02014
.02113	.02413	.02294	.01866	.02270	.02177
.01848	.02294	.04457	.04471	.03437	.02594
.01765	.01866	.04471	.06310	.03524	.02570
.02029	.02270	.03437	.03524	.03928	.03526
.02014	.02177	.02594	.02570	.03526	.03460

VARIANCE - COVARIANCE MATRIX FOR PLACEBO

.01818	.01905	.01917	.01362	.01106	.00715
.01905	.04004	.03347	.03122	.02651	.01864
.01917	.03347	.04323	.03825	.03132	.02212
.01362	.03122	.03825	.04579	.03755	.02684
.01106	.02651	.03132	.03755	.03555	.02626
.00715	.01864	.02212	.02684	.02626	.01988

VARIANCE-COVARIANCE MATRIX FOR STANDARD DRUG

.02087	.01517	.00780	.01066	.00982	.00678
.01517	.04652	.02743	.03317	.03355	.02931
.00780	.02743	.04666	.04071	.02899	.02227
.01066	.03317	.04071	.05180	.03665	.02760
.00982	.03355	.02899	.03665	.03525	.02993
.00678	.02931	.02227	.02760	.02993	.02741

COMMON VARIANCE-COVARIANCE MATRIX FOR CLINIC B

.02026	.01813	.01489	.01349	.01278	.01005
.01813	.03866	.02882	.02899	.02817	.02323
.01489	.02882	.04478	.04065	.03119	.02307
.01349	.02899	.04065	.05202	.03668	.02685
.01278	.02817	.03119	.03668	.03632	.02970
.01005	.02323	.02307	.02685	.02970	.02605

TABLE 16B (Continued)

FOR CLINIC C

VARIANCE-COVARIANCE MATRIX FOR TEST-DRUG

.00508	.00440	.00344	.00457	.00451	.00473
.00440	.00772	.00563	.00624	.00556	.00578
.00344	.00563	.00864	.00920	.00768	.00717
.00457	.00624	.00920	.01370	.01227	.01119
.00451	.00556	.00768	.01227	.01384	.01276
.00473	.00578	.00717	.01119	.01276	.01320

VARIANCE-COVARIANCE MATRIX FOR PLACEBO

.00409	.00478	.00501	.00451	.00471	.00458
.00478	.00867	.00818	.00733	.00834	.00813
.00501	.00818	.01000	.00858	.00939	.00939
.00451	.00733	.00858	.01093	.01109	.01144
.00471	.00834	.00939	.01109	.01587	.01543
.00458	.00813	.00939	.01144	.01543	.01543

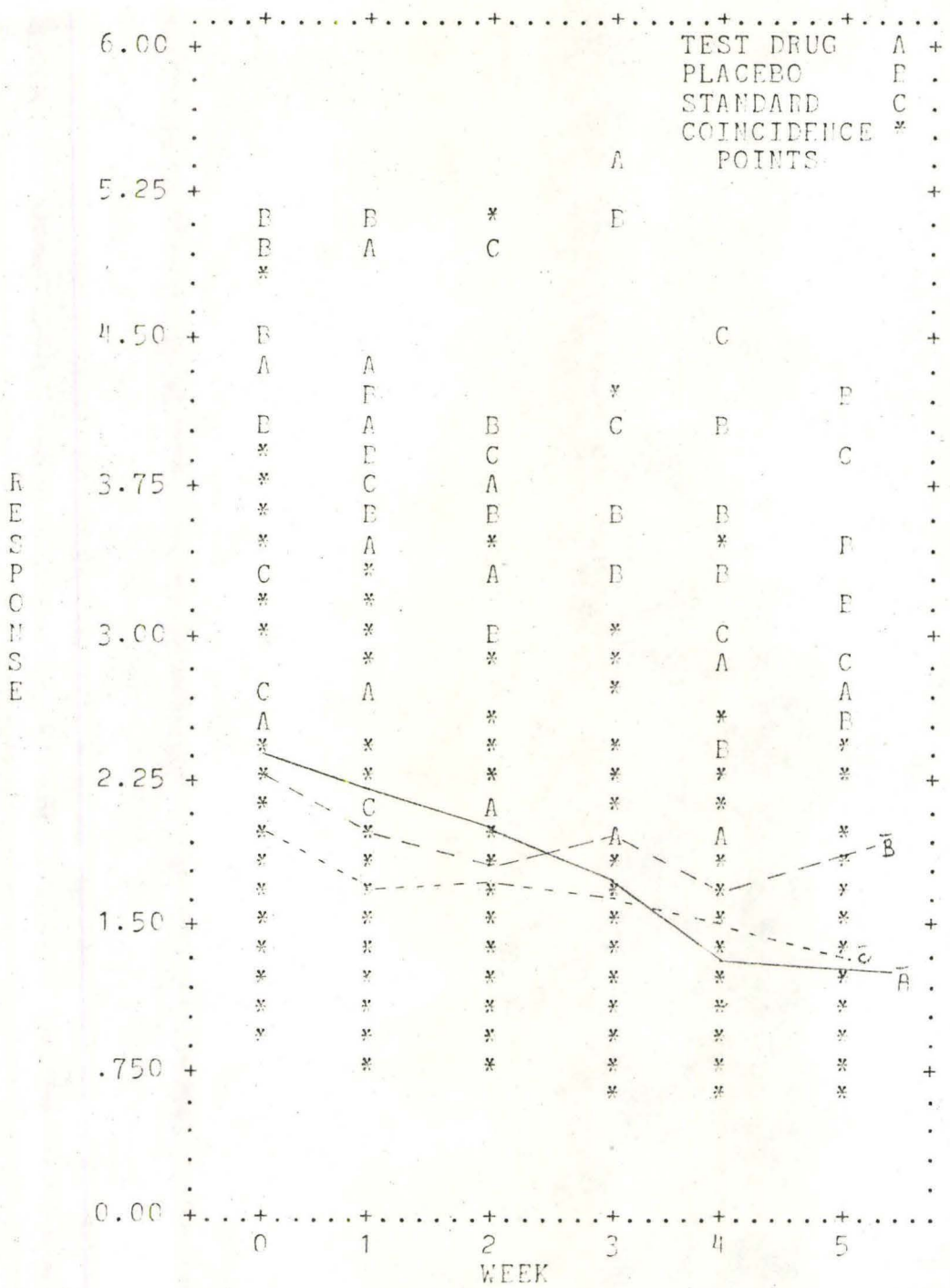
VARIANCE-COVARIANCE MATRIX FOR STANDARD DRUG

.00450	.00285	-.00003	-.00015	-.00003	-.00060
.00285	.00391	.00124	.00172	.00153	.00088
-.00003	.00124	.00805	.00620	.00458	.00386
-.00015	.00172	.00620	.01307	.01069	.01002
-.00003	.00153	.00458	.01069	.01063	.00966
-.00060	.00088	.00386	.01002	.00966	.01008

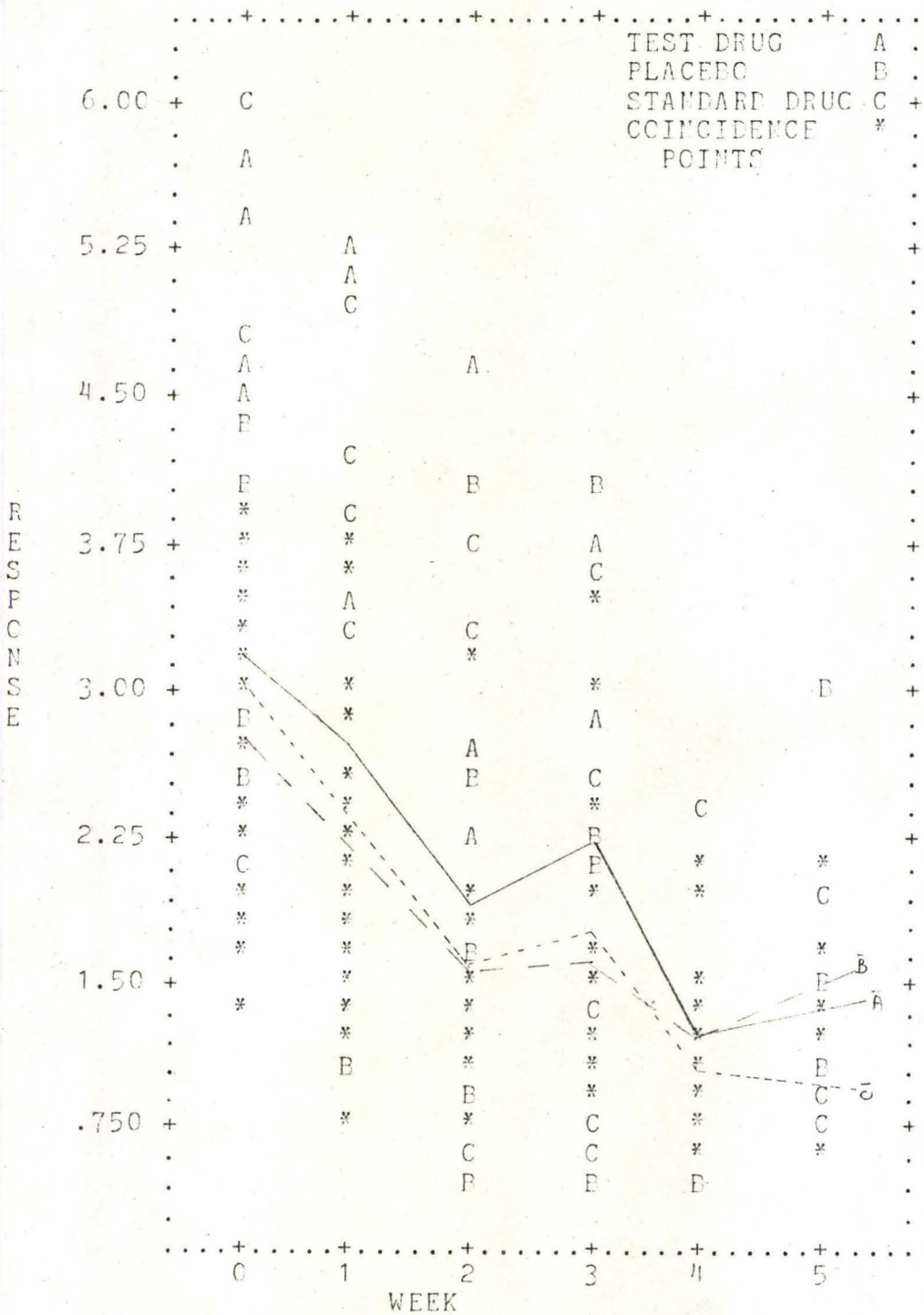
COMMON VARIANCE-COVARIANCE MTRIX FOR CLINIC C

.00457	.00403	.00285	.00304	.00312	.00297
.00403	.00681	.00507	.00515	.00519	.00499
.00285	.00507	.00809	.00803	.00725	.00685
.00304	.00515	.00803	.01258	.01137	.01090
.00312	.00519	.00725	.01137	.01349	.01265
.00297	.00499	.00685	.01090	.01265	.01294

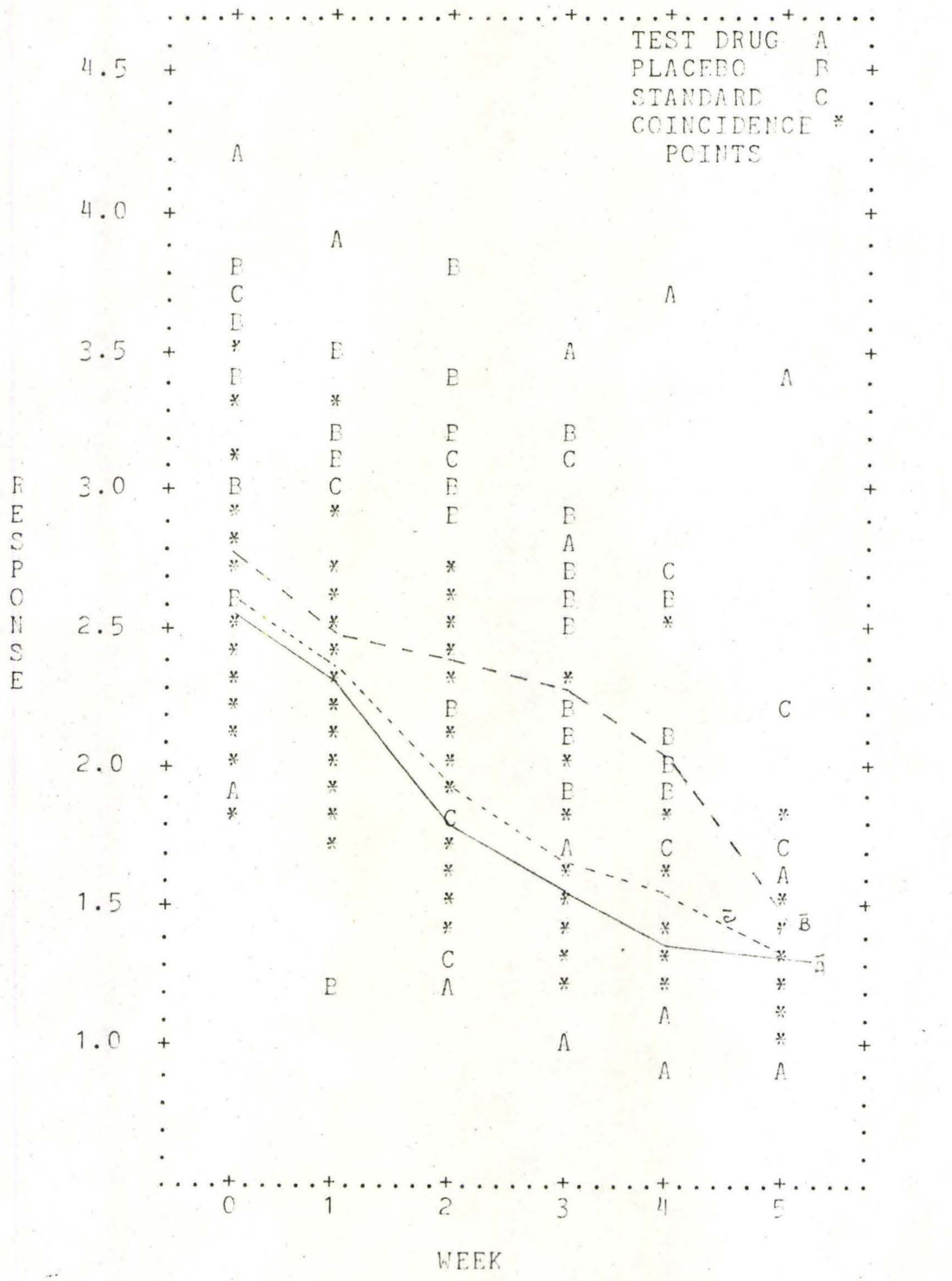
GRAPH 1. A PLOT OF PATIENTS' MEAN RESPONSES IN CLINIC A VS WEEKS



GRAPH 2. A PLOT OF PATIENTS' MEAN RESPONSES IN CLINIC B VS WEEKS



GRAPH 3. A PLOT OF PATIENTS' MEAN RESPONSES IN CLINIC C VS WEEKS



HOPKINS SELF-RATING SYMPTOM CHECKLIST

PATIENT IDENTIFICATION: _____

DATE: ____/____/____ VISIT: _____

INSTRUCTIONS: Listed below are 35 symptoms or problems that people sometimes have. Please read each one carefully and decide how much the symptoms bothered or distressed you during the past week, including today.

Decide how much the symptom affected you, NOT AT ALL? A LITTLE? QUITE A BIT? EXTREMELY? and place a check in the appropriate column to the right.

HOW MUCH WERE YOU BOTHERED BY THE FOLLOWING SYMPTOMS:
(Do not leave out any items)

SYMPTOMS	NOT AT ALL	A LITTLE	QUITE A BIT	EXTREMELY
1. Sweating				
2. Trouble getting your breath				
3. Suddenly scared for no reason				
4. Difficulty in speaking when you are excited.				
5. Feeling low in energy or slowed down				
6. Pains in the heart or chest				
7. Trouble remembering things.				
8. Hot or cold spells				
9. Blaming yourself for things				
10. A lump in your throat				
11. Feeling fearful				
12. Numbness or tingling in parts of your body				
13. Feeling critical of others				
14. Having to avoid certain things, places or activities because they frighten you.				

SYMPTOMS	NOT AT ALL	A LITTLE	QUITE A BIT	EXTREMELY
15. Having to do things very slowly in order to be sure you were doing them right.				
16. Heavy feelings in your arms or legs.				
17. Faintness or dizziness				
18. Crying easily				
19. Nervousness or shakiness inside				
20. Your feelings being easily hurt				
21. Constipation				
22. Loss of sexual interest or pleasure.				
23. Feeling easily annoyed or irritated.				
24. Poor appetite				
25. Difficulty making decisions				
26. Difficulty in falling asleep or staying asleep				
27. Feeling hopeless about the future				
28. Feeling blue				
29. Feeling lonely				
30. Temper outbursts you could not control				
31. Headaches				
32. Heart pounding or racing				
33. Trouble concentrating				
34. Your mind going blank				
35. Thoughts of ending your life				

WHITE COPY - McNEIL*
YELLOW COPY

PINK COPY - INVESTIGATOR

* Trademark

APPENDIX A

SECTION I

FACTOR COMPOSITION:

The factors employed in the analyses were derived from a factor analysis performed by Lipman et al on a sample of 1115 subjects. The 5 factors are :

FACTOR I GENERAL NEUROTIC FEELINGS

9. Blaming yourself for things
13. Feeling critical of others
20. Your feelings being easily hurt
23. Feeling easily annoyed or irritated
27. Feeling hopeless about the future
28. Feeling blue
29. Feeling lonely
30. Temper outburts you could not control
35. Thoughts of ending your life

FACTOR II SOMATIZATION

1. Sweating
2. Trouble getting your breath
6. Pains in the heart or chest
8. Hot or cold spells
10. A lump in your throat
12. Numbness or tingling of parts of your body
16. Heavy feelings in your arms and legs
17. Faintness of dizziness

FACTOR II SOMATIZATION (Cont'd)

26. Difficulty in falling asleep or staying asleep
31. Headaches
32. Heart pounding or racing

FACTOR III COGNITIVE PERFORMANCE - DIFFICULTY

4. Difficulty in speaking when you are excited
7. Trouble remembering things
15. Having to do things very slowly in order to be sure you were doing them right
25. Difficulty making decisions
33. Trouble concentrating
34. Your mind going blank

FACTOR IV DEPRESSION

18. Crying easily
22. Loss of sexual interest or pleasure
24. Poor appetite

FACTOR V FEAR/ANXIETY

3. Suddenly scared for no reason
11. Feeling fearful
14. Having to avoid certain things,places or activities because they frighten you
19. Nervousness or shakiness inside

APPENDIX B

SECTION I

TESTING THE EQUALITY OF SEVERAL VARIANCE-COVARIANCE MATRICES (Morrison 1971)(Pearson & Hartly 1972)

The hypotheis

$$H_o : \Sigma_1 = \Sigma_2 = \Sigma_3 = \Sigma_4 = \ldots = \Sigma_k$$

of the equality of the covariance matrices of k p-dimensional multinormal populations can be tested against the alternative of general positive definite matrices by a modified generalized likelihood-ratio statistics.

Let S_i be the unbiases estimate of Σ_i based on n_i degreesof freedom where $n_i = N - 1$ for the usual case of a random sample of N_i observation vector from the ith population.

When H_o is true

$$S = \frac{1}{\Sigma n_i} \sum_{i=1}^{k} n_i S_i$$

is the pooled estimate of the common covariance matrix. The test statistics is

$$M = \sum_{i=1}^{k} n_i \ln |S| - \sum_{i=1}^{k} n_i \ln |S_i|$$

and BOX(1949) has derived the following χ^2 and F approximations to the distribution of M

(a) χ^2 approximation $\quad M \sim \chi^2_{f_1} / (1-D_1)$

where $f_1 = \frac{1}{2} p(p-1)(k-1)$

$$D_1 = \frac{2p^2+3p-1}{6(p+1)(k-1)} \sum_{i=1}^{k} \frac{1}{n_i} - \frac{1}{\Sigma n_i}$$

(b) F-approximation $M \sim b F_{f_1, f_2}$,

where

$$f_1 = \tfrac{1}{2} p(p-1)(k-1)$$

$$f_2 = \frac{f_1 + 2}{D_2 - D_1^2}$$

$$D_1 = \frac{2p^2+3p-1}{6(p+1)(k-1)} \left\{ \sum_{i=1}^{k} \frac{1}{n_i^2} - \frac{1}{(\Sigma n_i)^2} \right\}$$

$$b = \frac{f_1}{1 - D_1 - \frac{f_1}{f_2}}$$

SECTION II

TESTING FOR UNIFORM MATRIX (EQUAL VARIANCE, EQUAL COVARIANCE (MORRISON 1971)

$$H_o: \quad \underset{\sim}{\Sigma} = \sigma^2 \begin{bmatrix} 1 & \rho & \rho & . & . & . & \rho \\ \rho & . & . & . & . & . & \rho \\ . & . & . & . & . & . & . \\ \rho & \rho & . & . & . & . & 1 \end{bmatrix}_{p \times q}$$

Let us suppose that the usual unbiased estimate $\underset{\sim}{S}$ of $\underset{\sim}{\Sigma}$ based on ν degree of freedom has been obtained, where $\nu = N - 1$ for a single random sample. Then the estimates of σ^2 and $\sigma^2\rho$ under null hypothesis are

$$s^2 = \frac{1}{p_i} \sum_{i=1}^{p} s_{ii}$$

$$s^2 r = \frac{1}{p(p-1)} \sum_{i \neq j} \sum s_{ij}$$

and the Wilks (1946) generalized likelihood ratio-statistic is

$$L = \frac{S}{(s^2)^p (1-r)^{p-1} [1+(p-1)r]}$$

BOX(1949,1950) has shown that

$$\chi^2 = -\left[\nu - \frac{p(p+1)^2(2p-3)}{6(p-1)(p^2+p-4)} \right] \ln L \sim \chi^2_{\nu=\frac{1}{2}p(p+1)-2}$$

when ν is large and null hypothesis is true.

SECTION III

MODEL AND HYPOTHEIS TESTINGS PROCEDURE OF MANOVA

The formation of multivariate analysis of variance to be present here are stated in a summary form. For more detailed theoretical results can be referred to Morrison (1971).

Let n denote the total number of experimental units in the design experiment . If we assume that p responses are measured on each of the n experimental units, then we have the pxn response matrix

$$\underset{\sim pxn}{Y} = \begin{bmatrix} y_{11} & y_{12} & \cdot & \cdot & \cdot & y_{1n} \\ \cdot & & & & & \cdot \\ \cdot & & & & & \cdot \\ y_{p1} & \cdot & \cdot & \cdot & \cdot & y_{pn} \end{bmatrix} = [Y_1, Y_2, \ldots Y_n]$$

where $\underset{\sim i}{Y'}$ represents the column vector of 'p' responses measured at the ith observation point in the experiment. The usual fixed model of MANOVA may then be written as

$$\underset{\sim pn}{Y'} = \underset{\sim nm}{A} \; \underset{\sim mp}{\xi} + \underset{\sim np}{e}$$

where , (i) $\underset{\simeq}{A}$ is the nxm design matrix whose elements completely describe the actual design under which the data is obtained and has rank

column of matrix $\underset{\sim}{\xi}$, i.e. it is used to state "between responses " hypothesis such as hypothesis that the effect of a treatment is the same on all(or a given subset) of the p responses. The $\underset{\sim}{C}$ matrix, on the other hand , is used to form linear combination among the m components of the model, i.e. it is used to state "between treatments" hypothesis. The choice of $\underset{\sim}{C}$ and $\underset{\sim}{M}$ depends on what testing hypotheses we are of interest.

Recall that the F-test of significance of the departure from the null hypothesis in the univariate multiple regression is the ratio of the mean regression-sum-of-squares (MSR) to the mean error-sum-of-squares (MSE)

$$F = MSR / MSE$$

The multivariate analogue of F is the ratio of the determinant of a u x u matrix $\underset{\sim}{S}_H$ of regression sum-of-squares and cross-product (Hypothesis sum of products) to the determinant of a u x u matrix $\underset{\sim}{S}_E$ of error-sum-of-squares and cross-products, where $\underset{\sim}{S}_H$ and $\underset{\sim}{S}_E$ are defined as :

$$\underset{\sim}{S}_H = \underset{\sim}{M}'\underset{\sim}{Y}'\underset{\sim}{A}(\underset{\sim}{A}'\underset{\sim}{A})^{-1}\underset{\sim}{C}'[\underset{\sim}{C}(\underset{\sim}{A}'\underset{\sim}{A})^{-1}\underset{\sim}{C}']^{-1}\underset{\sim}{C}(\underset{\sim}{A}'\underset{\sim}{A})^{-1}\underset{\sim}{A}'\underset{\sim}{Y}\underset{\sim}{M}$$

and

$$\underset{\sim}{S}_E = \underset{\sim}{M}'\underset{\sim}{Y}[\underset{\sim}{I}_n - \underset{\sim}{A}(\underset{\sim}{A}'\underset{\sim}{A})^{-1}\underset{\sim}{A}']\underset{\sim}{Y}\underset{\sim}{M}$$

However, the multivariate analogue of F-type ratio does not follow a distribution that is easily characterized or has standard tables available for testing hypotheses.

$r < m < n$;

(ii) $\underset{\sim}{\xi}$ is an m x p matrix of unknown parameters, the fixed effects of the factors involved in the experiement; here the $\underset{\sim}{\xi}$ for this analysis is

$$\underset{\sim}{\xi}_{3x6} = \begin{bmatrix} \xi_{11} & \xi_{12} & \xi_{13} & \xi_{14} & \xi_{15} & \xi_{16} \\ \xi_{21} & \xi_{22} & \xi_{23} & \xi_{24} & \xi_{25} & \xi_{26} \\ \xi_{31} & \xi_{32} & \xi_{33} & \xi_{34} & \xi_{35} & \xi_{36} \end{bmatrix}_{3x6}$$

(iii) $\underset{\sim}{\varepsilon}$ is n x p matrix whose rows are assumed to be a random sample of size n from non-singular p-variate normal $N[\underset{\sim}{0}_{px1}, \underset{\sim}{\Sigma}_{pxp}]$; and

(iv) p assumed to be < (n-r)

Under these assumptions it follows that the n vectors $\underset{\sim}{Y}_1$ .... $\underset{\sim}{Y}_n$ of (i) are independent samples each from $N[E(\underset{\sim}{Y}_i), \underset{\sim}{\Sigma}]$ where $\underset{\sim}{\Sigma}$ is common to all n vectors. The assumption that $p < (n-r)$ ensures the sample error matrix is positively definite almost everything.

Starting with the model, the MANOVA procedure tests hypotheses hypotheses of the form

$$H_o : \underset{\sim}{C}_{(sxm)} \underset{\sim}{\xi}_{(mxp)} \underset{\sim}{M}_{(pxu)} = \underset{\sim}{0}_{(sxu)}$$

where C is an sxm matrix of rank $s < r << m < n$ consisting of any set of linearly independent row vectors (since $\underset{\sim}{\Lambda}$ is of full column rank) and M is pxu matrix of rank $u < p$. *The* The M-matrix is structured to form linear combination of the

Therefore, the F-type ratio is put in one of the two equivalent forms by writing the determinantal equation as

$$| \underset{\sim}{S}_H \underset{\sim}{S}_E^{-1} - \lambda \underset{\sim}{I} | = 0 ,$$

or $$| \underset{\sim}{S}_H - \lambda \underset{\sim}{S}_E | = 0 ,$$

which is a polynomial of degree u, i.e.

$$\alpha_0 + \alpha_1\lambda + \alpha_2\lambda^2 + \ldots\ldots + \alpha_u\lambda^u = 0$$

The roots of this polynomial or its characteristic roots (eigenvalues) are denoted by $\lambda_1 , \lambda_2 , .., \lambda_u$ which are usually distinct and real, and $\lambda_1 > \lambda_2 > .. > \lambda_u$.

Four basic test criteria have been put forward by various authors. They are

(1) Wilk's likelihood ratio criterion

$$\Lambda = |\underset{\sim}{S}_H| \; / \; |\underset{\sim}{S}_H + \underset{\sim}{S}_E| = \prod_{i=1}^{u} \{ 1 \; / \; 1 + \lambda_i \}$$

(2) Lawley - Hotelling Trace Criterion

$$tr(\underset{\sim}{S}_H \underset{\sim}{S}_E^{-1}) = \sum_{i=1}^{u} \lambda_i$$

(3) Roy's largest root criterion

$$CH_{max}(\underset{\sim}{S}_H\underset{\sim}{S}_E^{-1}) \; / \; [1+CH_{max}(\underset{\sim}{S}_H\underset{\sim}{S}_E-1) = \theta = \lambda_1/(1+\lambda_1)$$

where λ_1 is the largest characteristic root of $\underset{\sim}{S}_H\underset{\sim}{S}_E^{-1}$

(4) Pillais Criterion

$$\text{tr } H\ (H + E)^{-1} = \sum_{i=1}^{u} \lambda_i \ / \ 1 + \lambda_i$$

Power Comparisons of the Test Criteria (Morrison 1976)

Pillai and jayachandran(1967),Roy,Gnanadesikan & Srivastava(1971) have compiled the powers of Roy,Wilks, T_o^2 tests and Pillais. For p=2 responses and alpha = 0.05, the powers of Wilks, T_o^2 and Pillais differed only in the third decimal place for small departures from the null hypothesis of zero population characteristic roots. For larger deviations the powers differed at most by 0.02. When the population roots were very different T_o^2 tended to have the highest power,while for equal roots,the power of Pillias (V) was highest. The power of Roy test was lowest for the alternatives considered,although the third-place decimals were too small to have proactical consequences. However, for the case of a single large population root the Roy statistics tended to have the highest empirical power.

APPENDIX B SECTION IV

The followings are the testing hypotheses we are of interest in this project.

(1) H_o: There is no difference in main effect due to treatment among the six-week measurements simultaneously.

Here we choose

$$\underset{\sim}{C} = \begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix}_{2x3}$$

and $\underset{\simeq}{M}$ as an identity matrix i.e.

$$\underset{\sim}{M} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}_{6x6}.$$

The matrix formulation of the joint hypothesis is

$$H_o : \underset{\sim}{C}\,\underset{\sim}{\xi}\,\underset{\sim}{M} = \underset{\sim}{0}$$

i.e.

$$\begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \xi_{10} & \xi_{11} & \xi_{12} & \xi_{13} & \xi_{14} & \xi_{15} \\ \xi_{20} & \xi_{21} & \xi_{22} & \xi_{23} & \xi_{24} & \xi_{25} \\ \xi_{30} & \xi_{31} & \xi_{32} & \xi_{33} & \xi_{34} & \xi_{35} \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} = \underset{\sim}{0}$$

$$\begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \xi_{10} & \xi_{11} & \xi_{12} & \xi_{13} & \xi_{14} & \xi_{15} \\ \xi_{20} & \xi_{21} & \xi_{22} & \xi_{23} & \xi_{24} & \xi_{25} \\ \xi_{30} & \xi_{31} & \xi_{32} & \xi_{33} & \xi_{34} & \xi_{35} \end{bmatrix} = \underset{\sim}{0}$$

$$\begin{bmatrix} \xi_{10}-\xi_{30} & \xi_{11}-\xi_{31} & \xi_{12}-\xi_{32} & \xi_{13}-\xi_{33} & \xi_{14}-\xi_{34} & \xi_{15}-\xi_{35} \\ \xi_{20}-\xi_{30} & \xi_{21}-\xi_{31} & \xi_{22}-\xi_{32} & \xi_{23}-\xi_{33} & \xi_{24}-\xi_{34} & \xi_{25}-\xi_{35} \end{bmatrix} = \underset{\sim}{0}$$

Therefore,

$$H_o : \begin{bmatrix} \xi_{10} \\ \xi_{11} \\ \xi_{12} \\ \xi_{13} \\ \xi_{14} \\ \xi_{15} \end{bmatrix} = \begin{bmatrix} \xi_{20} \\ \xi_{21} \\ \xi_{22} \\ \xi_{23} \\ \xi_{24} \\ \xi_{25} \end{bmatrix} = \begin{bmatrix} \xi_{30} \\ \xi_{31} \\ \xi_{32} \\ \xi_{33} \\ \xi_{34} \\ \xi_{35} \end{bmatrix}$$

(2) H_o : There is no difference due to the main effect of the times of measurement.

So we choose $\underset{\sim}{C}$ as a summation vector i.e.

$$\underset{\sim}{C} = [\,1 \quad 1 \quad 1\,]$$

where the hypothesis corresponding to the u elements of $\underset{\sim}{C}'_k \underset{\sim}{\xi}\ \underset{\sim}{M}_l$ will disregard the differences between treatment group means. We choose M as a contrast matrix where m_l is a column vector whose elements sum to zero. i.e.

$$\underset{\sim}{M} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 \\ 0 & -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & 0 & -1 \end{bmatrix}_{6x5}$$

Therefore, the resulting joint hypothesis is :

$$[\,1 \quad 1 \quad 1\,] \begin{bmatrix} \xi_{10} & \xi_{11} & \xi_{12} & \xi_{13} & \xi_{14} & \xi_{15} \\ \xi_{20} & \xi_{21} & \xi_{22} & \xi_{23} & \xi_{24} & \xi_{25} \\ \xi_{30} & \xi_{31} & \xi_{32} & \xi_{33} & \xi_{34} & \xi_{35} \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 \\ 0 & -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & 0 & -1 \end{bmatrix} = \underset{\sim}{0}$$

$$[\,1 \quad 1 \quad 1\,] \begin{bmatrix} \xi_{10}-\xi_{11} & \xi_{11}-\xi_{12} & \xi_{12}-\xi_{13} & \xi_{13}-\xi_{14} & \xi_{14}-\xi_{15} \\ \xi_{20}\ \xi_{21} & \xi_{21}\ \xi_{22} & \xi_{22}\ \xi_{23} & \xi_{23}\ \xi_{24} & \xi_{24}\ \xi_{25} \\ \xi_{30}\ \xi_{31} & \xi_{31}\ \xi_{32} & \xi_{32}\ \xi_{33} & \xi_{33}\ \xi_{34} & \xi_{34}\ \xi_{35} \end{bmatrix} = \underset{\sim}{0}$$

$$[\,\sum_{j=1}^{3}(\xi_{j0}-\xi_{j1}) \quad \sum_{j=1}^{3}(\xi_{j1}-\xi_{j2}) \cdots\cdots\cdots \sum_{j=1}^{3}(\xi_{j4}-\xi_{j5})\,] = \underset{\sim}{0}$$

Hence

$$H_o: \sum_{j=1}^{3}\xi_{j0} = \sum_{j=1}^{3}\xi_{j1} = \sum_{j=1}^{3}\xi_{j2} = \sum_{j=1}^{3}\xi_{j3} = \sum_{j=1}^{3}\xi_{j4} = \sum_{j=1}^{3}\xi_{j5}$$

(3) H_o : There is no interaction effect between the times of measurements (weeks) and treatment groups (drugs)

Here we choose both $\underset{\sim}{C}$ and $\underset{\sim}{M}$ as a contrasting matrix.

Therefore the resulting joint hypothesis is

$$\begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \xi_{10} & \xi_{11} & \xi_{12} & \xi_{13} & \xi_{14} & \xi_{15} \\ \xi_{20} & \xi_{21} & \xi_{22} & \xi_{23} & \xi_{24} & \xi_{25} \\ \xi_{30} & \xi_{31} & \xi_{32} & \xi_{33} & \xi_{34} & \xi_{35} \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ -1 & 1 & 0 & 0 & 0 \\ 0 & -1 & 1 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & 0 & -1 \end{bmatrix} = \underset{\simeq}{0}$$

$$\begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \xi_{10}-\xi_{11} & \xi_{11}-\xi_{12} & \xi_{12}-\xi_{13} & \xi_{13}-\xi_{14} & \xi_{14}-\xi_{15} \\ \xi_{20}-\xi_{21} & \xi_{21}-\xi_{22} & \xi_{22}-\xi_{23} & \xi_{23}-\xi_{24} & \xi_{24}-\xi_{25} \\ \xi_{30}-\xi_{31} & \xi_{31}-\xi_{32} & \xi_{32}-\xi_{33} & \xi_{33}-\xi_{34} & \xi_{34}-\xi_{35} \end{bmatrix} = \underset{\simeq}{0}$$

Hence

$$H_0 : \begin{bmatrix} \xi_{10}-\xi_{11} \\ \xi_{11}-\xi_{12} \\ \xi_{12}-\xi_{13} \\ \xi_{13}-\xi_{14} \\ \xi_{14}-\xi_{15} \end{bmatrix} = \begin{bmatrix} \xi_{20}-\xi_{21} \\ \xi_{21}-\xi_{22} \\ \xi_{22}-\xi_{23} \\ \xi_{23}-\xi_{24} \\ \xi_{24}-\xi_{25} \end{bmatrix} = \begin{bmatrix} \xi_{30}-\xi_{31} \\ \xi_{31}-\xi_{32} \\ \xi_{32}-\xi_{33} \\ \xi_{33}-\xi_{34} \\ \xi_{34}-\xi_{35} \end{bmatrix}$$

(4) H_o : There is no difference between the 3 treatment groups(drugs) when averaged over time

Here C matrix will be the same contrasting matrix, M matrix will be a summation matrix. So the resulting joint hypothesis will be :

$$\begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \xi_{10} & \xi_{11} & \xi_{12} & \xi_{13} & \xi_{14} & \xi_{15} \\ \xi_{20} & \xi_{21} & \xi_{22} & \xi_{23} & \xi_{24} & \xi_{25} \\ \xi_{30} & \xi_{31} & \xi_{32} & \xi_{33} & \xi_{34} & \xi_{35} \end{bmatrix} \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} = \begin{matrix} 0 \\ \simeq \end{matrix}$$

$$\begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & -1 \end{bmatrix} \begin{bmatrix} \sum_{j=1}^{3} \xi_{1j} \\ \sum_{j=1}^{3} \xi_{2j} \\ \sum_{j=1}^{3} \xi_{3j} \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$$

$$\begin{bmatrix} \sum_{j=0}^{5} \xi_{1j} - \sum_{j=0}^{5} \xi_{3j} \\ \sum_{j=0}^{5} \xi_{2j} - \sum_{j=0}^{5} \xi_{3j} \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}$$

Hence

$$H_o : \sum_{j=0}^{5} \xi_{1j} = \sum_{j=0}^{5} \xi_{2j} = \sum_{j=0}^{5} \xi_{3j}$$

(5) H_o : There is no difference among the 3 treatment groups when decrease in time

Same contrasting C matrix is used but M matrix is a polynomial composed of the property of orthogonality.

$$\underset{\sim}{M} = \begin{bmatrix} \text{LIN} & \text{QUAD} & \text{THIRD} & \text{FOURTH} & \text{FIFTH} \\ -5 & 5 & 5 & 1 & -1 \\ -3 & -1 & 7 & -3 & 5 \\ -1 & -4 & 4 & 2 & -10 \\ 1 & -4 & -4 & 2 & 10 \\ 3 & -1 & -7 & -3 & 5 \\ 5 & 5 & 5 & 1 & 1 \end{bmatrix}$$

Therefore the resulting joint hypothesis will be :-

$$H_o : \underset{\sim}{C}\ \underset{\sim}{\xi}\ \underset{\sim}{M} = \underset{\sim}{0}$$

where $\text{LIN} = -5\xi_{j0} - 3\xi_{j1} + \xi_{j2} + \xi_{j3} + 3\xi_{j4} + 5\xi_{j5}$

$\text{QUAD} = 5\xi_{j0} + \xi_{j1} - 4\xi_{j2} - 4\xi_{j3} - \xi_{j4} + 5\xi_{j5}$

$\text{THIRD} = -5\xi_{j0} + 7\xi_{j1} + 4\xi_{j2} - 4\xi_{j3} - 7\xi_{j4} + 5\xi_{j5}$

$\text{FOURTH} = \xi_{j0} - 3\xi_{j1} + 2\xi_{j2} + 2\xi_{j3} - 3\xi_{j4} + \xi_{j5}$

$\text{FIFTH} = -\xi_{j0} + 5\xi_{j1} - 10\xi_{j2} + 10\xi_{j3} + 5\xi_{j4} + \xi_{j5}$

where $j = 1,2,3$

(6) H_0 : On the average, the severity of symptoms does not change with time

Here C matrix is the same summation vector and M is the same orthogonal polynomial matrix used in testing hypothesis no. 5 .

REFERENCES

[1] Anderson,T.W. (1958). *An introduction to Multivariate Statistical Analysis.* New York Wiley.

[2] Beale, E.M.L. and R.J.A. Little (1975). *Missing Values in Multivariate Analysis.* J.Royal Statistical Soc. 37 Series B, p.129-145.

[3] Box,G.E.P. (1949). *A general Distribution Theory for a Class of Likelihood Ratio Criteria.* Biometrika 36, p.317-346.

[4] Cole,J.W.L. and Grizzle J.E. (1966) *Applications of Multivariate analysis of variance to repeated measurements.* Biometrics V.22, p.810-828.

[5] Cramer,E.M.,*Some Model Designs for psychopharmacology Experiments.* Proceedings of the Collegium International Neuro-psychopharmacologicum, Washington,D.C., 1966.

[6] Derogatis L.R. & Lipman R.S. et al (1974) *The Hopkins Symptom Checklist (HSCL): A Self-report Symptom Inventory.* Behav. Sci. March, 1974.

[7] Derogatis, L.R., Lipman R.S., Covi L., et al: *Factor Invariance of neurotic symptom dimensions in anxious and depressive neuroses.* Arch. Gen.Psych. 155, 1972.

[8] Dixon W.J.,Brown, M.B. *Biomedical Computer Programs,P-Series 1977.* Los Angeles, Univ. of Cal. Press.

[9] Draper, N.R. & Smith H. (1966) *Applied Regression Analysis*. New York John Wiley.

[10] Frane, J.W. (1976) *Some Simple Procedures For Handling Missing data in Multivariate Analysis*. Psychometrika, Vol 41,#3, p.409-415.

[11] Goldsmith,C.H. *Multivariate Analysis of Variance (MANOVA)* unpublished.

[12] Greenhouse,S.W. and Geisser S. (1959). *On Methods in the Analysis of Profile data*. Psychometrika 24, p.95-112.

[13] Grizzle,J.E. and David M. Allen (1969) *Analysis of Growth and Dose Response Curves*. Biometrics, V.25, p. 357 - 381.

[14] Lipman, R.S. et al. (1969) *Factors of Symptom Distress: Doctor ratings of anxious neurotic outpatients*. Psychiat. 1969, V.21, p.328 - 338.

[15] Morrison D.F. (1976) *Multivariate Statistical Methods*. 2nd Edition. McGraw Hill.

[16] Norman, H,Nie et al, Eli Cohen & Phil Burns (1977).*SPSS MANOVA -Mutilvariate Analysis of Variance and Covariance*. DOC. NO. 413 (Rev. A)

[17] Pearson, E.S. and Hartley, H.O. (1972) *Biometrika Tables for Statisticians*. Vol. 2. Cambridge.

[18] Rouanet, H. and LEpine,D. *Comparison Between Treatments in a Repeated Measurement Design:ANOVA and Multivariate Method*.Br.J.Math.& Stat.Psy.1970.V.23, pt.2. p.147-163.

[19] Searl,S.R. (1971) *Linear Models*. John Wiley,New York.