Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

Model 1: Fixed Effects Model to Test Heterogeneity, Adjusting for Baseline NAR (Nasal Airflow Resistance and Study with Treatment by Study Interaction

Checking the Treatment by Study Interaction Term to Test for Heterogeneity

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

TO = Baseline (A Covariate)

The Mixed Procedure

Model Information

Data Set	WORK.TEN_MG
Dependent Variable	LN240CHG
Covariance Structure	Variance Components
Group Effect	STUDY
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
TREAT	2	Drug Placebo
STUDY	5	2 3 4 6 7

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Class Level Information

Class	Levels	Values
PATIENT	82	2001 2005 2007 2012 2014 2018 2020 2021 2023 2024 3001 3003 3005 3008 3009 3015 3018 3023 3026 3032 3036 3039 3041 3044 3046 3048 4001 4003 4007 4010 4012 4017 4024 4026 4027 4030 4032 4034 4037 4039 4044 6001 6003 6005 6008 6010 6013 6017 6023 6026 6031 6034 6040 6041 6044 6046 6048 7001 7002 7003 7007 7008 7010 7014 7016 7017 7018 7020 7021 7025 7027 7028 7030 7031 7033 7034 7036 7041 7042 7044 7048 7050

Dimensions

Covariance Parameters	5
Columns in X	101
Columns in Z	0
Subjects	164
Max Obs Per Subject	1
Observations Used	164
Observations Not Used	0
Total Observations	164

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Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	132.49240567	
1	2	108.75622929	0.00000430
2	1	108.75616263	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Group	Estimate
Residual	STUDY 2	0.006120
Residual	STUDY 3	0.1381
Residual	STUDY 4	0.2493
Residual	STUDY 6	0.1141
Residual	STUDY 7	0.09454

Fit Statistics

-2 Res Log Likelihood	108.8
AIC (smaller is better)	118.8
AICC (smaller is better)	119.6
BIC (smaller is better)	134.3

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Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	23.74	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TO	1	61.2	24.58	<.0001
PATIENT(STUDY)	77	25.5	1.73	0.0610
STUDY	4	35.8	3.71	0.0125
TREAT	1	46.7	0.45	0.5040
TREAT*STUDY	4	32.1	1.60	0.1987

Least Squares Means

Effect	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
STUDY		2	-0.4001	0.07939	64.6	-5.04	<.0001	0.05	-0.5586	-0.2415
STUDY		3	-0.3179	0.06795	16.2	-4.68	0.0002	0.05	-0.4618	-0.1740
STUDY		4	-0.3137	0.09428	15.5	-3.33	0.0044	0.05	-0.5140	-0.1133
STUDY		6	-0.07504	0.05975	13.3	-1.26	0.2308	0.05	-0.2039	0.05379
STUDY		7	-0.1077	0.05085	32.5	-2.12	0.0419	0.05	-0.2112	-0.00420
TREAT	Drug		-0.2612	0.03899	47.8	-6.70	<.0001	0.05	-0.3396	-0.1828
TREAT	Placebo		-0.2246	0.03963	48.9	-5.67	<.0001	0.05	-0.3042	-0.1450
TREAT*STUDY	Drug	2	-0.4090	0.08043	65	-5.09	<.0001	0.05	-0.5696	-0.2484

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The Mixed Procedure

Least Squares Means

Effect	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT*STUDY	Drug	3	-0.4844	0.09362	15.2	-5.17	0.0001	0.05	-0.6837	-0.2851
TREAT*STUDY	Drug	4	-0.2623	0.1321	15.1	-1.99	0.0655	0.05	-0.5437	0.01902
TREAT*STUDY	Drug	6	-0.03539	0.08458	13.3	-0.42	0.6823	0.05	-0.2177	0.1469
TREAT*STUDY	Drug	7	-0.1147	0.06459	26	-1.78	0.0875	0.05	-0.2475	0.01807
TREAT*STUDY	Placebo	2	-0.3911	0.08216	65.1	-4.76	<.0001	0.05	-0.5552	-0.2271
TREAT*STUDY	Placebo	3	-0.1514	0.09578	16.1	-1.58	0.1335	0.05	-0.3543	0.05159
TREAT*STUDY	Placebo	4	-0.3650	0.1304	14.5	-2.80	0.0138	0.05	-0.6438	-0.08623
TREAT*STUDY	Placebo	6	-0.1147	0.08445	13.2	-1.36	0.1971	0.05	-0.2968	0.06742
TREAT*STUDY	Placebo	7	-0.1007	0.06977	30.6	-1.44	0.1589	0.05	-0.2431	0.04161

Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
STUDY		2		3	-0.08218	0.09073	31.6	-0.91	0.3719	0.05	-0.2671	0.1027
STUDY		2		4	-0.08638	0.1375	44.3	-0.63	0.5332	0.05	-0.3635	0.1908
STUDY		2		6	-0.3250	0.1009	36.3	-3.22	0.0027	0.05	-0.5296	-0.1204
STUDY		2		7	-0.2923	0.1139	63.4	-2.57	0.0126	0.05	-0.5199	-0.06478
STUDY		3		4	-0.00421	0.1198	30.4	-0.04	0.9722	0.05	-0.2487	0.2402
STUDY		3		6	-0.2428	0.09087	28.5	-2.67	0.0123	0.05	-0.4288	-0.05686
STUDY		3		7	-0.2102	0.09010	34.8	-2.33	0.0256	0.05	-0.3931	-0.02721
STUDY		4		6	-0.2386	0.1112	25.4	-2.15	0.0416	0.05	-0.4674	-0.00985
STUDY		4		7	-0.2060	0.1010	20.4	-2.04	0.0547	0.05	-0.4165	0.004536
STUDY		6		7	0.03268	0.07778	29.8	0.42	0.6774	0.05	-0.1262	0.1916
TREAT	Drug		Placebo		-0.03658	0.05432	46.7	-0.67	0.5040	0.05	-0.1459	0.07272

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Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT*STUDY	Drug	2	Drug	3	0.07541	0.1161	26.1	0.65	0.5216	0.05	-0.1632	0.3140
TREAT*STUDY	Drug	2	Drug	4	-0.1467	0.1682	31.3	-0.87	0.3899	0.05	-0.4896	0.1962
TREAT*STUDY	Drug	2	Drug	6	-0.3736	0.1197	28.4	-3.12	0.0041	0.05	-0.6187	-0.1285
TREAT*STUDY	Drug	2	Drug	7	-0.2943	0.1169	59.4	-2.52	0.0145	0.05	-0.5282	-0.06040
TREAT*STUDY	Drug	2	Placebo	2	-0.01788	0.03503	8.7	-0.51	0.6226	0.05	-0.09755	0.06180
TREAT*STUDY	Drug	2	Placebo	3	-0.2576	0.1099	23.2	-2.34	0.0280	0.05	-0.4849	-0.03036
TREAT*STUDY	Drug	2	Placebo	4	-0.04399	0.1626	28.6	-0.27	0.7887	0.05	-0.3768	0.2888
TREAT*STUDY	Drug	2	Placebo	6	-0.2943	0.1162	27	-2.53	0.0174	0.05	-0.5327	-0.05589
TREAT*STUDY	Drug	2	Placebo	7	-0.3083	0.1280	61.3	-2.41	0.0190	0.05	-0.5641	-0.05236
TREAT*STUDY	Drug	3	Drug	4	-0.2221	0.1639	27.9	-1.35	0.1863	0.05	-0.5578	0.1137
TREAT*STUDY	Drug	3	Drug	6	-0.4490	0.1266	27.9	-3.55	0.0014	0.05	-0.7084	-0.1897
TREAT*STUDY	Drug	3	Drug	7	-0.3697	0.1157	29.5	-3.20	0.0033	0.05	-0.6062	-0.1332
TREAT*STUDY	Drug	3	Placebo	2	-0.09329	0.1171	26.5	-0.80	0.4328	0.05	-0.3338	0.1472
TREAT*STUDY	Drug	3	Placebo	3	-0.3331	0.1319	15.1	-2.52	0.0233	0.05	-0.6142	-0.05196
TREAT*STUDY	Drug	3	Placebo	4	-0.1194	0.1619	27.1	-0.74	0.4672	0.05	-0.4515	0.2127
TREAT*STUDY	Drug	3	Placebo	6	-0.3697	0.1260	27.7	-2.93	0.0067	0.05	-0.6280	-0.1114
TREAT*STUDY	Drug	3	Placebo	7	-0.3837	0.1199	31.5	-3.20	0.0031	0.05	-0.6281	-0.1392
TREAT*STUDY	Drug	4	Drug	6	-0.2270	0.1560	24.9	-1.46	0.1581	0.05	-0.5482	0.09432
TREAT*STUDY	Drug	4	Drug	7	-0.1476	0.1431	20.5	-1.03	0.3142	0.05	-0.4457	0.1504
TREAT*STUDY	Drug	4	Placebo	2	0.1288	0.1693	31.9	0.76	0.4526	0.05	-0.2162	0.4738
TREAT*STUDY	Drug	4	Placebo	3	-0.1110	0.1672	29.4	-0.66	0.5119	0.05	-0.4527	0.2307
TREAT*STUDY	Drug	4	Placebo	4	0.1027	0.1825	14	0.56	0.5827	0.05	-0.2888	0.4941
TREAT*STUDY	Drug	4	Placebo	6	-0.1476	0.1569	25.3	-0.94	0.3555	0.05	-0.4706	0.1753
TREAT*STUDY	Drug	4	Placebo	7	-0.1616	0.1429	20.4	-1.13	0.2713	0.05	-0.4593	0.1361
TREAT*STUDY	Drug	6	Drug	7	0.07931	0.1056	28	0.75	0.4587	0.05	-0.1369	0.2955
TREAT*STUDY	Drug	6	Placebo	2	0.3557	0.1210	28.8	2.94	0.0064	0.05	0.1082	0.6032
TREAT*STUDY	Drug	6	Placebo	3	0.1160	0.1286	28.6	0.90	0.3748	0.05	-0.1473	0.3792

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Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT*STUDY	Drug	6	Placebo	4	0.3296	0.1548	24.4	2.13	0.0435	0.05	0.01039	0.6489
TREAT*STUDY	Drug	6	Placebo	6	0.07931	0.1195	13.3	0.66	0.5184	0.05	-0.1784	0.3371
TREAT*STUDY	Drug	6	Placebo	7	0.06536	0.1082	29.1	0.60	0.5506	0.05	-0.1560	0.2867
TREAT*STUDY	Drug	7	Placebo	2	0.2764	0.1184	59.7	2.33	0.0230	0.05	0.03955	0.5133
TREAT*STUDY	Drug	7	Placebo	3	0.03666	0.1194	31.3	0.31	0.7609	0.05	-0.2069	0.2802
TREAT*STUDY	Drug	7	Placebo	4	0.2503	0.1428	20.3	1.75	0.0947	0.05	-0.04730	0.5479
TREAT*STUDY	Drug	7	Placebo	6	-2.38E-7	0.1064	28.4	-0.00	1.0000	0.05	-0.2179	0.2179
TREAT*STUDY	Drug	7	Placebo	7	-0.01395	0.08796	23.9	-0.16	0.8753	0.05	-0.1955	0.1676
TREAT*STUDY	Placebo	2	Placebo	3	-0.2398	0.1108	23.6	-2.16	0.0408	0.05	-0.4687	-0.01086
TREAT*STUDY	Placebo	2	Placebo	4	-0.02611	0.1637	29.1	-0.16	0.8744	0.05	-0.3609	0.3087
TREAT*STUDY	Placebo	2	Placebo	6	-0.2764	0.1174	27.5	-2.35	0.0259	0.05	-0.5171	-0.03575
TREAT*STUDY	Placebo	2	Placebo	7	-0.2904	0.1295	61.5	-2.24	0.0286	0.05	-0.5494	-0.03139
TREAT*STUDY	Placebo	3	Placebo	4	0.2137	0.1646	28.2	1.30	0.2047	0.05	-0.1233	0.5506
TREAT*STUDY	Placebo	3	Placebo	6	-0.03666	0.1276	28.2	-0.29	0.7759	0.05	-0.2979	0.2246
TREAT*STUDY	Placebo	3	Placebo	7	-0.05061	0.1248	33.7	-0.41	0.6876	0.05	-0.3043	0.2031
TREAT*STUDY	Placebo	4	Placebo	6	-0.2503	0.1554	24.7	-1.61	0.1200	0.05	-0.5706	0.06999
TREAT*STUDY	Placebo	4	Placebo	7	-0.2643	0.1435	20.6	-1.84	0.0799	0.05	-0.5630	0.03443
TREAT*STUDY	Placebo	6	Placebo	7	-0.01395	0.1097	29.7	-0.13	0.8997	0.05	-0.2382	0.2103

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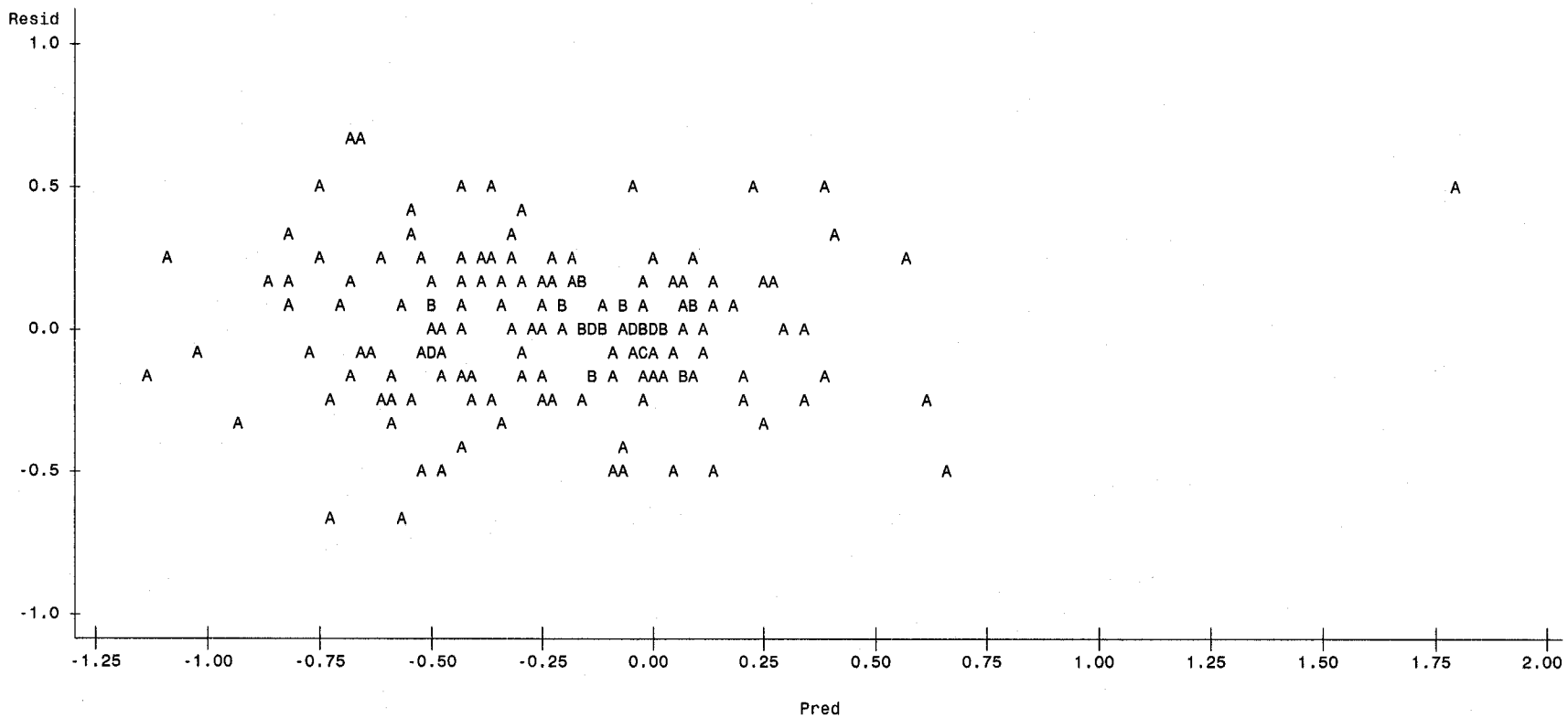
Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



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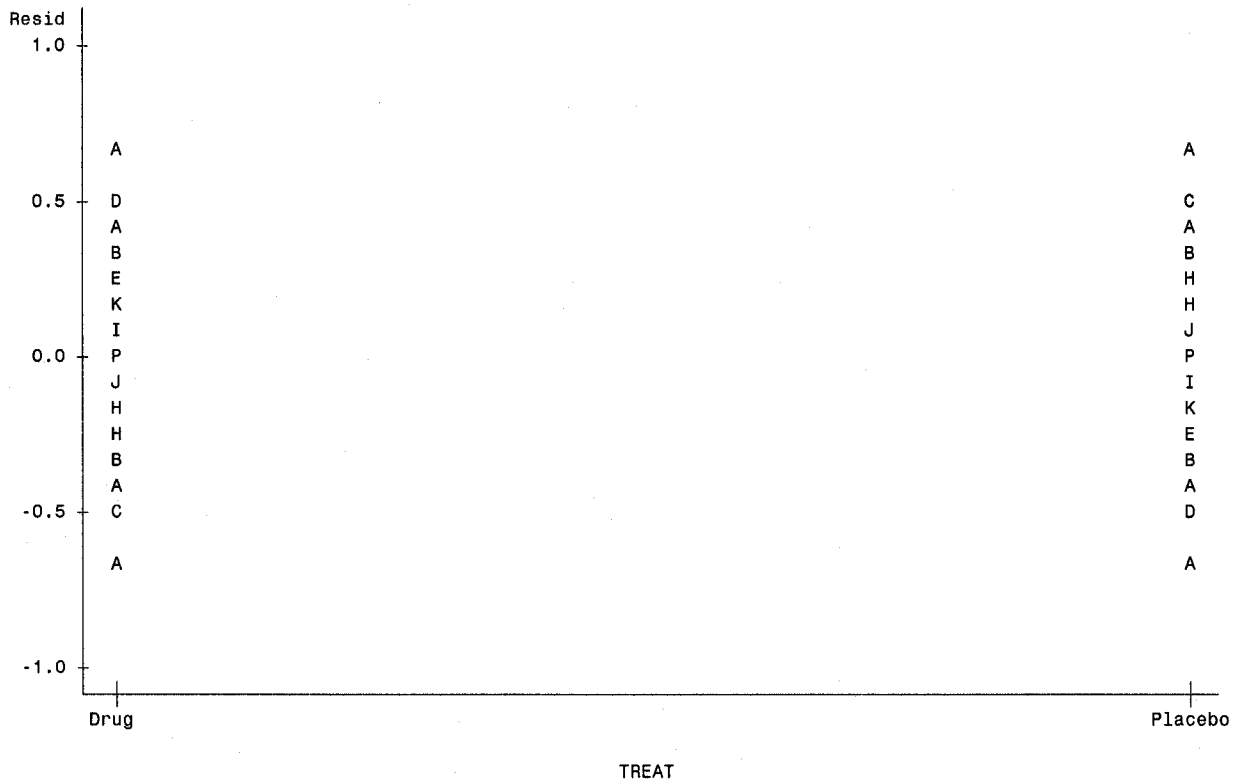
Plot of Resid*TREAT. Legend: A = 1 obs, B = 2 obs, etc.



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---------- TREAT=Drug ----------

The UNIVARIATE Procedure

Variable: Resid

Moments

N	82	Sum Weights	82
Mean	0	Sum Observations	0
Std Deviation	0.24194846	Variance	0.05853906
Skewness	0.05209861	Kurtosis	0.57934021
Uncorrected SS	4.74166377	Corrected SS	4.74166377
Coeff Variation	.	Std Error Mean	0.02671874

Basic Statistical Measures

Location		Variability	
Mean	0.000000	Std Deviation	0.24195
Median	0.010921	Variance	0.05854
Mode	.	Range	1.31104
		Interquartile Range	0.29660

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	0	Pr > |t|	1.0000
Sign	M	2	Pr >= |M|	0.7407
Signed Rank	S	2.5	Pr >= |S|	0.9909

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---------- TREAT=Drug ----------

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.98722	Pr < W	0.5960
Kolmogorov-Smirnov	D	0.074946	Pr > D	>0.1500
Cramer-von Mises	W-Sq	0.068404	Pr > W-Sq	>0.2500
Anderson-Darling	A-Sq	0.423922	Pr > A-Sq	>0.2500

Quantiles (Definition 5)

Quantile	Estimate
100% Max	0.6644732
99%	0.6644732
95%	0.4676892
90%	0.2845608
75% Q3	0.1331363
50% Median	0.0109214
25% Q1	-0.1634600
10%	-0.2554004
5%	-0.3874884
1%	-0.6465666
0% Min	-0.6465666

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---------- TREAT=Drug ----------

The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

----------Lowest----------			----------Highest----------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-0.646567	4010	4	0.467689	3046	81
-0.536801	6026	24	0.469075	7018	51
-0.511277	7002	43	0.484872	6005	18
-0.468033	4001	1	0.506875	4003	2
-0.387488	4012	5	0.664473	4017	6

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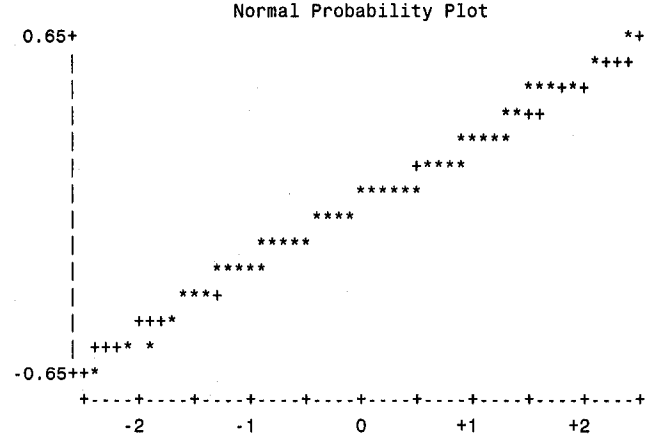
---------- TREAT=Drug ----------

The UNIVARIATE Procedure
Variable: Resid

```
Stem Leaf                     #             Boxplot
   6 6                        1                0
   5 1                        1                |
   4 2778                     4                |
   3 15                       2                |
   2 0012368                  7                |
   1 0333366779              10             +-----+
   0 011222333345566778      18             *--+--*
  -0 996555211111            12             |     |
  -1 998776542111            12             +-----+
  -2 76554322                 8                |
  -3 951                      3                |
  -4 7                        1                |
  -5 41                       2                |
  -6 5                        1                0
     ----+----+----+----+
 Multiply Stem.Leaf by 10**-1
```

Normal Probability Plot



Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

Model 1: Fixed Effects Model to Test Heterogeneity, Adjusting for Baseline NAR (Nasal Airflow Resistance and Study with Treatment by Study Interaction

Checking the Treatment by Study Interaction Term to Test for Heterogeneity

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

---------- TREAT=Placebo ----------

The UNIVARIATE Procedure

Variable: Resid

Moments

N	82	Sum Weights	82
Mean	0	Sum Observations	0
Std Deviation	0.24194846	Variance	0.05853906
Skewness	-0.0520986	Kurtosis	0.57934021
Uncorrected SS	4.74166377	Corrected SS	4.74166377
Coeff Variation	.	Std Error Mean	0.02671874

Basic Statistical Measures

Location		Variability	
Mean	0.00000	Std Deviation	0.24195
Median	-0.01092	Variance	0.05854
Mode	.	Range	1.31104
		Interquartile Range	0.29660

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	0	Pr > |t|	1.0000
Sign	M	-2	Pr >= |M|	0.7407
Signed Rank	S	-2.5	Pr >= |S|	0.9909

Meta-Analysis of Phenylephrine vs. Placebo
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Checking the Treatment by Study Interaction Term to Test for Heterogeneity
Patient Is Fixed
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

---------- TREAT=Placebo ----------

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.98722	Pr < W	0.5960
Kolmogorov-Smirnov	D	0.074946	Pr > D	>0.1500
Cramer-von Mises	W-Sq	0.068404	Pr > W-Sq	>0.2500
Anderson-Darling	A-Sq	0.423922	Pr > A-Sq	>0.2500

Quantiles (Definition 5)

Quantile	Estimate
100% Max	0.6465666
99%	0.6465666
95%	0.3874884
90%	0.2554004
75% Q3	0.1634600
50% Median	-0.0109214
25% Q1	-0.1331363
10%	-0.2845608
5%	-0.4676892
1%	-0.6644732
0% Min	-0.6644732

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes
Model 1: Fixed Effects Model to Test Heterogeneity, Adjusting for Baseline NAR (Nasal Airflow Resistance and Study with Treatment by Study Interaction
Checking the Treatment by Study Interaction Term to Test for Heterogeneity
Patient Is Fixed
Assuming Within Subject Variance Component Differs Across Studies
TO = Baseline (A Covariate)

---------- TREAT=Placebo ----------

The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

----------Lowest----------			----------Highest----------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-0.664473	4017	6	0.387488	4012	5
-0.506875	4003	2	0.468033	4001	1
-0.484872	6005	18	0.511277	7002	43
-0.469075	7018	51	0.536801	6026	24
-0.467689	3046	81	0.646567	4010	4

Meta-Analysis of Phenylephrine vs. Placebo

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Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

---------- TREAT=Placebo ----------

The UNIVARIATE Procedure

Variable: Resid

```
Stem Leaf                    #             Boxplot                                  Normal Probability Plot
   6 5                       1                0                  0.65+                                                  *+
   5 14                      2                |                     |                                             * *+++
   4 7                       1                |                     |                                           *+++
   3 159                     3                |                     |                                       +***
   2 22345567                8                |                     |                                   *****
   1 111245677899           12             +-----+                  |                               *****
   0 111112555699           12             |  +  |                  |                         +****
  -0 877665543333222110     18             *-----*                  |                    ******
  -1 9776633330             10             +-----+                  |                ****+
  -2 8632100                 7                |                     |            *****
  -3 51                      2                |                     |         ++**
  -4 8772                    4                |                     |     +*+***
  -5 1                       1                |                     | ++++
  -6 6                       1                0                 -0.65++*
     ----+----+----+----+                                           +----+----+----+----+----+----+----+----+----+----+
 Multiply Stem.Leaf by 10**-1                                           -2        -1         0        +1        +2
```

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

Model 1: Fixed Effects Model to Test Heterogeneity, Adjusting for Baseline NAR (Nasal Airflow Resistance and Study with Treatment by Study Interaction

Checking the Treatment by Study Interaction Term to Test for Heterogeneity

Patient Is Fixed

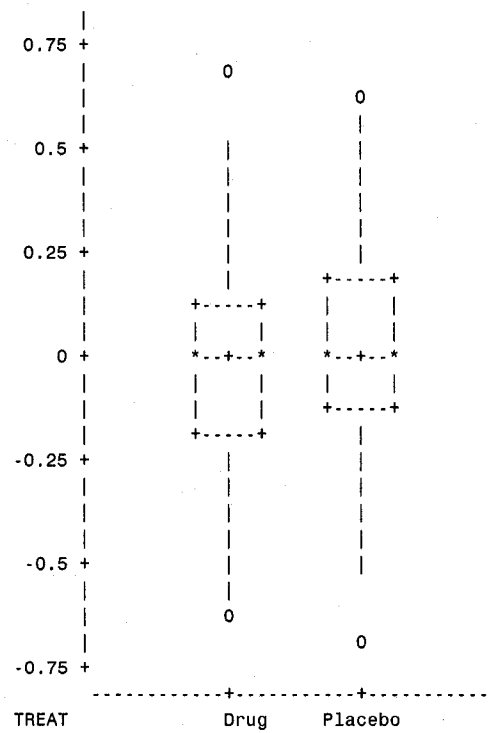
Assuming Within Subject Variance Component Differs Across Studies

TO = Baseline (A Covariate)

The UNIVARIATE Procedure

Variable: Resid

Schematic Plots



Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Model Information

Data Set	WORK.TEN_MG
Dependent Variable	LN240CHG
Covariance Structure	Variance Components
Group Effect	STUDY
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Prasad-Rao-Jeske-Kackar-Harville
Degrees of Freedom Method	Kenward-Roger

Class Level Information

Class	Levels	Values
STUDY	5	2 3 4 6 7
TREAT	2	Drug Placebo
PATIENT	82	2001 2005 2007 2012 2014 2018 2020 2021 2023 2024 3001 3003 3005 3008 3009 3015 3018 3023 3026 3032 3036 3039 3041 3044 3046 3048 4001 4003 4007 4010 4012 4017 4024 4026 4027 4030 4032 4034 4037 4039 4044 6001 6003 6005 6008 6010 6013 6017 6023 6026 6031 6034 6040 6041 6044 6046 6048 7001 7002 7003 7007 7008 7010 7014 7016 7017 7018 7020 7021 7025 7027 7028 7030 7031 7033 7034 7036 7041 7042 7044 7048 7050

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Dimensions

Covariance Parameters	5
Columns in X	91
Columns in Z	0
Subjects	164
Max Obs Per Subject	1
Observations Used	164
Observations Not Used	0
Total Observations	164

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	132.51154169	
1	2	106.12588256	0.00298806
2	1	106.05774644	0.00012048
3	1	106.05520753	0.00000024
4	1	106.05520263	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Group	Estimate
Residual	STUDY 2	0.005984
Residual	STUDY 3	0.1786
Residual	STUDY 4	0.2410

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Group	Estimate
Residual	STUDY 6	0.1118
Residual	STUDY 7	0.09151

Fit Statistics

-2 Res Log Likelihood	106.1
AIC (smaller is better)	116.1
AICC (smaller is better)	116.9
BIC (smaller is better)	131.6

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
4	26.46	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
T0	1	64.7	25.27	<.0001
PATIENT(STUDY)	77	28.6	1.68	0.0609
STUDY	4	38	3.79	0.0109
TREAT	1	16.1	0.41	0.5306

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Least Squares Means

Effect	TREAT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT	Drug	-0.2535	0.03299	63.1	-7.68	<.0001	0.05	-0.3194	-0.1876
TREAT	Placebo	-0.2331	0.03317	65.8	-7.03	<.0001	0.05	-0.2993	-0.1669

Differences of Least Squares Means

Effect	TREAT	TREAT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT	Drug	Placebo	-0.02041	0.03184	16.1	-0.64	0.5306	0.05	-0.08788	0.04707

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

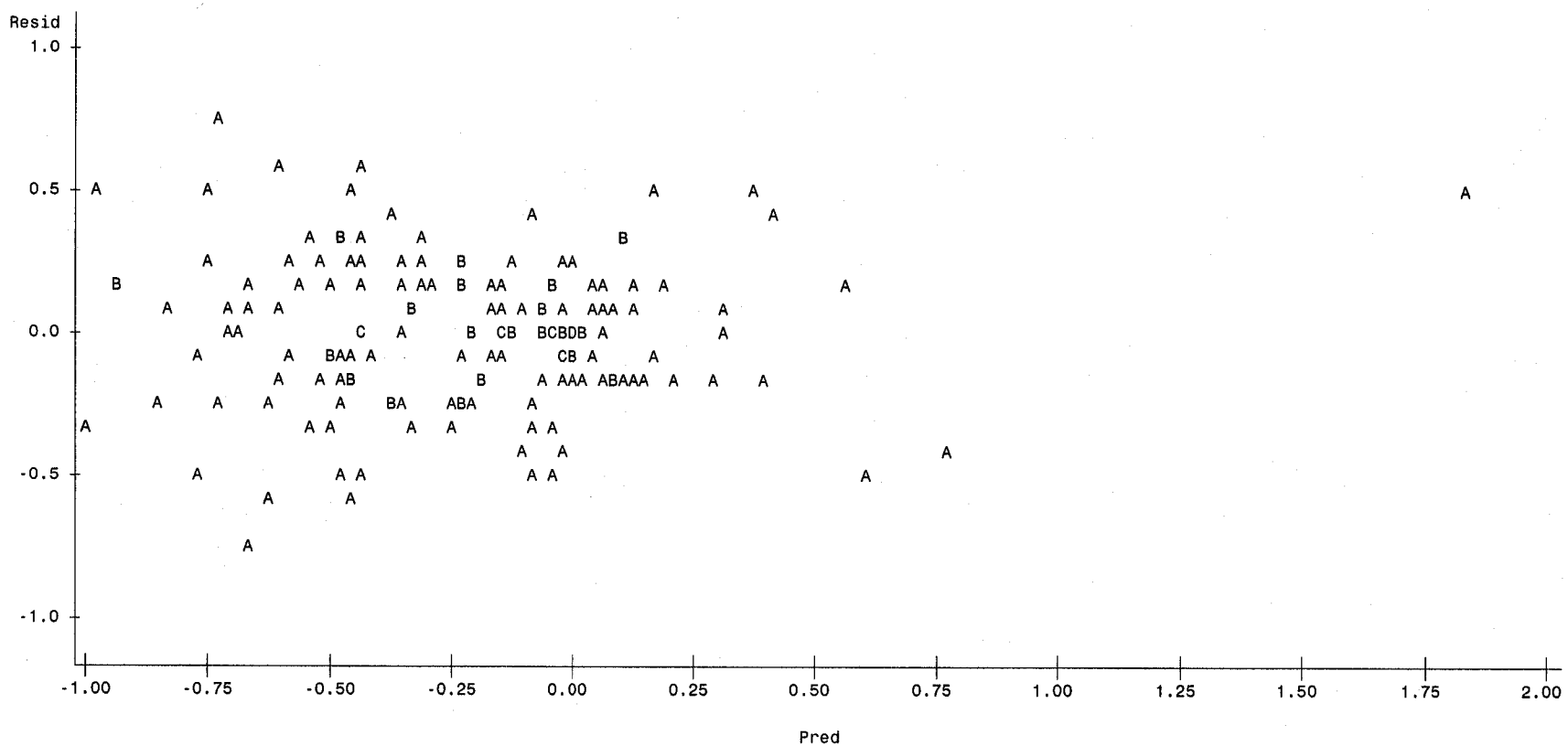
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

Plot of Resid*Pred. Legend: A = 1 obs, B = 2 obs, etc.



Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

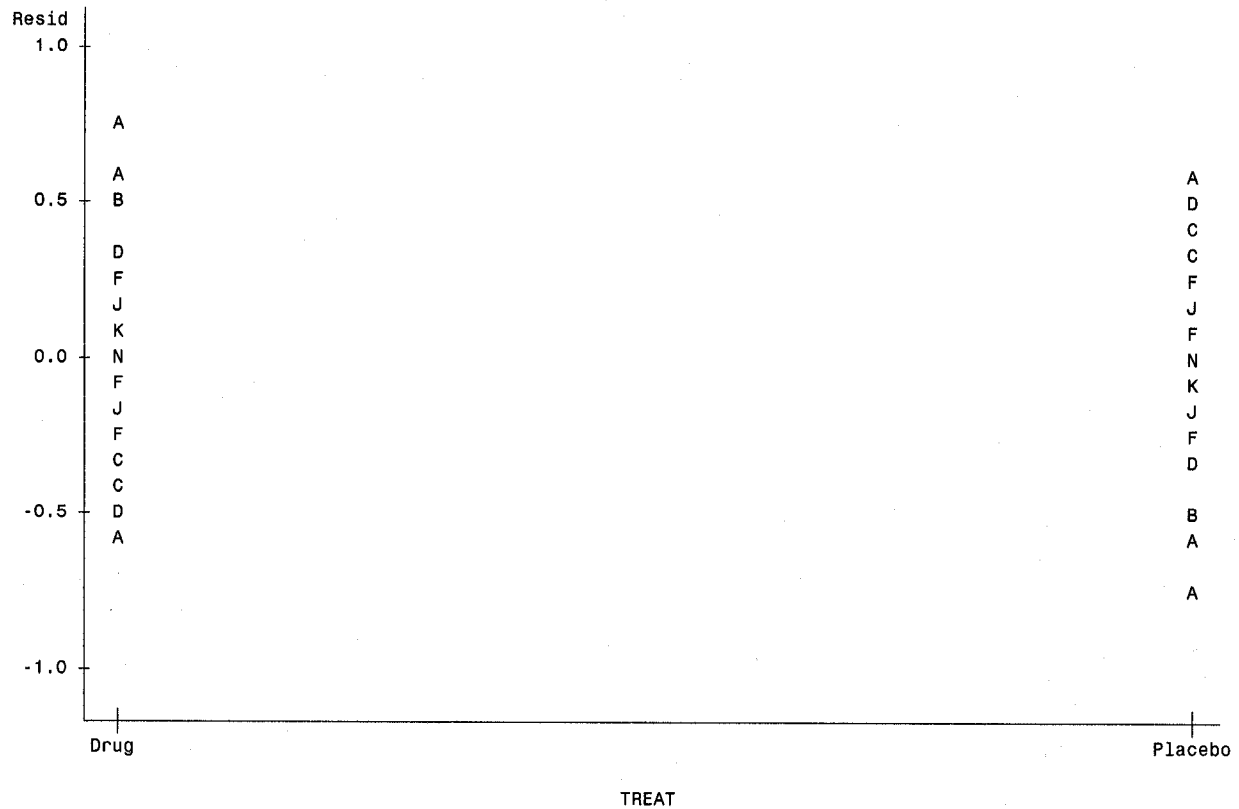
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

Plot of Resid*TREAT. Legend: A = 1 obs, B = 2 obs, etc.



Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

---------- TREAT=Drug ----------

The UNIVARIATE Procedure

Variable: Resid

Moments

N	82	Sum Weights	82
Mean	-0.0083496	Sum Observations	-0.6846685
Std Deviation	0.25388623	Variance	0.06445822
Skewness	0.08657692	Kurtosis	0.32526394
Uncorrected SS	5.22683224	Corrected SS	5.22111552
Coeff Variation	-3040.6934	Std Error Mean	0.02803704

Basic Statistical Measures

Location		Variability	
Mean	-0.00835	Std Deviation	0.25389
Median	0.01816	Variance	0.06446
Mode	.	Range	1.31129
		Interquartile Range	0.30094

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	-0.29781	Pr > |t|	0.7666
Sign	M	3	Pr >= |M|	0.5811
Signed Rank	S	-33.5	Pr >= |S|	0.8780

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Fixed
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

---------- TREAT=Drug ----------

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.987118	Pr < W	0.5892
Kolmogorov-Smirnov	D	0.07788	Pr > D	>0.1500
Cramer-von Mises	W-Sq	0.058992	Pr > W-Sq	>0.2500
Anderson-Darling	A-Sq	0.357448	Pr > A-Sq	>0.2500

Quantiles (Definition 5)

Quantile	Estimate
100% Max	0.7262818
99%	0.7262818
95%	0.3544724
90%	0.2778220
75% Q3	0.1369551
50% Median	0.0181559
25% Q1	-0.1639818
10%	-0.3310908
5%	-0.4672011
1%	-0.5850113
0% Min	-0.5850113

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Fixed
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

---------- TREAT=Drug ----------

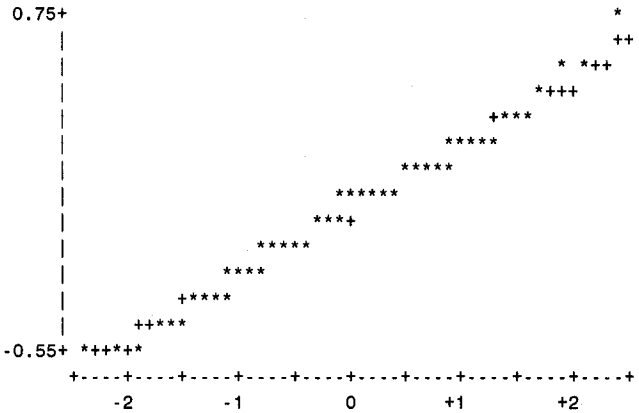
The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

Lowest			Highest		
Value	PATIENT	Obs	Value	PATIENT	Obs
-0.585011	4010	4	0.354472	7020	52
-0.510903	3008	70	0.470005	7018	51
-0.509468	7002	43	0.533564	6005	18
-0.481015	6026	24	0.568194	4003	2
-0.467201	3005	69	0.726282	4017	6

```
Stem Leaf                     #             Boxplot
   7 3                        1                0
   6                                           |
   5 37                       2                |
   4 7                        1                |
   3 0115                     4                |
   2 00122368                 8                |
   1 001233445699            12             +-----+
   0 1122233444456678        16             *-----*
  -0 65521100                8             |  +  |
  -1 996654443100            12             +-----+
  -2 8755511                 7                |
  -3 88332                   5                |
  -4 871                     3                |
  -5 911                     3                |
     ----+----+----+----+
 Multiply Stem.Leaf by 10**-1
```

Normal Probability Plot



Meta-Analysis of Phenylephrine vs. Placebo
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---------- TREAT=Placebo ----------

The UNIVARIATE Procedure
Variable: Resid

Moments

N	82	Sum Weights	82
Mean	0.00834962	Sum Observations	0.68466851
Std Deviation	0.25388623	Variance	0.06445822
Skewness	-0.0865769	Kurtosis	0.32526394
Uncorrected SS	5.22683224	Corrected SS	5.22111552
Coeff Variation	3040.69344	Std Error Mean	0.02803704

Basic Statistical Measures

Location		Variability	
Mean	0.00835	Std Deviation	0.25389
Median	-0.01816	Variance	0.06446
Mode	.	Range	1.31129
		Interquartile Range	0.30094

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	0.297807	Pr > |t|	0.7666
Sign	M	-3	Pr >= |M|	0.5811
Signed Rank	S	33.5	Pr >= |S|	0.8780

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---------- TREAT=Placebo ----------

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.987118	Pr < W	0.5892
Kolmogorov-Smirnov	D	0.07788	Pr > D	>0.1500
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Quantiles (Definition 5)

Quantile	Estimate
100% Max	0.5850113
99%	0.5850113
95%	0.4672011
90%	0.3310908
75% Q3	0.1639818
50% Median	-0.0181559
25% Q1	-0.1369551
10%	-0.2778220
5%	-0.3544724
1%	-0.7262818
0% Min	-0.7262818

Meta-Analysis of Phenylephrine vs. Placebo

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Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

---------- TREAT=Placebo ----------

The UNIVARIATE Procedure

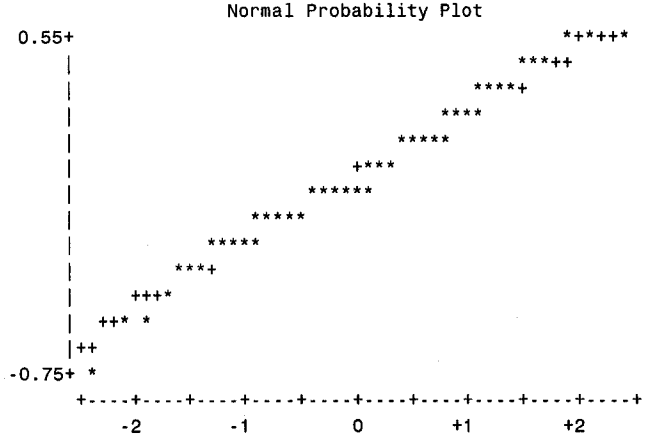
Variable: Resid

Extreme Observations

Lowest			Highest		
Value	PATIENT	Obs	Value	PATIENT	Obs
-0.726282	4017	6	0.467201	3005	69
-0.568194	4003	2	0.481015	6026	24
-0.533564	6005	18	0.509468	7002	43
-0.470005	7018	51	0.510903	3008	70
-0.354472	7020	52	0.585011	4010	4

```
Stem Leaf                     #             Boxplot
   5 119                      3                |
   4 178                      3                |
   3 23388                    5                |
   2 1155578                  7                |
   1 001344456699            12             +-----+
   0 00112556                 8             |  +  |
  -0 8766544443322211        16             *-----*
  -1 996544332100            12             +-----+
  -2 86322100                 8                |
  -3 5110                     4                |
  -4 7                        1                |
  -5 73                       2                |
  -6                                           |
  -7 3                        1                0
     ----+----+----+----+
 Multiply Stem.Leaf by 10**-1
```

Normal Probability Plot



Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: LN-Ratio (Post-baseline Nasal Airflow Resistance / Baseline Nasal Airflow Resistance) at 240 Minutes

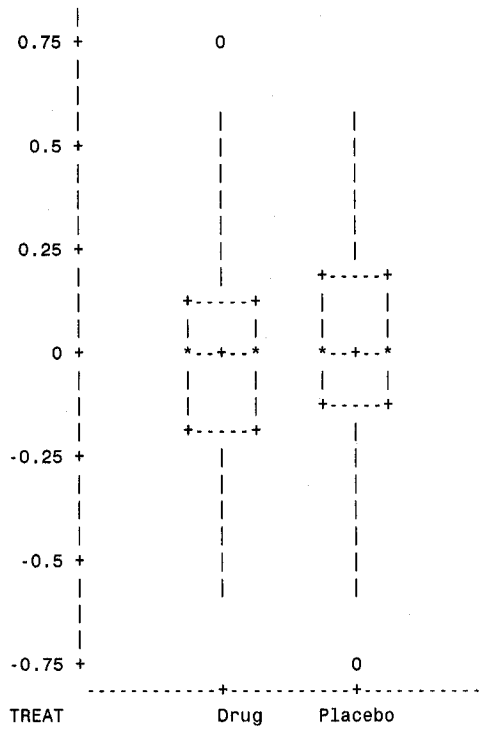
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The UNIVARIATE Procedure

Variable: Resid

Schematic Plots