Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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 Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure

Variable: Resid

```
Stem Leaf                          #          Boxplot                          Normal Probability Plot
  12 8                             1             *                  12.5+                                                  *
  11                                                                   |
  10                                                                   |
   9                                                                   |
   8                                                                   |
   7 0                             1             0                     |                                              *  +
   6 6                             1             0                     |                                           *++++
   5 007                           3             0                   5.5+                                        *+*+
   4 0444                          4             |                     |                                     ***+
   3 456                           3             |                     |                                  +***
   2 00113                         5             |                     |                              ++++**
   1 002223445555689              15          +-----+                  |                           ++******
   0 0222244444444555667889999    25          *--+--*                  |                       ******
  -0 98887755554421111100         20          |     |                  |                   ******
  -1 987766433311                 12          +-----+                -1.5+                ****+
  -2 86432200                      8             |                     |             ***++
  -3 8855220                       7             |                     |         *****
  -4 510                           3             |                     |       +*++
  -5 7                             1             |                     |     +++*
  -6 320                           3             0                     | ++*+**
  -7                                                                   |+
  -8 7                             1             0                  -8.5+*
     ----+----+----+----+----+                                          +----+----+----+----+----+----+----+----+----+----+
                                                                            -2        -1         0        +1        +2
```

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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 Random
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Moments

N	113	Sum Weights	113
Mean	0	Sum Observations	0
Std Deviation	2.55524073	Variance	6.5292552
Skewness	0.54696367	Kurtosis	2.47220782
Uncorrected SS	731.276583	Corrected SS	731.276583
Coeff Variation	.	Std Error Mean	0.24037683

Basic Statistical Measures

Location		Variability	
Mean	0.00000	Std Deviation	2.55524
Median	-0.05707	Variance	6.52926
Mode	.	Range	17.73373
		Interquartile Range	2.57930

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	0	Pr > |t|	1.0000
Sign	M	-5.5	Pr >= |M|	0.3469
Signed Rank	S	-167.5	Pr >= |S|	0.6334

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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 Random
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	0.957049	Pr < W	0.0011
Kolmogorov-Smirnov	D	0.117658	Pr > D	<0.0100
Cramer-von Mises	W-Sq	0.313299	Pr > W-Sq	<0.0050
Anderson-Darling	A-Sq	1.552702	Pr > A-Sq	<0.0050

Quantiles (Definition 5)

Quantile	Estimate
100% Max	10.1565026
99%	7.6407600
95%	3.7383425
90%	3.2870302
75% Q3	1.1457209
50% Median	-0.0570745
25% Q1	-1.4335773
10%	-3.0689066
5%	-3.7567882
1%	-6.0283250
0% Min	-7.5772270

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
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Checking the Treatment by Study Interaction Term to Test for Heterogeneity
Patient Is Random
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
-7.57723	5043	96	4.59172	6008	19
-6.02832	7042	63	4.68436	7001	42
-4.77175	7003	44	6.01668	4037	13
-4.47744	7021	53	7.64076	5029	91
-4.07374	3018	73	10.15650	3026	75

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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 Random
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

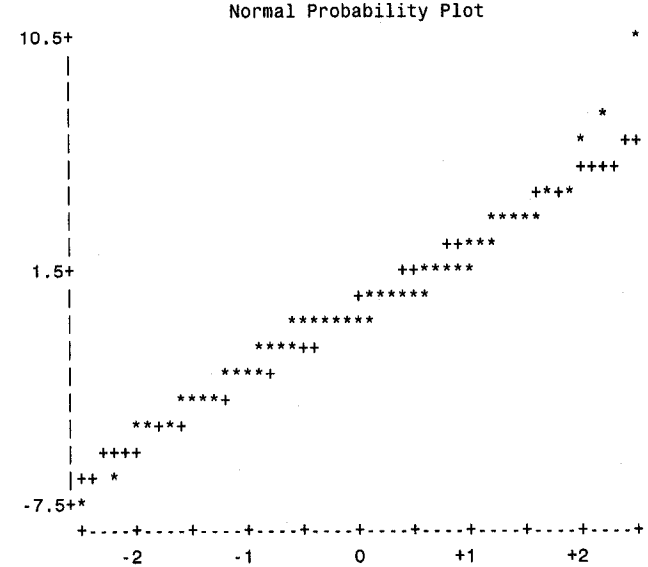
---------- TREAT=Placebo ----------

The UNIVARIATE Procedure
Variable: Resid

Stem	Leaf	#	Boxplot
10	2	1	*
9			
8			
7	6	1	0
6	0	1	0
5			
4	67	2	|
3	023456777	9	|
2	1468	4	|
1	00112223677889	14	+-----+
0	0012222223344455579	19	| + |
-0	887776655544433322221111100000	30	*-----*
-1	9876664421	10	+-----+
-2	9987322000	10	|
-3	8774311	7	|
-4	851	3	|
-5			
-6	0	1	0
-7	6	1	0

----+----+----+----+----+----+

Normal Probability Plot



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Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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 Random
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

The UNIVARIATE Procedure
Variable: Resid

Schematic Plots

```
      |
   15 +
      |
      |          *
      |
   10 +                       *
      |
      |          0           0
      |          0           0
    5 +          |           |
      |          |           |
      |          |           |
      |       +-----+     +-----+
    0 +       *--+--*     *--+--*
      |       +-----+     +-----+
      |          |           |
      |          |           |
   -5 +          |           |
      |          0           0
      |                      0
      |          0
  -10 +
       ------------+-----------+-----------
TREAT             Drug     Placebo
```

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

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

Patient Is Random

Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies

TO = Baseline (A Covariate)

The Mixed Procedure

Model Information

Data Set	WORK.TEN_MG
Dependent Variable	T45CHG
Covariance Structure	Compound Symmetry
Subject Effect	PATIENT(STUDY)
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	7	1 2 3 4 5 6 7
TREAT	2	Drug Placebo

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

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

Patient Is Random

Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies

TO = Baseline (A Covariate)

The Mixed Procedure

Class Level Information

Class	Levels	Values
PATIENT	113	1002 1007 1008 1011 1013 1016 1017 1018 1020 1026 1030 1031 1034 1035 1037 1038 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 5001 5010 5013 5015 5021 5022 5025 5027 5029 5030 5032 5034 5035 5043 5046 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	14
Columns in X	11
Columns in Z	0
Subjects	113
Max Obs Per Subject	2
Observations Used	226

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
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Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
TO = Baseline (A Covariate)

The Mixed Procedure

Dimensions

Observations Not Used	0
Total Observations	226

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1304.54918198	
1	2	1207.01267372	0.03908759
2	1	1205.04245197	0.00199292
3	1	1204.16975058	0.00009977
4	1	1204.12789354	0.00000050
5	1	1204.12769092	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
Variance	PATIENT(STUDY)	STUDY 1	6.8141
CS	PATIENT(STUDY)	STUDY 1	-2.0068
Variance	PATIENT(STUDY)	STUDY 2	1.1526
CS	PATIENT(STUDY)	STUDY 2	-0.2107
Variance	PATIENT(STUDY)	STUDY 3	14.7243
CS	PATIENT(STUDY)	STUDY 3	-1.9774
Variance	PATIENT(STUDY)	STUDY 4	12.9930
CS	PATIENT(STUDY)	STUDY 4	4.5009

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

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

Patient Is Random

Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies

TO = Baseline (A Covariate)

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
Variance	PATIENT(STUDY)	STUDY 5	16.8748
CS	PATIENT(STUDY)	STUDY 5	-5.5207
Variance	PATIENT(STUDY)	STUDY 6	16.5762
CS	PATIENT(STUDY)	STUDY 6	2.9902
Variance	PATIENT(STUDY)	STUDY 7	30.5229
CS	PATIENT(STUDY)	STUDY 7	25.9311

Fit Statistics

-2 Res Log Likelihood	1204.1
AIC (smaller is better)	1232.1
AICC (smaller is better)	1234.2
BIC (smaller is better)	1270.3

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
13	100.42	<.0001

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
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Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
T0 = Baseline (A Covariate)

The Mixed Procedure

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
T0	1	119	8.91	0.0035
STUDY	6	44.3	2.54	0.0335
TREAT	1	16.2	44.63	<.0001

Least Squares Means

Effect	TREAT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT	Drug	-3.2243	0.3439	74.6	-9.38	<.0001	0.05	-3.9094	-2.5392
TREAT	Placebo	-0.5110	0.3450	74.9	-1.48	0.1428	0.05	-1.1984	0.1763

Differences of Least Squares Means

Effect	TREAT	TREAT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT	Drug	Placebo	-2.7133	0.4061	16.2	-6.68	<.0001	0.05	-3.5732	-1.8533

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

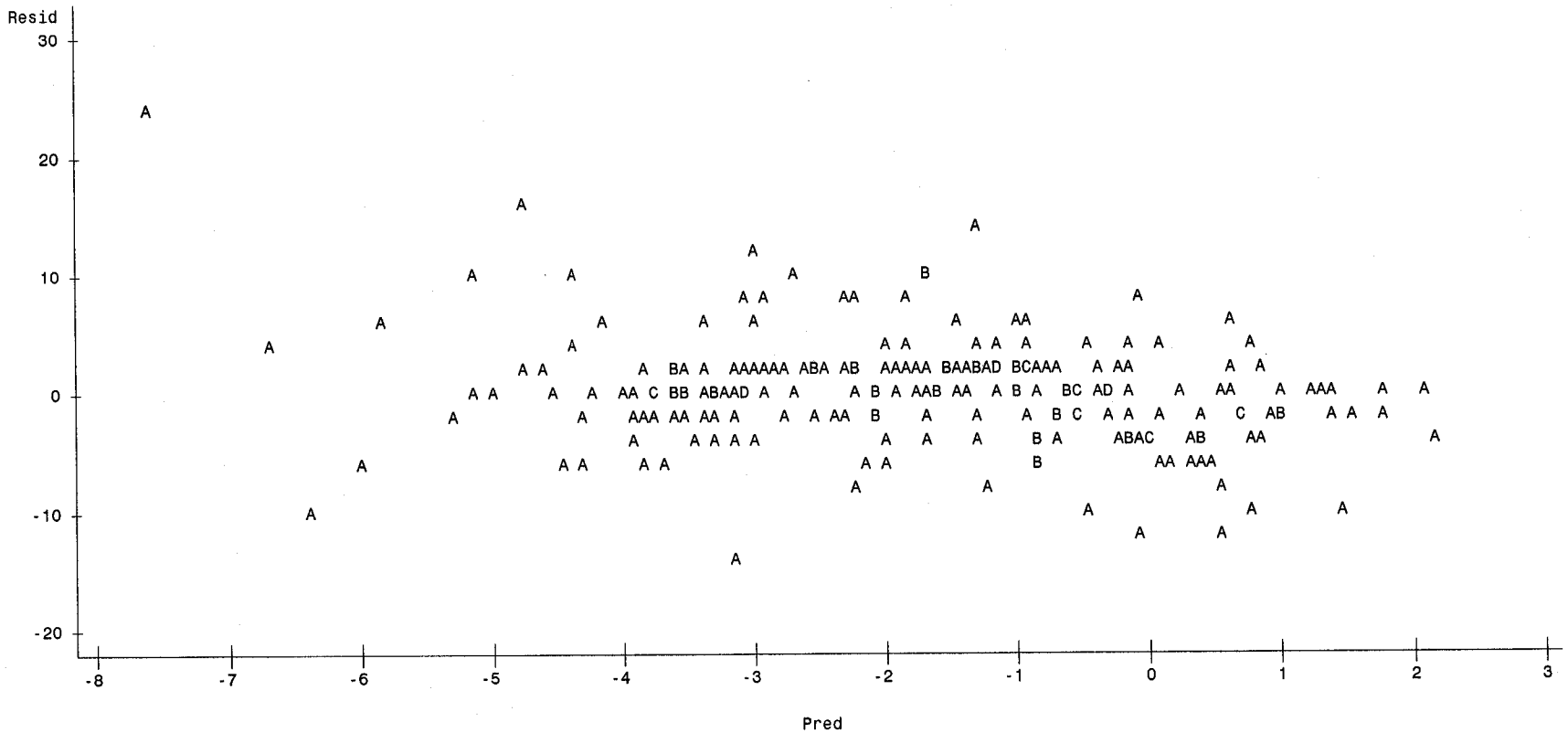
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Random

Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies

T0 = Baseline (A Covariate)

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



Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

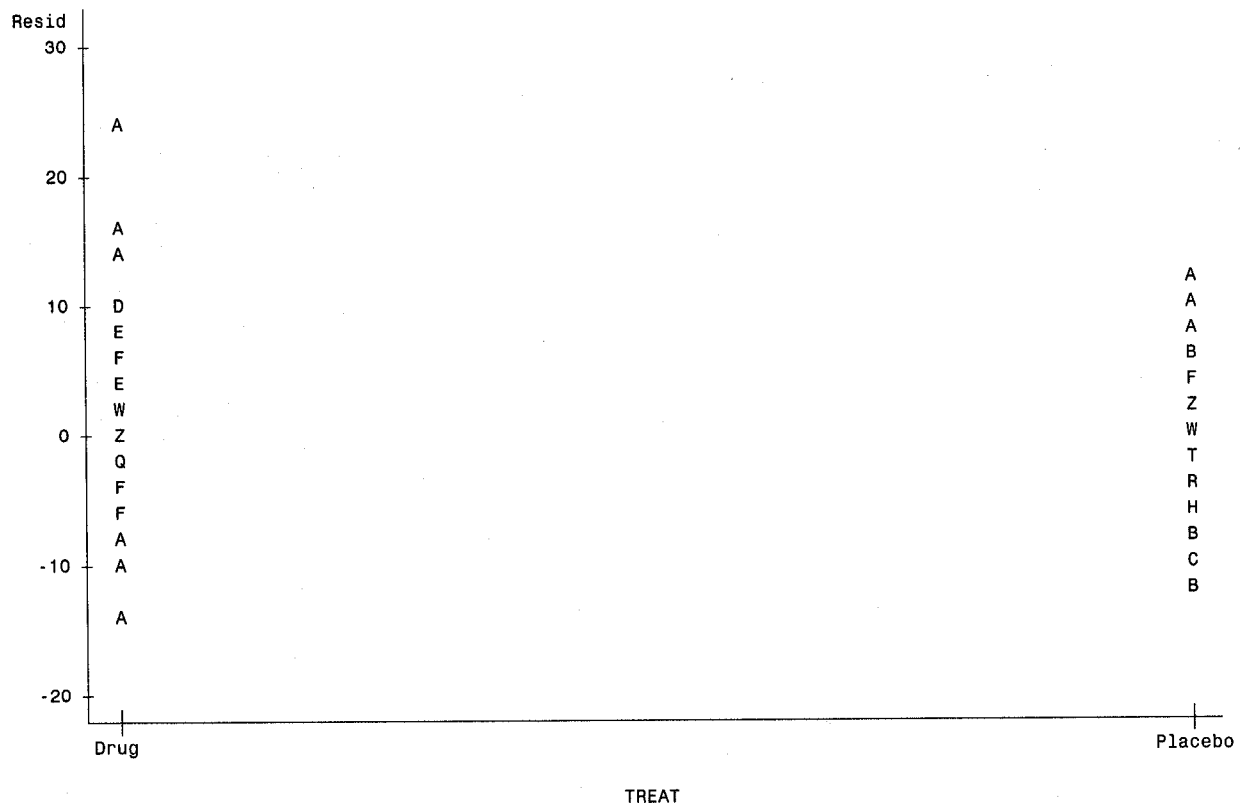
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

Patient Is Random

Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies

T0 = Baseline (A Covariate)

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



NOTE: 9 obs hidden.

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Moments

N	113	Sum Weights	113
Mean	0.93850473	Sum Observations	106.051034
Std Deviation	4.94755633	Variance	24.4783136
Skewness	1.22154932	Kurtosis	5.50714153
Uncorrected SS	2841.10052	Corrected SS	2741.57113
Coeff Variation	527.174364	Std Error Mean	0.46542695

Basic Statistical Measures

Location		Variability	
Mean	0.938505	Std Deviation	4.94756
Median	0.392723	Variance	24.47831
Mode	.	Range	39.61479
		Interquartile Range	3.63786

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	2.016438	Pr > |t|	0.0461
Sign	M	13.5	Pr >= |M|	0.0141
Signed Rank	S	619.5	Pr >= |S|	0.0758

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.894387	Pr < W	<0.0001
Kolmogorov-Smirnov	D	0.163884	Pr > D	<0.0100
Cramer-von Mises	W-Sq	0.691058	Pr > W-Sq	<0.0050
Anderson-Darling	A-Sq	3.490028	Pr > A-Sq	<0.0050

Quantiles (Definition 5)

Quantile	Estimate
100% Max	24.799692
99%	16.736172
95%	9.786149
90%	7.258138
75% Q3	2.164174
50% Median	0.392723
25% Q1	-1.473683
10%	-4.339680
5%	-5.720377
1%	-9.188675
0% Min	-14.815103

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
TO = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

----------Lowest----------			----------Highest----------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-14.81510	7030	57	9.80257	6046	30
-9.18868	3001	67	9.93533	7044	64
-7.70355	7020	52	13.90820	7021	53
-6.06159	7048	65	16.73617	7002	43
-5.80397	6003	17	24.79969	7042	63

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
T0 = Baseline (A Covariate)

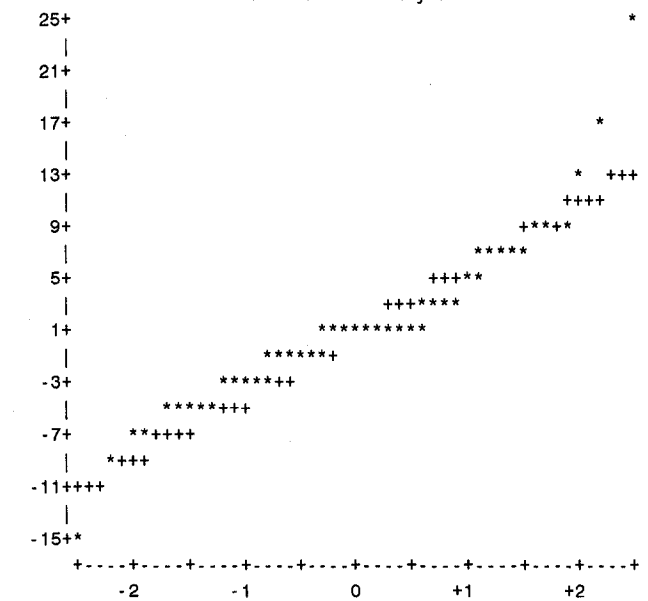
---------- TREAT=Drug ----------

The UNIVARIATE Procedure
Variable: Resid

Stem	Leaf	#	Boxplot
24	8	1	*
22			
20			
18			
16	7	1	*
14			
12	9	1	*
10			
8	00889	5	0
6	0573478	7	0
4	9128	4	|
2	012238884488	12	+-----+
0	000111222233344555678999000112233334679	39	*--+--*
-0	85521199765443332	17	+-----+
-2	22207655533320	14	|
-4	87433743	8	|
-6	71	2	0
-8	2	1	0
-10			
-12			
-14	8	1	*

----+----+----+----+----+----+----+----

Normal Probability Plot



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Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Moments

N	113	Sum Weights	113
Mean	-0.9385047	Sum Observations	-106.05103
Std Deviation	3.98552418	Variance	15.884403
Skewness	-0.1142127	Kurtosis	1.19085796
Uncorrected SS	1878.58253	Corrected SS	1779.05313
Coeff Variation	-424.66746	Std Error Mean	0.37492658

Basic Statistical Measures

Location		Variability	
Mean	-0.93850	Std Deviation	3.98552
Median	-0.61704	Variance	15.88440
Mode	1.54666	Range	24.45778
		Interquartile Range	4.89545

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	-2.50317	Pr > |t|	0.0138
Sign	M	-4.5	Pr >= |M|	0.4519
Signed Rank	S	-821.5	Pr >= |S|	0.0179

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.976485	Pr < W	0.0436
Kolmogorov-Smirnov	D	0.081513	Pr > D	0.0650
Cramer-von Mises	W-Sq	0.139616	Pr > W-Sq	0.0338
Anderson-Darling	A-Sq	0.897623	Pr > A-Sq	0.0222

Quantiles (Definition 5)

Quantile	Estimate
100% Max	12.026873
99%	9.580222
95%	4.981640
90%	2.962853
75% Q3	1.543511
50% Median	-0.617044
25% Q1	-3.351938
10%	-5.385915
5%	-8.585146
1%	-11.271500
0% Min	-12.430907

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

----------Lowest----------			----------Highest----------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-12.43091	7030	57	5.88485	5029	91
-11.27150	7048	65	6.50281	7028	56
-10.22840	7014	48	7.47563	4037	13
-9.13051	5043	96	9.58022	3026	75
-9.05509	7027	55	12.02687	7002	43

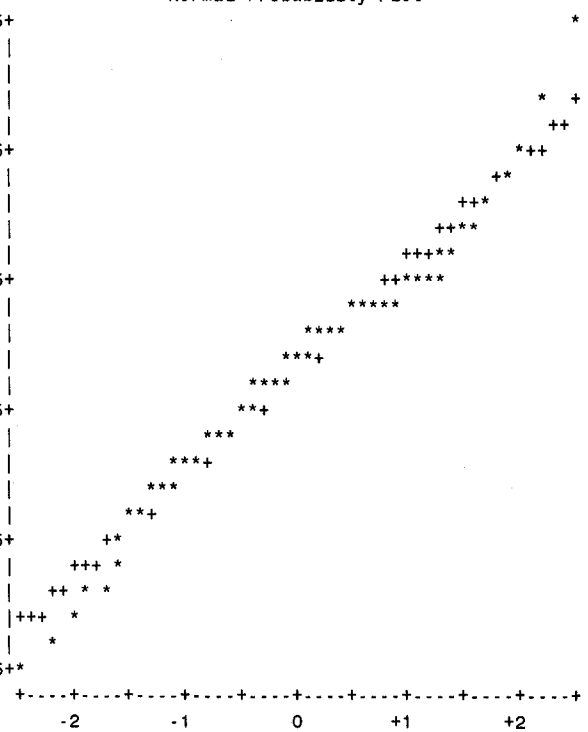
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Stem	Leaf	#	Boxplot
12	0	1	0
11			
10			
9	6	1	0
8			
7	5	1	|
6	5	1	|
5	09	2	|
4	46	2	|
3	0122	4	|
2	2225579	7	|
1	111334455556679999	18	+-----+
0	111222344466789	15	| |
-0	9762220	7	*--+--*
-1	977643221100	12	| |
-2	333221000	9	| |
-3	98865442100	11	+-----+
-4	9997751	7	|
-5	74322	5	|
-6	877	3	|
-7	8	1	|
-8	6	1	|
-9	11	2	|
-10	2	1	|
-11	3	1	0
-12	4	1	0
	----+----+----+----+		

Normal Probability Plot



Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction
Patient Is Random
Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies
TO = Baseline (A Covariate)

The UNIVARIATE Procedure
Variable: Resid

Schematic Plots

```
     |
  30 +
     |
     |          *
     |
  20 +
     |          *
     |          *
     |                     0
  10 +          0          0
     |          0          |
     |          |          |
     |       +-----+     +-----+
   0 +       *--+--*     *--+--*
     |       +-----+     +-----+
     |          |          |
     |          0          |
 -10 +          0          |
     |                     0
     |          *
     |
 -20 +
       ----------+----------+----------
TREAT            Drug     Placebo
```

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

The Mixed Procedure

Model Information

Data Set	WORK.TEN_MG
Dependent Variable	T45CHG
Covariance Structures	Variance Components, Compound Symmetry
Subject Effect	PATIENT(STUDY)
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	7	1 2 3 4 5 6 7
TREAT	2	Drug Placebo

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

The Mixed Procedure

Class Level Information

Class	Levels	Values
PATIENT	113	1002 1007 1008 1011 1013 1016 1017 1018 1020 1026 1030 1031 1034 1035 1037 1038 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 5001 5010 5013 5015 5021 5022 5025 5027 5029 5030 5032 5034 5035 5043 5046 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	16
Columns in X	4
Columns in Z	21
Subjects	1
Max Obs Per Subject	226
Observations Used	226
Observations Not Used	0

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

The Mixed Procedure

Dimensions

Total Observations	226

Parameter Search

CovP1	CovP2	CovP3	CovP4	CovP5	CovP6	CovP7	CovP8	CovP9	CovP10	CovP11	CovP12	CovP13	CovP14	CovP15
0.2000	0.2000	0.2000	0.2000	0.2000	0.2000	0.2000	0.2000	0.2000	0.2000	0.2000	0.2000	0.2000	0.2000	0.2000

Parameter Search

CovP16	Res Log Like	-2 Res Log Like
0.2000	-5685.0496	11370.0992

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
1	2	7768.12486146	0.48459049
2	1	5394.29424684	0.46920891
3	1	3838.35028545	0.44404054
4	1	2826.47313359	0.40571168
5	3	1808.90881908	0.29419329
6	1	1536.85511498	0.22095945
7	1	1372.85178685	0.14971216
8	1	1278.45316397	0.08972382
9	1	1227.87691790	0.04640368
10	1	1203.56456761	0.01990829
11	1	1193.64482090	0.00647005

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
12	1	1190.56882977	0.00128025
13	1	1189.99705665	0.00009379
14	1	1189.95835960	0.00000086
15	1	1189.95802228	0.00000000

Convergence criteria met.

Estimated R Matrix
for Subject 1

Row	Col1	Col2
1	2.3433	0.4760
2	0.4760	2.3433

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
STUDY			0
STUDY*TREAT			2.7062
Variance	PATIENT(STUDY)	STUDY 1	1.8673
CS	PATIENT(STUDY)	STUDY 1	0.4760
Variance	PATIENT(STUDY)	STUDY 2	0.8910
CS	PATIENT(STUDY)	STUDY 2	-0.08085
Variance	PATIENT(STUDY)	STUDY 3	15.1388
CS	PATIENT(STUDY)	STUDY 3	-2.2219

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
Variance	PATIENT(STUDY)	STUDY 4	8.7726
CS	PATIENT(STUDY)	STUDY 4	6.3058
Variance	PATIENT(STUDY)	STUDY 5	14.1277
CS	PATIENT(STUDY)	STUDY 5	-4.1791
Variance	PATIENT(STUDY)	STUDY 6	10.1008
CS	PATIENT(STUDY)	STUDY 6	6.0918
Variance	PATIENT(STUDY)	STUDY 7	21.2690
CS	PATIENT(STUDY)	STUDY 7	30.5480

Fit Statistics

-2 Res Log Likelihood	1190.0
AIC (smaller is better)	1220.0
AICC (smaller is better)	1222.3
BIC (smaller is better)	1219.1

PARMS Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
15	10180.14	<.0001

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

The Mixed Procedure

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
T0	1	139	10.40	0.0016
TREAT	1	11.6	2.02	0.1816

Least Squares Means

Effect	TREAT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT	Drug	-2.7464	0.7055	12.3	-3.89	0.0020	0.05	-4.2791	-1.2138
TREAT	Placebo	-1.3658	0.7065	12.4	-1.93	0.0763	0.05	-2.8994	0.1678

Differences of Least Squares Means

Effect	TREAT	TREAT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT	Drug	Placebo	-1.3806	0.9715	11.6	-1.42	0.1816	0.05	-3.5051	0.7438

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

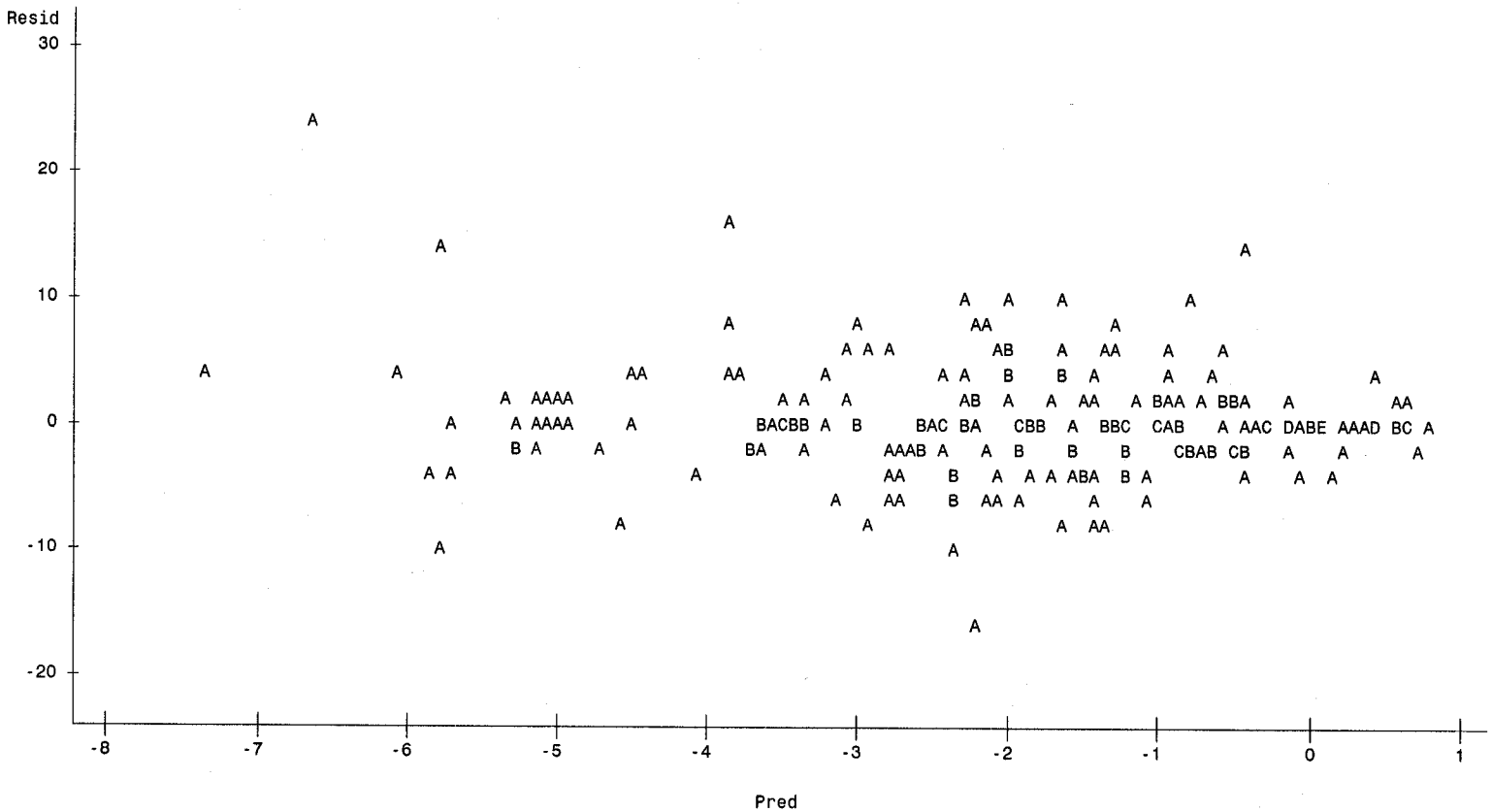
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR

Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance

Patient, Study, and Study by Treatment Interaction Are Random

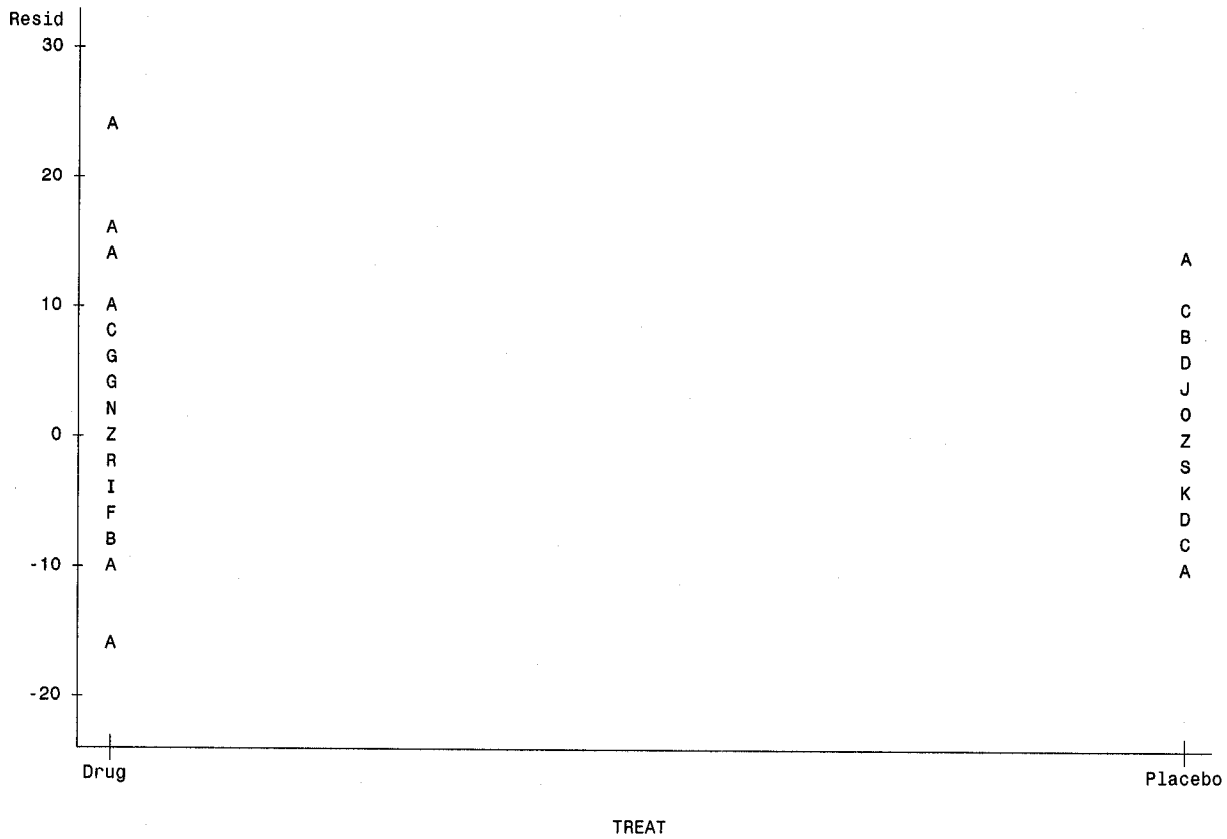
T0 = Baseline (A Covariate)

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



Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

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



NOTE: 29 obs hidden.

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Moments

N	113	Sum Weights	113
Mean	0.40060541	Sum Observations	45.2684112
Std Deviation	4.8041554	Variance	23.0799091
Skewness	1.11901759	Kurtosis	5.97869558
Uncorrected SS	2603.08459	Corrected SS	2584.94982
Coeff Variation	1199.2238	Std Error Mean	0.45193692

Basic Statistical Measures

Location		Variability	
Mean	0.400605	Std Deviation	4.80416
Median	0.070070	Variance	23.07991
Mode	.	Range	39.52555
		Interquartile Range	3.25670

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	0.886419	Pr > |t|	0.3773
Sign	M	1.5	Pr >= |M|	0.8509
Signed Rank	S	101.5	Pr >= |S|	0.7727

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.893068	Pr < W	<0.0001
Kolmogorov-Smirnov	D	0.158303	Pr > D	<0.0100
Cramer-von Mises	W-Sq	0.661716	Pr > W-Sq	<0.0050
Anderson-Darling	A-Sq	3.398049	Pr > A-Sq	<0.0050

Quantiles (Definition 5)

Quantile	Estimate
100% Max	23.8260538
99%	15.8187433
95%	8.3981458
90%	5.8803194
75% Q3	1.6212369
50% Median	0.0700703
25% Q1	-1.6354624
10%	-4.0789334
5%	-6.4008825
1%	-9.7809562
0% Min	-15.6994927

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

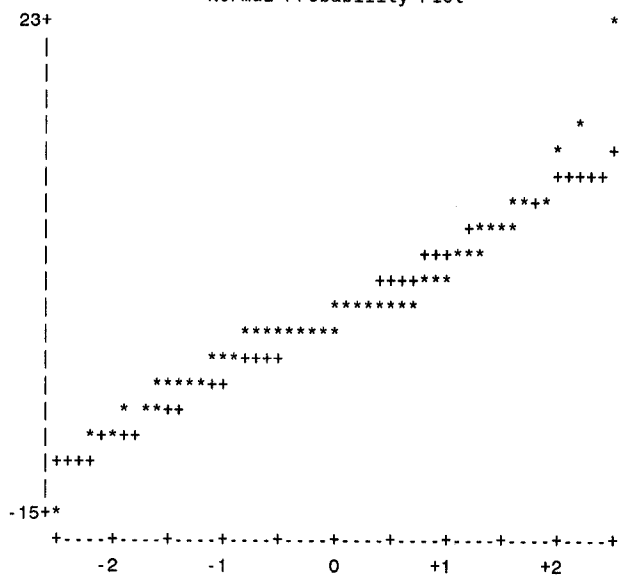
----------Lowest----------			----------Highest---------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-15.69949	7030	57	8.52089	4024	7
-9.78096	3001	67	9.08012	7044	64
-8.57035	7020	52	13.06007	7021	53
-7.24035	6003	17	15.81874	7002	43
-6.92302	7048	65	23.82605	7042	63

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

```
Stem Leaf                                  #             Boxplot                                  Normal Probability Plot
  22 8                                     1                *                    23+                                                  *
  20                                                                               |
  18                                                                               |
  16                                                                               |
  14 8                                     1                *                    |                                              *
  12 1                                     1                *                    |                                           *    +
  10                                                                               |                                           +++++
   8 451                                   3                0                    |                                       **+*
   6 58906                                 5                0                    |                                   +****
   4 566389                                6                |                    |                               +++***
   2 0122662399                           10                |                    |                           ++++***
   0 11233444445666788899900025666 67     31             +--+--+                 |                       ********
  -0 98877665522110009998777644322210     32             +-----+                 |                *********
  -2 855418530                            9                |                    |             ***++++
  -4 98823100                             8                |                    |        *****++
  -6 294                                  3                0                    |      * **++
  -8 86                                   2                0                    |   *+*++
 -10                                                                             |++++
 -12                                                                             |
 -14 7                                    1                *                   -15+*
     ----+----+----+----+----+----+--                                                +----+----+----+----+----+----+----+----+----+----+
                                                                                        -2        -1         0        +1        +2
```



Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Moments

N	113	Sum Weights	113
Mean	0.13577023	Sum Observations	15.3420361
Std Deviation	3.77263418	Variance	14.2327687
Skewness	0.61792983	Kurtosis	2.13161843
Uncorrected SS	1596.15308	Corrected SS	1594.07009
Coeff Variation	2778.69026	Std Error Mean	0.35489957

Basic Statistical Measures

Location		Variability	
Mean	0.13577	Std Deviation	3.77263
Median	-0.02726	Variance	14.23277
Mode	-0.02726	Range	24.38741
		Interquartile Range	3.54599

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	0.38256	Pr > |t|	0.7028
Sign	M	-1.5	Pr >= |M|	0.8509
Signed Rank	S	-21.5	Pr >= |S|	0.9512

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.955805	Pr < W	0.0009
Kolmogorov-Smirnov	D	0.114581	Pr > D	<0.0100
Cramer-von Mises	W-Sq	0.325693	Pr > W-Sq	<0.0050
Anderson-Darling	A-Sq	1.705135	Pr > A-Sq	<0.0050

Quantiles (Definition 5)

Quantile	Estimate
100% Max	14.8479482
99%	9.9010819
95%	7.1217297
90%	4.3670902
75% Q3	1.7346667
50% Median	-0.0272621
25% Q1	-1.8113235
10%	-3.8960370
5%	-6.1602152
1%	-8.3922852
0% Min	-9.5394634

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

----------Lowest----------			----------Highest----------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-9.53946	7030	57	7.32924	7044	64
-8.39229	7048	65	9.01582	4037	13
-7.88226	5043	96	9.39490	7028	56
-7.31850	7014	48	9.90108	3026	75
-6.24675	4032	11	14.84795	7002	43

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

```
Stem Leaf                    #             Boxplot                                  Normal Probability Plot
  14 8                       1                *                  14.5+                                                  *
  13                                                                |
  12                                                                |
  11                                                                |
  10                                                                |
   9 049                     3                0                      |                                          ** * ++
   8                                                                |                                            +++
   7 13                      2                0                      |                                        ** ++
   6 059                     3                |                      |                                      ***++
   5 8                       1                |                      |                                     +*+
   4 046                     3                |                      |                                   ++*
   3 0134468                 7                |                      |                                +****
   2 23566                   5                |                   2.5+                             +++**
   1 1356777789             10             +-----+                   |                           ++****
   0 01112233334446667789   20             |  +  |                   |                        ******
  -0 87775544333222211000   20             *-----*                   |                     *****
  -1 88886643311            11             +-----+                   |                  ****
  -2 85543221                8                |                      |                ***+
  -3 98664443                8                |                      |            ****+
  -4 831                     3                |                      |           **++
  -5 71                      2                |                      |         **+
  -6 22                      2                |                      |       +**
  -7 93                      2                0                      |    +**
  -8 4                       1                0                      | ++*
  -9 5                       1                0                  -9.5+*
     ----+----+----+----+                                           +----+----+----+----+----+----+----+----+----+----+
                                                                        -2        -1         0        +1        +2
```

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance) at 45 Minutes, Adjusting for Baseline NAR
Model 3: Random Effects Model, Adjusting for Baseline Nasal Airflow Resistance
Patient, Study, and Study by Treatment Interaction Are Random
T0 = Baseline (A Covariate)

The UNIVARIATE Procedure
Variable: Resid

Schematic Plots

```
      |
   30 +
      |
      |          *
      |
   20 +
      |
      |          *          *
      |          *
   10 +          0          0
      |          0          0
      |          |          |
      |       +-----+     +-----+
    0 +       *--+--*     *--+--*
      |       +-----+     +-----+
      |          |          |
      |          0          0
  -10 +          0          0
      |
      |          *
      |
  -20 +
        ----------+----------+----------
TREAT            Drug     Placebo
```

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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)

The Mixed Procedure

Model Information

Data Set	WORK.TEN_MG
Dependent Variable	T45CHG
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	7	1 2 3 4 5 6 7

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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

Class Level Information

Class	Levels	Values
PATIENT	113	1002 1007 1008 1011 1013 1016 1017 1018 1020 1026 1030 1031 1034 1035 1037 1038 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 5001 5010 5013 5015 5021 5022 5025 5027 5029 5030 5032 5034 5035 5043 5046 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	7
Columns in X	138
Columns in Z	0
Subjects	226
Max Obs Per Subject	1

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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)

The Mixed Procedure

Dimensions

Observations Used	226
Observations Not Used	0
Total Observations	226

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	647.58939578	
1	2	611.50377349	0.00000003
2	1	611.50376758	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Group	Estimate
Residual	STUDY 1	1.5635
Residual	STUDY 2	1.0153
Residual	STUDY 3	17.7600
Residual	STUDY 4	8.1993
Residual	STUDY 5	9.8251
Residual	STUDY 6	9.6132
Residual	STUDY 7	18.2716

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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)

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	611.5
AIC (smaller is better)	625.5
AICC (smaller is better)	626.7
BIC (smaller is better)	649.4

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
6	36.09	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
T0	1	79.3	23.19	<.0001
PATIENT(STUDY)	106	32.7	2.04	0.0109
STUDY	6	46.9	5.69	0.0002
TREAT	1	79.9	7.78	0.0066
TREAT*STUDY	6	39.9	13.47	<.0001

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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)

The Mixed Procedure

Least Squares Means

Effect	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
STUDY		1	-5.2070	0.6106	82.7	-8.53	<.0001	0.05	-6.4216	-3.9924
STUDY		2	-4.6609	0.6363	79.8	-7.33	<.0001	0.05	-5.9271	-3.3946
STUDY		3	-2.7176	0.7460	14.4	-3.64	0.0026	0.05	-4.3140	-1.1212
STUDY		4	-0.5424	0.6252	22.9	-0.87	0.3947	0.05	-1.8361	0.7514
STUDY		5	-1.3821	0.5746	13.1	-2.41	0.0316	0.05	-2.6223	-0.1418
STUDY		6	-0.8008	0.5655	15.5	-1.42	0.1765	0.05	-2.0025	0.4008
STUDY		7	0.9472	0.7057	36.1	1.34	0.1879	0.05	-0.4840	2.3784
TREAT	Drug		-2.6051	0.2841	80.4	-9.17	<.0001	0.05	-3.1706	-2.0397
TREAT	Placebo		-1.4987	0.2884	80.8	-5.20	<.0001	0.05	-2.0725	-0.9249
TREAT*STUDY	Drug	1	-8.1120	0.6395	71.4	-12.68	<.0001	0.05	-9.3871	-6.8369
TREAT*STUDY	Drug	2	-6.3699	0.6676	62.2	-9.54	<.0001	0.05	-7.7043	-5.0354
TREAT*STUDY	Drug	3	-3.5441	1.0537	14.3	-3.36	0.0045	0.05	-5.7995	-1.2887
TREAT*STUDY	Drug	4	-0.2307	0.8337	19.5	-0.28	0.7849	0.05	-1.9724	1.5110
TREAT*STUDY	Drug	5	-1.4352	0.8115	13.1	-1.77	0.1003	0.05	-3.1874	0.3170
TREAT*STUDY	Drug	6	-0.2003	0.7922	15.2	-0.25	0.8038	0.05	-1.8868	1.4862
TREAT*STUDY	Drug	7	1.6562	0.9071	28	1.83	0.0786	0.05	-0.2019	3.5142
TREAT*STUDY	Placebo	1	-2.3020	0.6593	73.3	-3.49	0.0008	0.05	-3.6160	-0.9880
TREAT*STUDY	Placebo	2	-2.9519	0.6824	64	-4.33	<.0001	0.05	-4.3151	-1.5887
TREAT*STUDY	Placebo	3	-1.8911	1.0578	14.5	-1.79	0.0948	0.05	-4.1531	0.3709
TREAT*STUDY	Placebo	4	-0.8540	0.7981	17.3	-1.07	0.2993	0.05	-2.5355	0.8274
TREAT*STUDY	Placebo	5	-1.3290	0.8105	13	-1.64	0.1250	0.05	-3.0797	0.4218
TREAT*STUDY	Placebo	6	-1.4013	0.7835	14.9	-1.79	0.0941	0.05	-3.0728	0.2702
TREAT*STUDY	Placebo	7	0.2383	0.9548	32.2	0.25	0.8045	0.05	-1.7061	2.1827

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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)

The Mixed Procedure

Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
STUDY		1		2	-0.5461	0.3167	22.5	-1.72	0.0984	0.05	-1.2021	0.1098
STUDY		1		3	-2.4894	0.9403	27.5	-2.65	0.0133	0.05	-4.4169	-0.5619
STUDY		1		4	-4.6646	1.0743	65.7	-4.34	<.0001	0.05	-6.8097	-2.5195
STUDY		1		5	-3.8249	0.8025	33.7	-4.77	<.0001	0.05	-5.4564	-2.1935
STUDY		1		6	-4.4062	0.9225	41	-4.78	<.0001	0.05	-6.2693	-2.5431
STUDY		1		7	-6.1542	1.1338	81.3	-5.43	<.0001	0.05	-8.4101	-3.8984
STUDY		2		3	-1.9433	0.9560	28.4	-2.03	0.0515	0.05	-3.9004	0.01380
STUDY		2		4	-4.1185	1.0972	67.2	-3.75	0.0004	0.05	-6.3084	-1.9287
STUDY		2		5	-3.2788	0.8205	35.8	-4.00	0.0003	0.05	-4.9433	-1.6143
STUDY		2		6	-3.8601	0.9435	42	-4.09	0.0002	0.05	-5.7642	-1.9560
STUDY		2		7	-5.6081	1.1560	82.8	-4.85	<.0001	0.05	-7.9074	-3.3088
STUDY		3		4	-2.1752	0.9873	30.7	-2.20	0.0352	0.05	-4.1898	-0.1607
STUDY		3		5	-1.3355	0.9395	27.5	-1.42	0.1664	0.05	-3.2616	0.5905
STUDY		3		6	-1.9168	0.9420	26.5	-2.03	0.0520	0.05	-3.8514	0.01779
STUDY		3		7	-3.6649	1.0410	38.1	-3.52	0.0011	0.05	-5.7721	-1.5576
STUDY		4		5	0.8397	0.8699	35	0.97	0.3410	0.05	-0.9263	2.6057
STUDY		4		6	0.2584	0.7844	30	0.33	0.7441	0.05	-1.3434	1.8603
STUDY		4		7	-1.4896	0.7995	37.3	-1.86	0.0703	0.05	-3.1091	0.1299
STUDY		5		6	-0.5813	0.8151	29.9	-0.71	0.4813	0.05	-2.2463	1.0837
STUDY		5		7	-2.3293	0.9306	43.7	-2.50	0.0161	0.05	-4.2053	-0.4534
STUDY		6		7	-1.7481	0.8465	40.2	-2.07	0.0454	0.05	-3.4585	-0.03762
TREAT	Drug		Placebo		-1.1064	0.3966	79.9	-2.79	0.0066	0.05	-1.8956	-0.3172
TREAT*STUDY	Drug	1	Drug	2	-1.7422	0.4473	22.4	-3.89	0.0008	0.05	-2.6688	-0.8155
TREAT*STUDY	Drug	1	Drug	3	-4.5679	1.2391	23.1	-3.69	0.0012	0.05	-7.1306	-2.0052
TREAT*STUDY	Drug	1	Drug	4	-7.8813	1.2385	50.7	-6.36	<.0001	0.05	-10.3681	-5.3945
TREAT*STUDY	Drug	1	Drug	5	-6.6768	1.0006	24.6	-6.67	<.0001	0.05	-8.7393	-4.6143
TREAT*STUDY	Drug	1	Drug	6	-7.9117	1.1042	32.1	-7.16	<.0001	0.05	-10.1606	-5.6628

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
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The Mixed Procedure

Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT*STUDY	Drug	1	Drug	7	-9.7682	1.2531	61.2	-7.80	<.0001	0.05	-12.2738	-7.2626
TREAT*STUDY	Drug	1	Placebo	1	-5.8100	0.4427	14.9	-13.13	<.0001	0.05	-6.7541	-4.8660
TREAT*STUDY	Drug	1	Placebo	2	-5.1601	0.4487	22.6	-11.50	<.0001	0.05	-6.0892	-4.2310
TREAT*STUDY	Drug	1	Placebo	3	-6.2209	1.1928	20.9	-5.22	<.0001	0.05	-8.7017	-3.7400
TREAT*STUDY	Drug	1	Placebo	4	-7.2580	1.1753	46.3	-6.18	<.0001	0.05	-9.6233	-4.8926
TREAT*STUDY	Drug	1	Placebo	5	-6.7830	1.0082	25.1	-6.73	<.0001	0.05	-8.8591	-4.7070
TREAT*STUDY	Drug	1	Placebo	6	-6.7107	1.0727	30.6	-6.26	<.0001	0.05	-8.8996	-4.5218
TREAT*STUDY	Drug	1	Placebo	7	-8.3503	1.3397	67.8	-6.23	<.0001	0.05	-11.0239	-5.6768
TREAT*STUDY	Drug	2	Drug	3	-2.8258	1.2542	23.6	-2.25	0.0338	0.05	-5.4167	-0.2349
TREAT*STUDY	Drug	2	Drug	4	-6.1392	1.2620	52.1	-4.86	<.0001	0.05	-8.6716	-3.6067
TREAT*STUDY	Drug	2	Drug	5	-4.9347	1.0171	25.9	-4.85	<.0001	0.05	-7.0259	-2.8435
TREAT*STUDY	Drug	2	Drug	6	-6.1695	1.1249	32.7	-5.48	<.0001	0.05	-8.4589	-3.8802
TREAT*STUDY	Drug	2	Drug	7	-8.0260	1.2745	63	-6.30	<.0001	0.05	-10.5730	-5.4791
TREAT*STUDY	Drug	2	Placebo	1	-4.0679	0.4464	22.3	-9.11	<.0001	0.05	-4.9930	-3.1427
TREAT*STUDY	Drug	2	Placebo	2	-3.4179	0.4509	8.92	-7.58	<.0001	0.05	-4.4394	-2.3965
TREAT*STUDY	Drug	2	Placebo	3	-4.4787	1.2058	21.3	-3.71	0.0013	0.05	-6.9841	-1.9734
TREAT*STUDY	Drug	2	Placebo	4	-5.5158	1.1980	47.6	-4.60	<.0001	0.05	-7.9250	-3.1066
TREAT*STUDY	Drug	2	Placebo	5	-5.0409	1.0250	26.4	-4.92	<.0001	0.05	-7.1463	-2.9355
TREAT*STUDY	Drug	2	Placebo	6	-4.9685	1.0927	31.2	-4.55	<.0001	0.05	-7.1966	-2.7405
TREAT*STUDY	Drug	2	Placebo	7	-6.6082	1.3623	69.5	-4.85	<.0001	0.05	-9.3256	-3.8907
TREAT*STUDY	Drug	3	Drug	4	-3.3134	1.3394	27.9	-2.47	0.0197	0.05	-6.0576	-0.5691
TREAT*STUDY	Drug	3	Drug	5	-2.1089	1.3306	27.6	-1.58	0.1244	0.05	-4.8363	0.6185
TREAT*STUDY	Drug	3	Drug	6	-3.3438	1.3165	25.9	-2.54	0.0174	0.05	-6.0504	-0.6371
TREAT*STUDY	Drug	3	Drug	7	-5.2003	1.3872	33.3	-3.75	0.0007	0.05	-8.0214	-2.3792
TREAT*STUDY	Drug	3	Placebo	1	-1.2421	1.2497	23.6	-0.99	0.3304	0.05	-3.8237	1.3395
TREAT*STUDY	Drug	3	Placebo	2	-0.5922	1.2623	24	-0.47	0.6432	0.05	-3.1976	2.0133
TREAT*STUDY	Drug	3	Placebo	3	-1.6529	1.4939	14.4	-1.11	0.2867	0.05	-4.8487	1.5428

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The Mixed Procedure

Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT*STUDY	Drug	3	Placebo	4	-2.6900	1.3185	26.9	-2.04	0.0513	0.05	-5.3960	0.01591
TREAT*STUDY	Drug	3	Placebo	5	-2.2151	1.3298	27.6	-1.67	0.1071	0.05	-4.9411	0.5109
TREAT*STUDY	Drug	3	Placebo	6	-2.1428	1.3118	25.7	-1.63	0.1146	0.05	-4.8408	0.5552
TREAT*STUDY	Drug	3	Placebo	7	-3.7824	1.4175	35	-2.67	0.0115	0.05	-6.6600	-0.9047
TREAT*STUDY	Drug	4	Drug	5	1.2045	1.1829	32	1.02	0.3162	0.05	-1.2051	3.6141
TREAT*STUDY	Drug	4	Drug	6	-0.03039	1.0939	29.3	-0.03	0.9780	0.05	-2.2666	2.2058
TREAT*STUDY	Drug	4	Drug	7	-1.8869	1.1332	37.5	-1.67	0.1042	0.05	-4.1820	0.4082
TREAT*STUDY	Drug	4	Placebo	1	2.0713	1.2558	51.8	1.65	0.1051	0.05	-0.4489	4.5914
TREAT*STUDY	Drug	4	Placebo	2	2.7212	1.2750	52.9	2.13	0.0375	0.05	0.1638	5.2787
TREAT*STUDY	Drug	4	Placebo	3	1.6604	1.3735	29.5	1.21	0.2363	0.05	-1.1465	4.4674
TREAT*STUDY	Drug	4	Placebo	4	0.6233	1.0490	14.1	0.59	0.5618	0.05	-1.6251	2.8717
TREAT*STUDY	Drug	4	Placebo	5	1.0983	1.1774	31.6	0.93	0.3580	0.05	-1.3010	3.4975
TREAT*STUDY	Drug	4	Placebo	6	1.1706	1.1049	29.8	1.06	0.2979	0.05	-1.0864	3.4276
TREAT*STUDY	Drug	4	Placebo	7	-0.4690	1.1310	37.3	-0.41	0.6807	0.05	-2.7599	1.8219
TREAT*STUDY	Drug	5	Drug	6	-1.2349	1.1426	29.4	-1.08	0.2886	0.05	-3.5705	1.1007
TREAT*STUDY	Drug	5	Drug	7	-3.0914	1.2318	37.6	-2.51	0.0165	0.05	-5.5860	-0.5967
TREAT*STUDY	Drug	5	Placebo	1	0.8668	1.0121	25.3	0.86	0.3998	0.05	-1.2161	2.9497
TREAT*STUDY	Drug	5	Placebo	2	1.5167	1.0259	26.5	1.48	0.1511	0.05	-0.5903	3.6237
TREAT*STUDY	Drug	5	Placebo	3	0.4559	1.3290	27.5	0.34	0.7341	0.05	-2.2685	3.1804
TREAT*STUDY	Drug	5	Placebo	4	-0.5812	1.1538	30.2	-0.50	0.6181	0.05	-2.9369	1.7746
TREAT*STUDY	Drug	5	Placebo	5	-0.1062	1.1447	13	-0.09	0.9275	0.05	-2.5797	2.3672
TREAT*STUDY	Drug	5	Placebo	6	-0.03388	1.1341	29	-0.03	0.9764	0.05	-2.3533	2.2856
TREAT*STUDY	Drug	5	Placebo	7	-1.6735	1.2730	40.6	-1.31	0.1960	0.05	-4.2453	0.8983
TREAT*STUDY	Drug	6	Drug	7	-1.8565	1.1624	38.4	-1.60	0.1184	0.05	-4.2089	0.4959
TREAT*STUDY	Drug	6	Placebo	1	2.1017	1.1191	32.8	1.88	0.0693	0.05	-0.1756	4.3790
TREAT*STUDY	Drug	6	Placebo	2	2.7516	1.1362	33.3	2.42	0.0211	0.05	0.4407	5.0625
TREAT*STUDY	Drug	6	Placebo	3	1.6908	1.3332	26.5	1.27	0.2157	0.05	-1.0468	4.4285

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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

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The Mixed Procedure

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	0.6537	1.0799	28.6	0.61	0.5497	0.05	-1.5561	2.8635
TREAT*STUDY	Drug	6	Placebo	5	1.1287	1.1398	29.3	0.99	0.3302	0.05	-1.2016	3.4589
TREAT*STUDY	Drug	6	Placebo	6	1.2010	1.0973	14.5	1.09	0.2915	0.05	-1.1444	3.5464
TREAT*STUDY	Drug	6	Placebo	7	-0.4386	1.1832	39.5	-0.37	0.7128	0.05	-2.8309	1.9537
TREAT*STUDY	Drug	7	Placebo	1	3.9582	1.2687	62.5	3.12	0.0027	0.05	1.4224	6.4940
TREAT*STUDY	Drug	7	Placebo	2	4.6081	1.2863	63.9	3.58	0.0007	0.05	2.0384	7.1778
TREAT*STUDY	Drug	7	Placebo	3	3.5473	1.4138	34.8	2.51	0.0169	0.05	0.6766	6.4181
TREAT*STUDY	Drug	7	Placebo	4	2.5102	1.1303	37.3	2.22	0.0325	0.05	0.2206	4.7998
TREAT*STUDY	Drug	7	Placebo	5	2.9851	1.2275	37.3	2.43	0.0199	0.05	0.4986	5.4717
TREAT*STUDY	Drug	7	Placebo	6	3.0575	1.1693	38.8	2.61	0.0127	0.05	0.6918	5.4231
TREAT*STUDY	Drug	7	Placebo	7	1.4179	1.2151	24.1	1.17	0.2547	0.05	-1.0895	3.9252
TREAT*STUDY	Placebo	1	Placebo	2	0.6499	0.4470	22.3	1.45	0.1598	0.05	-0.2762	1.5760
TREAT*STUDY	Placebo	1	Placebo	3	-0.4109	1.2017	21.4	-0.34	0.7358	0.05	-2.9074	2.0857
TREAT*STUDY	Placebo	1	Placebo	4	-1.4480	1.1919	47.5	-1.21	0.2304	0.05	-3.8451	0.9492
TREAT*STUDY	Placebo	1	Placebo	5	-0.9730	1.0199	25.9	-0.95	0.3489	0.05	-3.0700	1.1240
TREAT*STUDY	Placebo	1	Placebo	6	-0.9007	1.0870	31.3	-0.83	0.4136	0.05	-3.1168	1.3154
TREAT*STUDY	Placebo	1	Placebo	7	-2.5403	1.3564	69	-1.87	0.0653	0.05	-5.2463	0.1657
TREAT*STUDY	Placebo	2	Placebo	3	-1.0608	1.2127	21.6	-0.87	0.3913	0.05	-3.5783	1.4567
TREAT*STUDY	Placebo	2	Placebo	4	-2.0979	1.2105	48.5	-1.73	0.0894	0.05	-4.5311	0.3353
TREAT*STUDY	Placebo	2	Placebo	5	-1.6230	1.0340	27	-1.57	0.1281	0.05	-3.7445	0.4986
TREAT*STUDY	Placebo	2	Placebo	6	-1.5506	1.1035	31.7	-1.41	0.1697	0.05	-3.7993	0.6981
TREAT*STUDY	Placebo	2	Placebo	7	-3.1902	1.3748	70.4	-2.32	0.0232	0.05	-5.9320	-0.4484
TREAT*STUDY	Placebo	3	Placebo	4	-1.0371	1.3463	28.2	-0.77	0.4475	0.05	-3.7940	1.7198
TREAT*STUDY	Placebo	3	Placebo	5	-0.5622	1.3295	27.5	-0.42	0.6757	0.05	-3.2875	2.1632
TREAT*STUDY	Placebo	3	Placebo	6	-0.4898	1.3246	26.2	-0.37	0.7145	0.05	-3.2115	2.2318
TREAT*STUDY	Placebo	3	Placebo	7	-2.1294	1.4528	37	-1.47	0.1512	0.05	-5.0731	0.8142
TREAT*STUDY	Placebo	4	Placebo	5	0.4749	1.1492	29.9	0.41	0.6823	0.05	-1.8723	2.8222

Meta-Analysis of Phenylephrine vs. Placebo

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The Mixed Procedure

Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT*STUDY	Placebo	4	Placebo	6	0.5473	1.0872	29	0.50	0.6185	0.05	-1.6764	2.7709
TREAT*STUDY	Placebo	4	Placebo	7	-1.0923	1.1371	37.8	-0.96	0.3428	0.05	-3.3947	1.2100
TREAT*STUDY	Placebo	5	Placebo	6	0.07234	1.1319	28.9	0.06	0.9495	0.05	-2.2429	2.3876
TREAT*STUDY	Placebo	5	Placebo	7	-1.5673	1.2674	40.1	-1.24	0.2234	0.05	-4.1284	0.9939
TREAT*STUDY	Placebo	6	Placebo	7	-1.6396	1.1950	40.1	-1.37	0.1777	0.05	-4.0546	0.7754

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

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

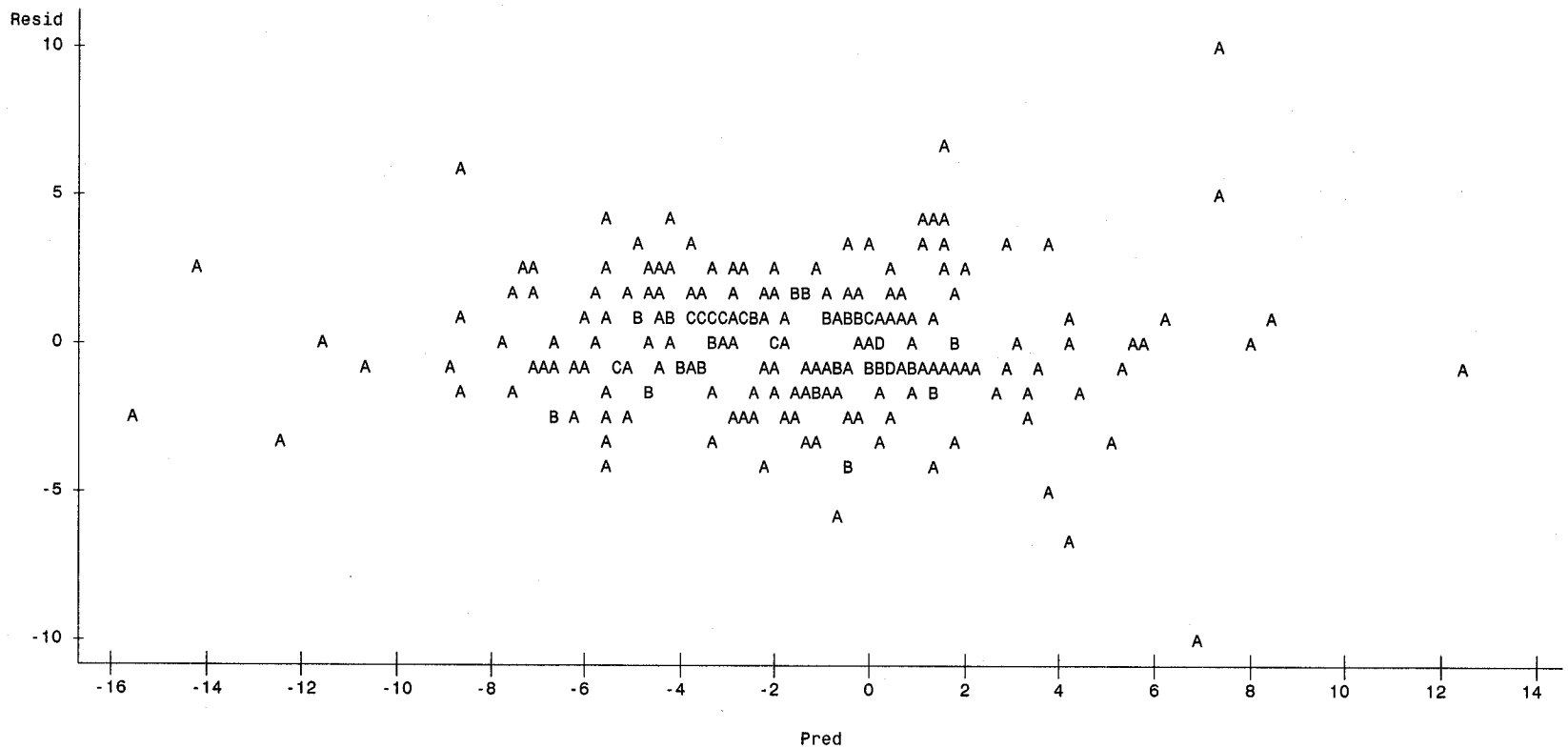
Checking the Treatment by Study Interaction Term to Test for Heterogeneity

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

TO = Baseline (A Covariate)

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: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

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

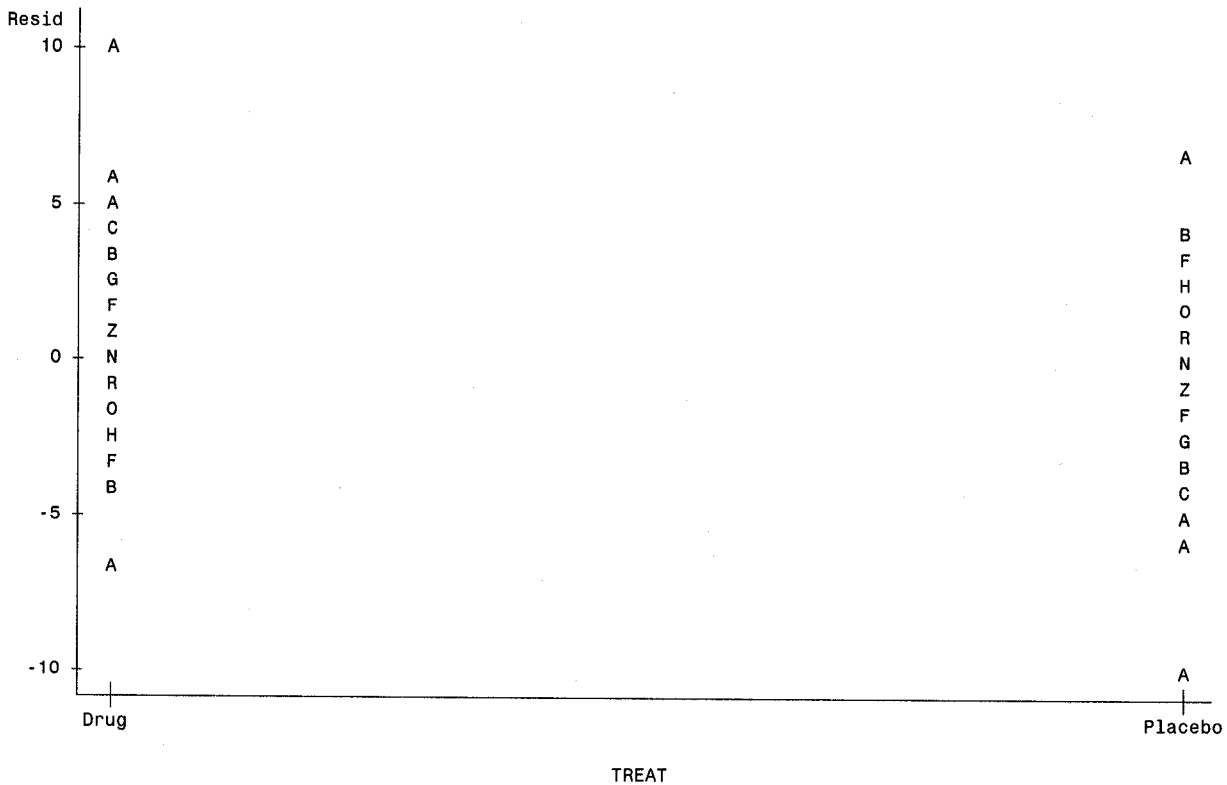
Checking the Treatment by Study Interaction Term to Test for Heterogeneity

Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

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



NOTE: 4 obs hidden.

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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=Drug ----------

The UNIVARIATE Procedure
Variable: Resid

Moments

N	113	Sum Weights	113
Mean	0	Sum Observations	0
Std Deviation	2.23909636	Variance	5.01355251
Skewness	0.75850199	Kurtosis	3.03699196
Uncorrected SS	561.517881	Corrected SS	561.517881
Coeff Variation	.	Std Error Mean	0.21063647

Basic Statistical Measures

Location		Variability	
Mean	0.000000	Std Deviation	2.23910
Median	0.010370	Variance	5.01355
Mode	.	Range	16.07101
		Interquartile Range	2.42054

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	0	Pr > |t|	1.0000
Sign	M	0.5	Pr >= |M|	1.0000
Signed Rank	S	-145.5	Pr >= |S|	0.6787

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
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Patient Is Fixed
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The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.95524	Pr < W	0.0008
Kolmogorov-Smirnov	D	0.109204	Pr > D	<0.0100
Cramer-von Mises	W-Sq	0.168511	Pr > W-Sq	0.0144
Anderson-Darling	A-Sq	1.053601	Pr > A-Sq	0.0090

Quantiles (Definition 5)

Quantile	Estimate
100% Max	9.8089222
99%	5.8273434
95%	3.8841541
90%	2.6075866
75% Q3	1.0262716
50% Median	0.0103697
25% Q1	-1.3942684
10%	-2.5536582
5%	-3.6429412
1%	-4.2912191
0% Min	-6.2620837

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes
Model 1: Fixed Effects Model to Test Heterogeneity, Adjusting for Baseline NAR (Nasal Airflow Resistance and Study with Treatment by Study Interaction
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Assuming Within Subject Variance Component Differs Across Studies
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---------- TREAT=Drug ----------

The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

----------Lowest----------			----------Highest----------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-6.26208	3026	75	4.44119	7003	44
-4.29122	7020	52	4.53419	5027	90
-3.89213	4001	1	5.37142	7021	53
-3.74613	7001	42	5.82734	3018	73
-3.64684	4037	13	9.80892	7042	63

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Assuming Within Subject Variance Component Differs Across Studies
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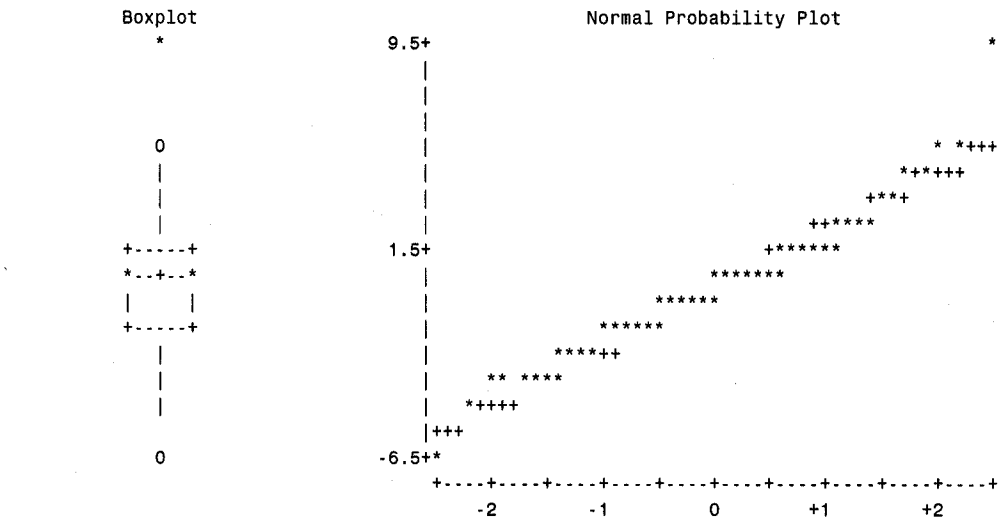
---------- TREAT=Drug ----------

The UNIVARIATE Procedure
Variable: Resid

```
Stem Leaf                     #             Boxplot
   9 8                        1                *
   8
   7
   6
   5 48                       2                0
   4 45                       2                |
   3 349                      3                |
   2 2356668                  7                |
   1 00001111112344589       17             +-----+
   0 0112233455566667778888999 25           *--+--*
  -0 9888886655554422100     19             |     |
  -1 98776665554433322210    20             +-----+
  -2 87643222                8                |
  -3 9766642                 7                |
  -4 3                       1                |
  -5
  -6 3                       1                0
     ----+----+----+----+----+
```



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Variable: Resid

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Mode	.	Range	16.07101
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Test	-Statistic-		-----p Value------	
Student's t	t	0	Pr > |t|	1.0000
Sign	M	-0.5	Pr >= |M|	1.0000
Signed Rank	S	145.5	Pr >= |S|	0.6787

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Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.95524	Pr < W	0.0008
Kolmogorov-Smirnov	D	0.109204	Pr > D	<0.0100
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95%	3.6429412
90%	2.5536582
75% Q3	1.3942684
50% Median	-0.0103697
25% Q1	-1.0262716
10%	-2.6075866
5%	-3.8841541
1%	-5.8273434
0% Min	-9.8089222

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T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

----------Lowest----------			----------Highest----------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-9.80892	7042	63	3.64684	4037	13
-5.82734	3018	73	3.74613	7001	42
-5.37142	7021	53	3.89213	4001	1
-4.53419	5027	90	4.29122	7020	52
-4.44119	7003	44	6.26208	3026	75

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

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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

```
Stem Leaf                          #             Boxplot                                  Normal Probability Plot
   6 3                             1                0                    6.5+                                                  *
   5                                                                        |                                                +++
   4 3                             1                |                        |                                           ++++*
   3 2466679                       7                |                        |                                      **** **
   2 22234678                      8                |                        |                                 ++*****
   1 01222333445556667789         20             +-----+                     |                              ******
   0 0012244555566888889          19             |  +  |                     |                         ******
  -0 99988887776666555433221 10   25             *-----*                     |                    *******
  -1 98544321111110000            17             +-----+                  -1.5+               ******+
  -2 8666532                       7                |                        |            *****++
  -3 943                           3                |                        |         +**+
  -4 54                            2                |                        |    +++*+*
  -5 84                            2                0                        |+++* *
  -6                                                                         |
  -7                                                                         |
  -8                                                                         |
  -9 8                             1                *                    -9.5+*
     ----+----+----+----+----+                                                +----+----+----+----+----+----+----+----+----+----+
                                                                                  -2        -1         0        +1        +2
```

Meta-Analysis of Phenylephrine vs. Placebo

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Patient Is Fixed

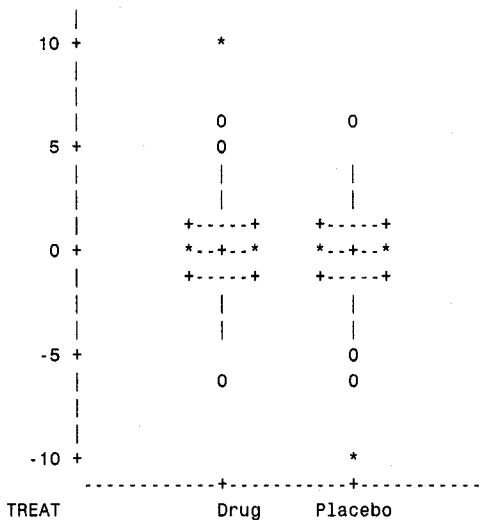
Assuming Within Subject Variance Component Differs Across Studies

TO = Baseline (A Covariate)

The UNIVARIATE Procedure

Variable: Resid

Schematic Plots



Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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	T45CHG
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	7	1 2 3 4 5 6 7
TREAT	2	Drug Placebo

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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

Class Level Information

Class	Levels	Values
PATIENT	113	1002 1007 1008 1011 1013 1016 1017 1018 1020 1026 1030 1031 1034 1035 1037 1038 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 5001 5010 5013 5015 5021 5022 5025 5027 5029 5030 5032 5034 5035 5043 5046 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	7
Columns in X	124
Columns in Z	0
Subjects	226
Max Obs Per Subject	1
Observations Used	226

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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

Observations Not Used	0
Total Observations	226

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	692.69554670	
1	2	681.62204567	0.00138182
2	1	681.25788539	0.00011031
3	1	681.23056608	0.00000066
4	1	681.23040738	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Group	Estimate
Residual	STUDY 1	8.0973
Residual	STUDY 2	1.7397
Residual	STUDY 3	16.8536
Residual	STUDY 4	11.6996
Residual	STUDY 5	11.5145
Residual	STUDY 6	14.8700
Residual	STUDY 7	24.2361

Appendix 3

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)

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	681.2
AIC (smaller is better)	695.2
AICC (smaller is better)	696.3
BIC (smaller is better)	719.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
6	11.47	0.0750

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
T0	1	51.9	16.07	0.0002
PATIENT(STUDY)	106	26.8	1.24	0.2628
STUDY	6	34	3.33	0.0109
TREAT	1	15.9	20.80	0.0003

Least Squares Means

Effect	TREAT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT	Drug	-3.1444	0.3374	74.9	-9.32	<.0001	0.05	-3.8164	-2.4723
TREAT	Placebo	-0.9524	0.3421	77.9	-2.78	0.0067	0.05	-1.6336	-0.2713

Appendix 3

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)

The Mixed Procedure

Differences of Least Squares Means

Effect	TREAT	TREAT	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT	Drug	Placebo	-2.1919	0.4806	15.9	-4.56	0.0003	0.05	-3.2115	-1.1723

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

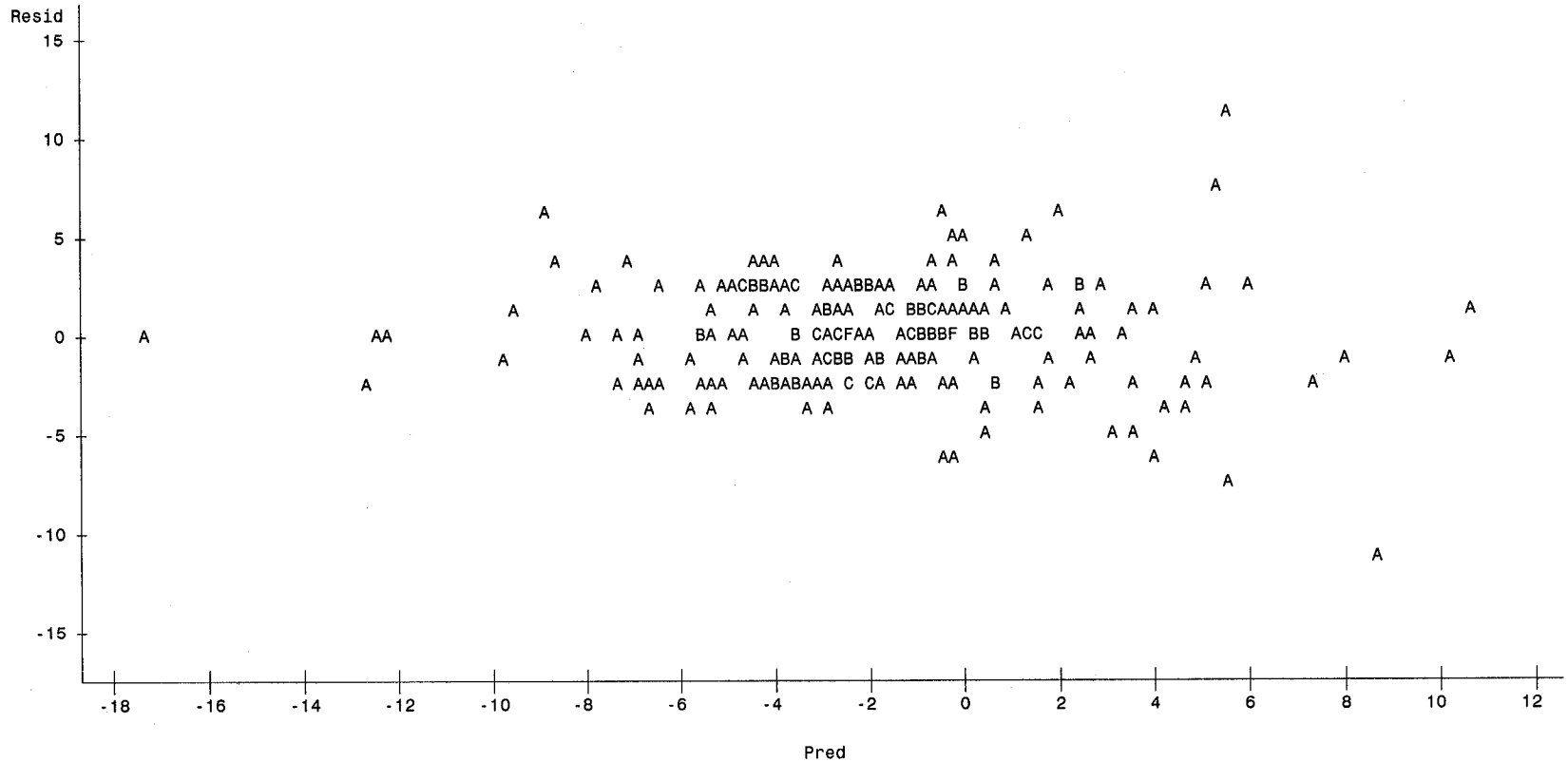
Model 2: Fixed Effects Model, Adjusting for Baseline Nasal Airflow Resistance and Study without Treatment by Study Interaction

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.



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Patient Is Fixed

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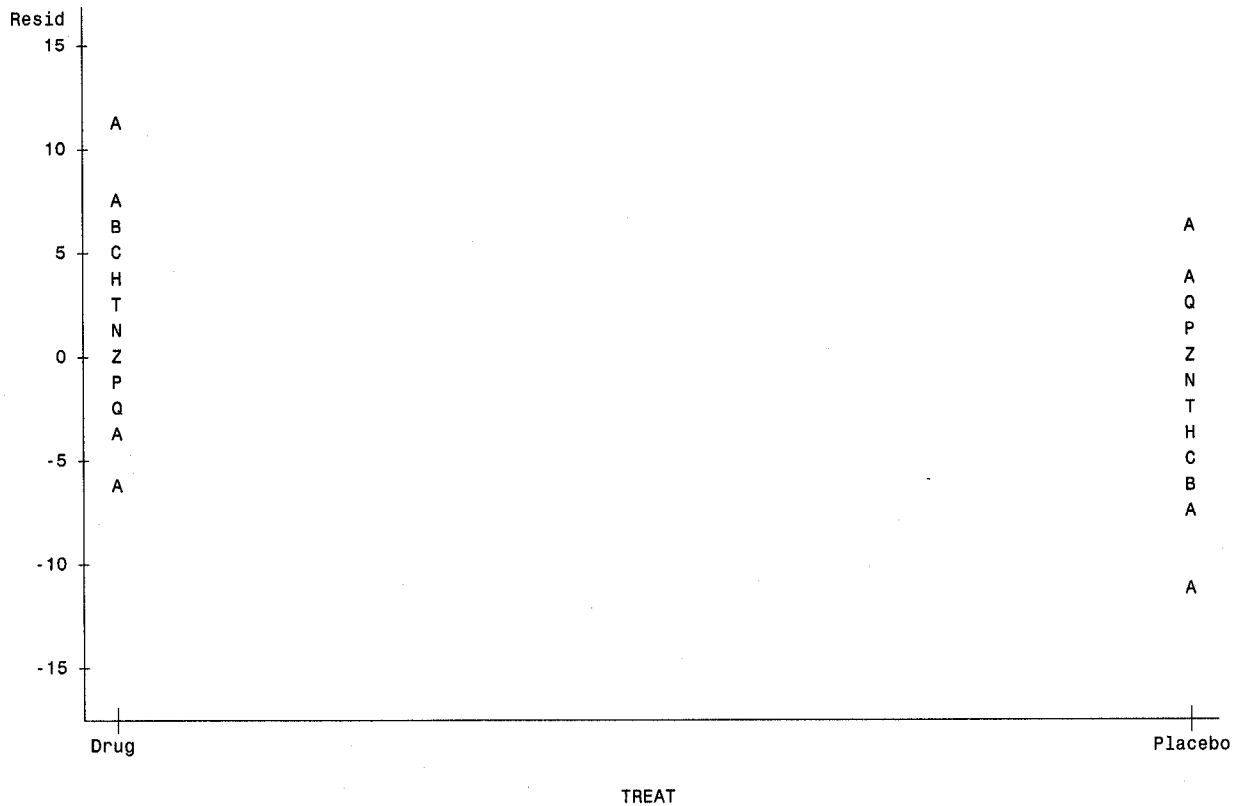
T0 = Baseline (A Covariate)

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



NOTE: 6 obs hidden.

Appendix 3

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Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

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Patient Is Fixed

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure

Variable: Resid

Moments

N	113	Sum Weights	113
Mean	0.69227893	Sum Observations	78.227519
Std Deviation	2.56738238	Variance	6.59145228
Skewness	0.84781818	Kurtosis	2.21227908
Uncorrected SS	792.397918	Corrected SS	738.242655
Coeff Variation	370.859529	Std Error Mean	0.24151902

Basic Statistical Measures

Location		Variability	
Mean	0.692279	Std Deviation	2.56738
Median	0.284721	Variance	6.59145
Mode	.	Range	17.57453
		Interquartile Range	3.16529

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	2.866354	Pr > |t|	0.0050
Sign	M	7.5	Pr >= |M|	0.1876
Signed Rank	S	818.5	Pr >= |S|	0.0184

Meta-Analysis of Phenylephrine vs. Placebo
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Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.957393	Pr < W	0.0012
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Anderson-Darling	A-Sq	0.837756	Pr > A-Sq	0.0311

Quantiles (Definition 5)

Quantile	Estimate
100% Max	11.608759
99%	7.188947
95%	5.573807
90%	3.656459
75% Q3	2.208601
50% Median	0.284721
25% Q1	-0.956693
10%	-2.354957
5%	-2.619981
1%	-3.149067
0% Min	-5.965771

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The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

----------Lowest----------			----------Highest----------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-5.96577	3026	75	5.58832	5027	90
-3.14907	1020	106	6.05638	3018	73
-3.02795	1026	107	6.26008	7003	44
-2.91807	3001	67	7.18895	7021	53
-2.85962	1008	100	11.60876	7042	63

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The UNIVARIATE Procedure
Variable: Resid

```
Stem Leaf                    #             Boxplot                                  Normal Probability Plot
  11 6                       1                0                  11.5+                                                  *
  10                                                                |
   9                                                                |
   8                                                                |
   7 2                       1                0                      |                                              *  +
   6 13                      2                |                      |                                          **++++
   5 166                     3                |                      |                                       **+++
   4 03                      2                |                      |                                    +**+
   3 01235789                8                |                      |                                ++****
   2 0002234557788999       16             +-----+                2.5+                             ******
   1 002334567788899        15             |     |                   |                         ****
   0 1122223334555669       16             *--+--*                   |                     *****
  -0 98777766665554442000   20             |     |                   |                 ******
  -1 99864221100            11             +-----+                   |              ****
  -2 996665544333210        15                |                      |      * *******
  -3 10                      2                |                      |   * * ++++
  -4                                                                |   ++++
  -5                                                                |*++
  -6 0                       1                0                  -6.5+
     ----+----+----+----+                                           +----+----+----+----+----+----+----+----+----+----+
                                                                        -2        -1         0        +1        +2
```

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T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Moments

N	113	Sum Weights	113
Mean	-0.6922789	Sum Observations	-78.227519
Std Deviation	2.56738238	Variance	6.59145228
Skewness	-0.8478182	Kurtosis	2.21227908
Uncorrected SS	792.397918	Corrected SS	738.242655
Coeff Variation	-370.85953	Std Error Mean	0.24151902

Basic Statistical Measures

Location		Variability	
Mean	-0.69228	Std Deviation	2.56738
Median	-0.28472	Variance	6.59145
Mode	.	Range	17.57453
		Interquartile Range	3.16529

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	-2.86635	Pr > |t|	0.0050
Sign	M	-7.5	Pr >= |M|	0.1876
Signed Rank	S	-818.5	Pr >= |S|	0.0184

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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=Placebo ----------

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.957393	Pr < W	0.0012
Kolmogorov-Smirnov	D	0.086522	Pr > D	0.0372
Cramer-von Mises	W-Sq	0.11546	Pr > W-Sq	0.0728
Anderson-Darling	A-Sq	0.837756	Pr > A-Sq	0.0311

Quantiles (Definition 5)

Quantile	Estimate
100% Max	5.965771
99%	3.149067
95%	2.619981
90%	2.354957
75% Q3	0.956693
50% Median	-0.284721
25% Q1	-2.208601
10%	-3.656459
5%	-5.573807
1%	-7.188947
0% Min	-11.608759

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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=Placebo ----------

The UNIVARIATE Procedure
Variable: Resid

Extreme Observations

----------Lowest----------			----------Highest----------		
Value	PATIENT	Obs	Value	PATIENT	Obs
-11.60876	7042	63	2.85962	1008	100
-7.18895	7021	53	2.91807	3001	67
-6.26008	7003	44	3.02795	1026	107
-6.05638	3018	73	3.14907	1020	106
-5.58832	5027	90	5.96577	3026	75

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 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=Placebo ----------

The UNIVARIATE Procedure

Variable: Resid

```
Stem Leaf                    #             Boxplot                                  Normal Probability Plot
   6 0                       1                0                   6.5+
   5                                                                |                                                  ++*
   4                                                                |                                              ++++
   3 01                      2                |                     |                                          ++++ * *
   2 012333445566699        15                |                     |                                      ******* *
   1 00112246899            11             +-----+                  |                                  ****
   0 00024445556666777789   20             |     |                  |                            ******
  -0 9665554333222211       16             *--+--*                  |                        *****
  -1 998887765433200        15             |     |                  |                     ****
  -2 9998877554322000       16             +-----+                -2.5+               ******
  -3 98753210                8                |                     |            ****++
  -4 30                      2                |                     |          +**+
  -5 661                     3                |                     |      +++**
  -6 31                      2                |                     | +++++**
  -7 2                       1                0                     |+  *
  -8                                                                |
  -9                                                                |
 -10                                                                |
 -11 6                       1                0                  -11.5+*
     ----+----+----+----+                                           +----+----+----+----+----+----+----+----+----+----+
                                                                        -2        -1         0        +1        +2
```

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 45 Minutes

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

Patient Is Fixed

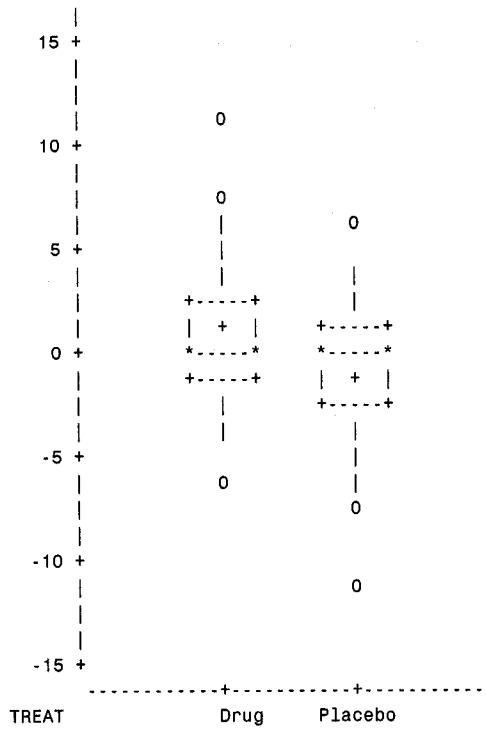
Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The UNIVARIATE Procedure

Variable: Resid

Schematic Plots



Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

TO = Baseline (A Covariate)

The Mixed Procedure

Model Information

Data Set	WORK.TEN_MG
Dependent Variable	T60CHG
Covariance Structure	Variance Components
Subject Effect	PATIENT(STUDY)
Group Effects	STUDY, 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	7	1 2 3 4 5 6 7

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Class Level Information

Class	Levels	Values
PATIENT	113	1002 1007 1008 1011 1013 1016 1017 1018 1020 1026 1030 1031 1034 1035 1037 1038 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 5001 5010 5013 5015 5021 5022 5025 5027 5029 5030 5032 5034 5035 5043 5046 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	14
Columns in X	25
Columns in Z Per Subject	7
Subjects	113
Max Obs Per Subject	2

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Dimensions

Observations Used	226
Observations Not Used	0
Total Observations	226

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1330.65365152	
1	3	1221.17416093	0.00146138
2	3	1220.70247873	0.00021727
3	1	1220.61213989	0.00000182
4	1	1220.61137673	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
Intercept	PATIENT(STUDY)	STUDY 1	0
Intercept	PATIENT(STUDY)	STUDY 2	0
Intercept	PATIENT(STUDY)	STUDY 3	0
Intercept	PATIENT(STUDY)	STUDY 4	2.6275
Intercept	PATIENT(STUDY)	STUDY 5	0
Intercept	PATIENT(STUDY)	STUDY 6	0
Intercept	PATIENT(STUDY)	STUDY 7	0

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

TO = Baseline (A Covariate)

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
Residual		STUDY 1	3.3140
Residual		STUDY 2	0.6932
Residual		STUDY 3	28.0220
Residual		STUDY 4	16.1483
Residual		STUDY 5	12.0566
Residual		STUDY 6	28.5886
Residual		STUDY 7	58.4210

Fit Statistics

-2 Res Log Likelihood	1220.6
AIC (smaller is better)	1236.6
AICC (smaller is better)	1237.3
BIC (smaller is better)	1258.4

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TO	1	166	20.66	<.0001
STUDY	6	78.8	2.03	0.0711
TREAT	1	149	8.53	0.0040
TREAT*STUDY	6	71.1	4.98	0.0003

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

TO = Baseline (A Covariate)

The Mixed Procedure

Least Squares Means

Effect	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
STUDY		1	-4.2195	0.4755	92.5	-8.87	<.0001	0.05	-5.1638	-3.2751
STUDY		2	-3.5088	0.4106	136	-8.55	<.0001	0.05	-4.3208	-2.6969
STUDY		3	-4.2061	0.9361	29.9	-4.49	<.0001	0.05	-6.1182	-2.2940
STUDY		4	-2.1044	0.8706	13.5	-2.42	0.0304	0.05	-3.9782	-0.2306
STUDY		5	-2.1446	0.6347	27.8	-3.38	0.0022	0.05	-3.4452	-0.8441
STUDY		6	-1.9754	0.9491	30.2	-2.08	0.0460	0.05	-3.9132	-0.03764
STUDY		7	-1.6582	1.1039	49.1	-1.50	0.1395	0.05	-3.8764	0.5601
TREAT	Drug		-3.6671	0.4103	165	-8.94	<.0001	0.05	-4.4773	-2.8570
TREAT	Placebo		-1.9949	0.4114	165	-4.85	<.0001	0.05	-2.8072	-1.1825
TREAT*STUDY	Drug	1	-7.0035	0.5700	59.3	-12.29	<.0001	0.05	-8.1439	-5.8631
TREAT*STUDY	Drug	2	-5.4252	0.4467	87.7	-12.15	<.0001	0.05	-6.3129	-4.5376
TREAT*STUDY	Drug	3	-5.8296	1.3234	29.9	-4.40	0.0001	0.05	-8.5329	-3.1262
TREAT*STUDY	Drug	4	-2.9104	1.1436	27.5	-2.54	0.0168	0.05	-5.2549	-0.5660
TREAT*STUDY	Drug	5	-2.2035	0.8973	27.8	-2.46	0.0206	0.05	-4.0421	-0.3649
TREAT*STUDY	Drug	6	-1.2300	1.3405	30.1	-0.92	0.3661	0.05	-3.9675	1.5074
TREAT*STUDY	Drug	7	-1.0677	1.5400	47.3	-0.69	0.4915	0.05	-4.1653	2.0298
TREAT*STUDY	Placebo	1	-1.4354	0.5784	62	-2.48	0.0158	0.05	-2.5917	-0.2791
TREAT*STUDY	Placebo	2	-1.5924	0.4550	91.4	-3.50	0.0007	0.05	-2.4962	-0.6886
TREAT*STUDY	Placebo	3	-2.5827	1.3247	29.9	-1.95	0.0606	0.05	-5.2882	0.1229
TREAT*STUDY	Placebo	4	-1.2984	1.1340	26.9	-1.14	0.2623	0.05	-3.6256	1.0289
TREAT*STUDY	Placebo	5	-2.0858	0.8969	27.8	-2.33	0.0276	0.05	-3.9238	-0.2478
TREAT*STUDY	Placebo	6	-2.7208	1.3386	29.9	-2.03	0.0510	0.05	-5.4548	0.01313
TREAT*STUDY	Placebo	7	-2.2486	1.5509	48.2	-1.45	0.1536	0.05	-5.3664	0.8693

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
STUDY		1		2	-0.7106	0.3721	43.8	-1.91	0.0627	0.05	-1.4607	0.03942
STUDY		1		3	-0.01334	1.0418	42.7	-0.01	0.9898	0.05	-2.1146	2.0879
STUDY		1		4	-2.1151	1.0638	25.6	-1.99	0.0576	0.05	-4.3035	0.07343
STUDY		1		5	-2.0748	0.7789	52.3	-2.66	0.0102	0.05	-3.6375	-0.5121
STUDY		1		6	-2.2440	1.0894	46.3	-2.06	0.0451	0.05	-4.4365	-0.05158
STUDY		1		7	-2.5613	1.2655	72.8	-2.02	0.0467	0.05	-5.0836	-0.03898
STUDY		2		3	0.6973	1.0134	38.6	0.69	0.4955	0.05	-1.3532	2.7478
STUDY		2		4	-1.4044	1.0396	22.9	-1.35	0.1899	0.05	-3.5554	0.7466
STUDY		2		5	-1.3642	0.7404	44.4	-1.84	0.0721	0.05	-2.8559	0.1275
STUDY		2		6	-1.5334	1.0639	42.3	-1.44	0.1569	0.05	-3.6800	0.6133
STUDY		2		7	-1.8507	1.2454	67.8	-1.49	0.1419	0.05	-4.3361	0.6347
STUDY		3		4	-2.1017	1.2824	40.2	-1.64	0.1090	0.05	-4.6932	0.4898
STUDY		3		5	-2.0615	1.1303	51.5	-1.82	0.0740	0.05	-4.3301	0.2072
STUDY		3		6	-2.2307	1.3346	59.8	-1.67	0.0999	0.05	-4.9005	0.4391
STUDY		3		7	-2.5480	1.4512	79.3	-1.76	0.0830	0.05	-5.4363	0.3403
STUDY		4		5	0.04025	1.0836	28.8	0.04	0.9706	0.05	-2.1768	2.2573
STUDY		4		6	-0.1290	1.2738	39.3	-0.10	0.9199	0.05	-2.7048	2.4469
STUDY		4		7	-0.4463	1.3719	47.2	-0.33	0.7464	0.05	-3.2058	2.3133
STUDY		5		6	-0.1692	1.1442	51.8	-0.15	0.8830	0.05	-2.4653	2.1269
STUDY		5		7	-0.4865	1.2790	74	-0.38	0.7048	0.05	-3.0349	2.0619
STUDY		6		7	-0.3173	1.4426	77.3	-0.22	0.8265	0.05	-3.1896	2.5550
TREAT	Drug		Placebo		-1.6723	0.5727	149	-2.92	0.0040	0.05	-2.8039	-0.5406
TREAT*STUDY	Drug	1	Drug	2	-1.5783	0.5261	43.7	-3.00	0.0044	0.05	-2.6387	-0.5179
TREAT*STUDY	Drug	1	Drug	3	-1.1740	1.4431	40.2	-0.81	0.4207	0.05	-4.0901	1.7421
TREAT*STUDY	Drug	1	Drug	4	-4.0931	1.3399	45.3	-3.05	0.0038	0.05	-6.7913	-1.3949
TREAT*STUDY	Drug	1	Drug	5	-4.8000	1.0511	46.2	-4.57	<.0001	0.05	-6.9156	-2.6845
TREAT*STUDY	Drug	1	Drug	6	-5.7735	1.4802	41.6	-3.90	0.0003	0.05	-8.7615	-2.7855

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

The Mixed Procedure

Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT*STUDY	Drug	1	Drug	7	-5.9358	1.6806	62.5	-3.53	0.0008	0.05	-9.2948	-2.5768
TREAT*STUDY	Drug	1	Placebo	1	-5.5681	0.6438	29	-8.65	<.0001	0.05	-6.8847	-4.2515
TREAT*STUDY	Drug	1	Placebo	2	-5.4111	0.5265	43.9	-10.28	<.0001	0.05	-6.4723	-4.3499
TREAT*STUDY	Drug	1	Placebo	3	-4.4208	1.4282	39	-3.10	0.0036	0.05	-7.3097	-1.5320
TREAT*STUDY	Drug	1	Placebo	4	-5.7052	1.3182	43.5	-4.33	<.0001	0.05	-8.3626	-3.0477
TREAT*STUDY	Drug	1	Placebo	5	-4.9177	1.0539	46.5	-4.67	<.0001	0.05	-7.0384	-2.7970
TREAT*STUDY	Drug	1	Placebo	6	-4.2827	1.4714	40.9	-2.91	0.0058	0.05	-7.2544	-1.3109
TREAT*STUDY	Drug	1	Placebo	7	-4.7550	1.7057	64.9	-2.79	0.0070	0.05	-8.1617	-1.3482
TREAT*STUDY	Drug	2	Drug	3	0.4043	1.3991	35.9	0.29	0.7742	0.05	-2.4334	3.2421
TREAT*STUDY	Drug	2	Drug	4	-2.5148	1.2955	39.4	-1.94	0.0594	0.05	-5.1343	0.1047
TREAT*STUDY	Drug	2	Drug	5	-3.2217	0.9891	38	-3.26	0.0024	0.05	-5.2240	-1.2195
TREAT*STUDY	Drug	2	Drug	6	-4.1952	1.4384	37.4	-2.92	0.0060	0.05	-7.1087	-1.2817
TREAT*STUDY	Drug	2	Drug	7	-4.3575	1.6449	57.2	-2.65	0.0104	0.05	-7.6511	-1.0639
TREAT*STUDY	Drug	2	Placebo	1	-3.9898	0.5258	43.7	-7.59	<.0001	0.05	-5.0497	-2.9299
TREAT*STUDY	Drug	2	Placebo	2	-3.8328	0.3725	18	-10.29	<.0001	0.05	-4.6153	-3.0503
TREAT*STUDY	Drug	2	Placebo	3	-2.8425	1.3829	34.7	-2.06	0.0474	0.05	-5.6509	-0.03414
TREAT*STUDY	Drug	2	Placebo	4	-4.1269	1.2723	37.6	-3.24	0.0025	0.05	-6.7033	-1.5504
TREAT*STUDY	Drug	2	Placebo	5	-3.3394	0.9921	38.3	-3.37	0.0017	0.05	-5.3473	-1.3315
TREAT*STUDY	Drug	2	Placebo	6	-2.7044	1.4290	36.7	-1.89	0.0663	0.05	-5.6006	0.1919
TREAT*STUDY	Drug	2	Placebo	7	-3.1767	1.6713	59.6	-1.90	0.0622	0.05	-6.5203	0.1670
TREAT*STUDY	Drug	3	Drug	4	-2.9191	1.7479	57.2	-1.67	0.1004	0.05	-6.4189	0.5807
TREAT*STUDY	Drug	3	Drug	5	-3.6261	1.5991	51.6	-2.27	0.0276	0.05	-6.8356	-0.4166
TREAT*STUDY	Drug	3	Drug	6	-4.5995	1.8832	59.5	-2.44	0.0176	0.05	-8.3672	-0.8318
TREAT*STUDY	Drug	3	Drug	7	-4.7618	2.0297	77.3	-2.35	0.0215	0.05	-8.8032	-0.7204
TREAT*STUDY	Drug	3	Placebo	1	-4.3942	1.4465	40.5	-3.04	0.0042	0.05	-7.3166	-1.4717
TREAT*STUDY	Drug	3	Placebo	2	-4.2371	1.4018	36.1	-3.02	0.0046	0.05	-7.0799	-1.3944
TREAT*STUDY	Drug	3	Placebo	3	-3.2469	1.8728	29.9	-1.73	0.0933	0.05	-7.0720	0.5783

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT*STUDY	Drug	3	Placebo	4	-4.5312	1.7418	56.7	-2.60	0.0118	0.05	-8.0196	-1.0428
TREAT*STUDY	Drug	3	Placebo	5	-3.7437	1.5989	51.6	-2.34	0.0231	0.05	-6.9528	-0.5347
TREAT*STUDY	Drug	3	Placebo	6	-3.1087	1.8820	59.4	-1.65	0.1039	0.05	-6.8740	0.6566
TREAT*STUDY	Drug	3	Placebo	7	-3.5810	2.0376	78	-1.76	0.0828	0.05	-7.6376	0.4756
TREAT*STUDY	Drug	4	Drug	5	-0.7070	1.4595	53.4	-0.48	0.6301	0.05	-3.6339	2.2200
TREAT*STUDY	Drug	4	Drug	6	-1.6804	1.7484	56.3	-0.96	0.3406	0.05	-5.1826	1.8217
TREAT*STUDY	Drug	4	Drug	7	-1.8427	1.8950	69.4	-0.97	0.3342	0.05	-5.6228	1.9373
TREAT*STUDY	Drug	4	Placebo	1	-1.4751	1.3460	45.8	-1.10	0.2788	0.05	-4.1846	1.2345
TREAT*STUDY	Drug	4	Placebo	2	-1.3180	1.3003	39.8	-1.01	0.3169	0.05	-3.9464	1.3104
TREAT*STUDY	Drug	4	Placebo	3	-0.3278	1.7579	57.9	-0.19	0.8527	0.05	-3.8466	3.1911
TREAT*STUDY	Drug	4	Placebo	4	-1.6121	1.4683	13.9	-1.10	0.2908	0.05	-4.7624	1.5382
TREAT*STUDY	Drug	4	Placebo	5	-0.8246	1.4578	53.3	-0.57	0.5740	0.05	-3.7483	2.0991
TREAT*STUDY	Drug	4	Placebo	6	-0.1896	1.7511	56.5	-0.11	0.9142	0.05	-3.6967	3.3175
TREAT*STUDY	Drug	4	Placebo	7	-0.6619	1.8945	69.4	-0.35	0.7279	0.05	-4.4410	3.1172
TREAT*STUDY	Drug	5	Drug	6	-0.9735	1.6154	51.6	-0.60	0.5494	0.05	-4.2155	2.2686
TREAT*STUDY	Drug	5	Drug	7	-1.1358	1.7862	72	-0.64	0.5269	0.05	-4.6964	2.4249
TREAT*STUDY	Drug	5	Placebo	1	-0.7681	1.0553	46.7	-0.73	0.4703	0.05	-2.8914	1.3552
TREAT*STUDY	Drug	5	Placebo	2	-0.6111	0.9925	38.4	-0.62	0.5417	0.05	-2.6196	1.3975
TREAT*STUDY	Drug	5	Placebo	3	0.3792	1.5986	51.5	0.24	0.8134	0.05	-2.8294	3.5878
TREAT*STUDY	Drug	5	Placebo	4	-0.9051	1.4507	52.7	-0.62	0.5354	0.05	-3.8152	2.0050
TREAT*STUDY	Drug	5	Placebo	5	-0.1177	1.2679	27.7	-0.09	0.9267	0.05	-2.7160	2.4807
TREAT*STUDY	Drug	5	Placebo	6	0.5174	1.6131	51.4	0.32	0.7497	0.05	-2.7203	3.7551
TREAT*STUDY	Drug	5	Placebo	7	0.04509	1.7971	73	0.03	0.9801	0.05	-3.5364	3.6266
TREAT*STUDY	Drug	6	Drug	7	-0.1623	2.0325	76.7	-0.08	0.9366	0.05	-4.2098	3.8851
TREAT*STUDY	Drug	6	Placebo	1	0.2054	1.4844	41.9	0.14	0.8906	0.05	-2.7905	3.2012
TREAT*STUDY	Drug	6	Placebo	2	0.3624	1.4418	37.6	0.25	0.8029	0.05	-2.5573	3.2821
TREAT*STUDY	Drug	6	Placebo	3	1.3527	1.8877	59.8	0.72	0.4764	0.05	-2.4235	5.1288

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

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	0.06832	1.7452	56.1	0.04	0.9689	0.05	-3.4276	3.5642
TREAT*STUDY	Drug	6	Placebo	5	0.8558	1.6146	51.6	0.53	0.5984	0.05	-2.3848	4.0964
TREAT*STUDY	Drug	6	Placebo	6	1.4908	1.8906	29.8	0.79	0.4366	0.05	-2.3713	5.3530
TREAT*STUDY	Drug	6	Placebo	7	1.0185	2.0370	77.1	0.50	0.6185	0.05	-3.0376	5.0747
TREAT*STUDY	Drug	7	Placebo	1	0.3677	1.6851	62.9	0.22	0.8280	0.05	-2.9997	3.7351
TREAT*STUDY	Drug	7	Placebo	2	0.5247	1.6484	57.5	0.32	0.7514	0.05	-2.7754	3.8248
TREAT*STUDY	Drug	7	Placebo	3	1.5150	2.0367	77.9	0.74	0.4592	0.05	-2.5398	5.5697
TREAT*STUDY	Drug	7	Placebo	4	0.2306	1.8944	69.4	0.12	0.9035	0.05	-3.5481	4.0094
TREAT*STUDY	Drug	7	Placebo	5	1.0181	1.7850	71.9	0.57	0.5702	0.05	-2.5404	4.5765
TREAT*STUDY	Drug	7	Placebo	6	1.6531	2.0340	76.8	0.81	0.4189	0.05	-2.3972	5.7035
TREAT*STUDY	Drug	7	Placebo	7	1.1808	2.1632	46.5	0.55	0.5878	0.05	-3.1722	5.5339
TREAT*STUDY	Placebo	1	Placebo	2	0.1570	0.5260	43.7	0.30	0.7667	0.05	-0.9032	1.2172
TREAT*STUDY	Placebo	1	Placebo	3	1.1473	1.4311	39.2	0.80	0.4276	0.05	-1.7468	4.0413
TREAT*STUDY	Placebo	1	Placebo	4	-0.1370	1.3238	44	-0.10	0.9180	0.05	-2.8050	2.5309
TREAT*STUDY	Placebo	1	Placebo	5	0.6504	1.0581	47.1	0.61	0.5417	0.05	-1.4782	2.7790
TREAT*STUDY	Placebo	1	Placebo	6	1.2855	1.4753	41.2	0.87	0.3886	0.05	-1.6936	4.2645
TREAT*STUDY	Placebo	1	Placebo	7	0.8132	1.7107	65.3	0.48	0.6361	0.05	-2.6030	4.2294
TREAT*STUDY	Placebo	2	Placebo	3	0.9903	1.3852	34.8	0.71	0.4794	0.05	-1.8223	3.8028
TREAT*STUDY	Placebo	2	Placebo	4	-0.2941	1.2768	38	-0.23	0.8191	0.05	-2.8788	2.2907
TREAT*STUDY	Placebo	2	Placebo	5	0.4934	0.9956	38.7	0.50	0.6230	0.05	-1.5210	2.5078
TREAT*STUDY	Placebo	2	Placebo	6	1.1284	1.4322	36.9	0.79	0.4358	0.05	-1.7736	4.0304
TREAT*STUDY	Placebo	2	Placebo	7	0.6562	1.6752	59.9	0.39	0.6967	0.05	-2.6948	4.0071
TREAT*STUDY	Placebo	3	Placebo	4	-1.2843	1.7499	57.3	-0.73	0.4660	0.05	-4.7880	2.2193
TREAT*STUDY	Placebo	3	Placebo	5	-0.4969	1.5988	51.6	-0.31	0.7572	0.05	-3.7057	2.7120
TREAT*STUDY	Placebo	3	Placebo	6	0.1382	1.8854	59.7	0.07	0.9418	0.05	-3.6336	3.9099
TREAT*STUDY	Placebo	3	Placebo	7	-0.3341	2.0470	78.8	-0.16	0.8708	0.05	-4.4087	3.7405
TREAT*STUDY	Placebo	4	Placebo	5	0.7875	1.4493	52.6	0.54	0.5892	0.05	-2.1200	3.6949

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Differences of Least Squares Means

Effect	TREAT	STUDY	TREAT	STUDY	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
TREAT*STUDY	Placebo	4	Placebo	6	1.4225	1.7469	56.2	0.81	0.4189	0.05	-2.0767	4.9217
TREAT*STUDY	Placebo	4	Placebo	7	0.9502	1.8959	69.5	0.50	0.6178	0.05	-2.8315	4.7320
TREAT*STUDY	Placebo	5	Placebo	6	0.6350	1.6125	51.4	0.39	0.6953	0.05	-2.6016	3.8716
TREAT*STUDY	Placebo	5	Placebo	7	0.1628	1.7955	72.9	0.09	0.9280	0.05	-3.4159	3.7414
TREAT*STUDY	Placebo	6	Placebo	7	-0.4723	2.0396	77.3	-0.23	0.8175	0.05	-4.5335	3.5889

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 Minutes

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

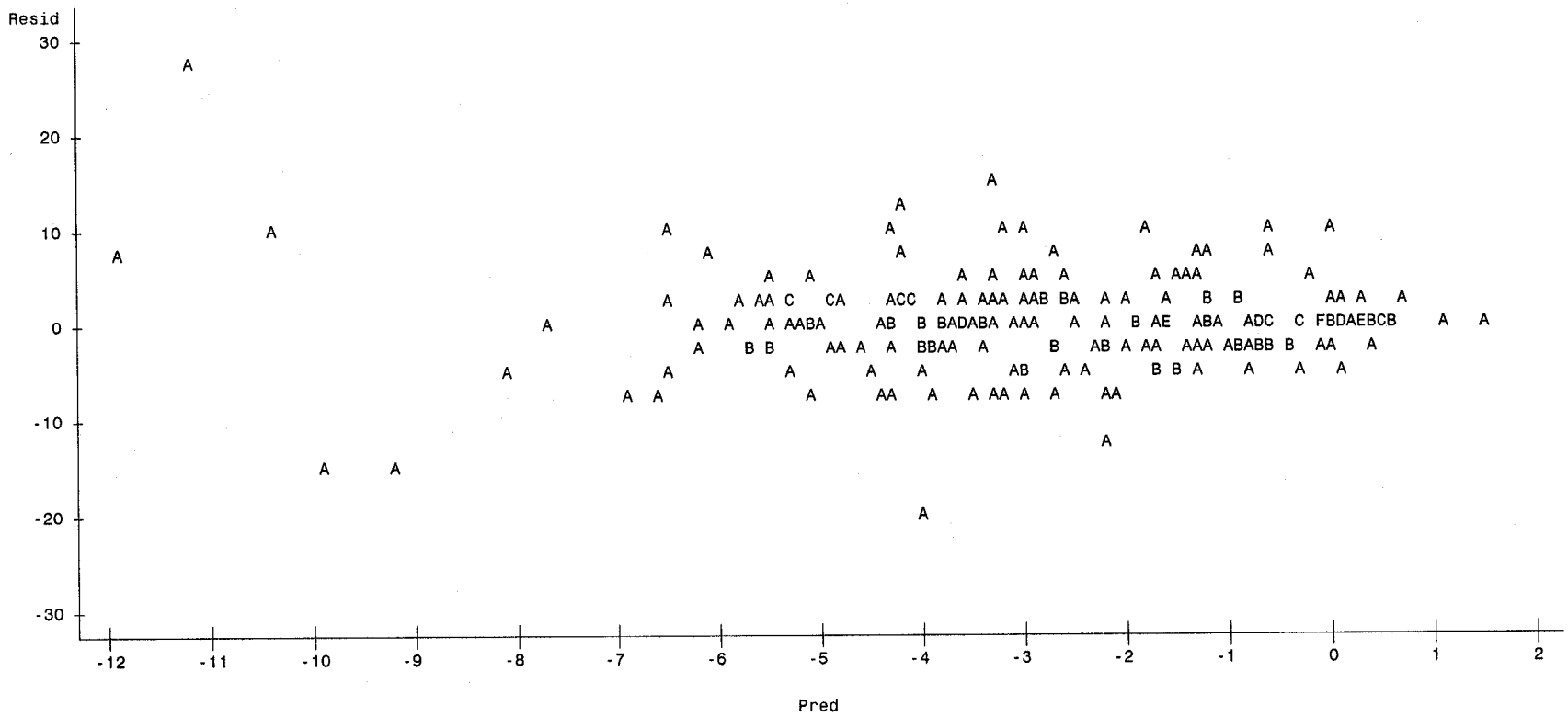
Checking the Treatment by Study Interaction Term to Test for Heterogeneity

Patient Is Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

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



Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 Minutes

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

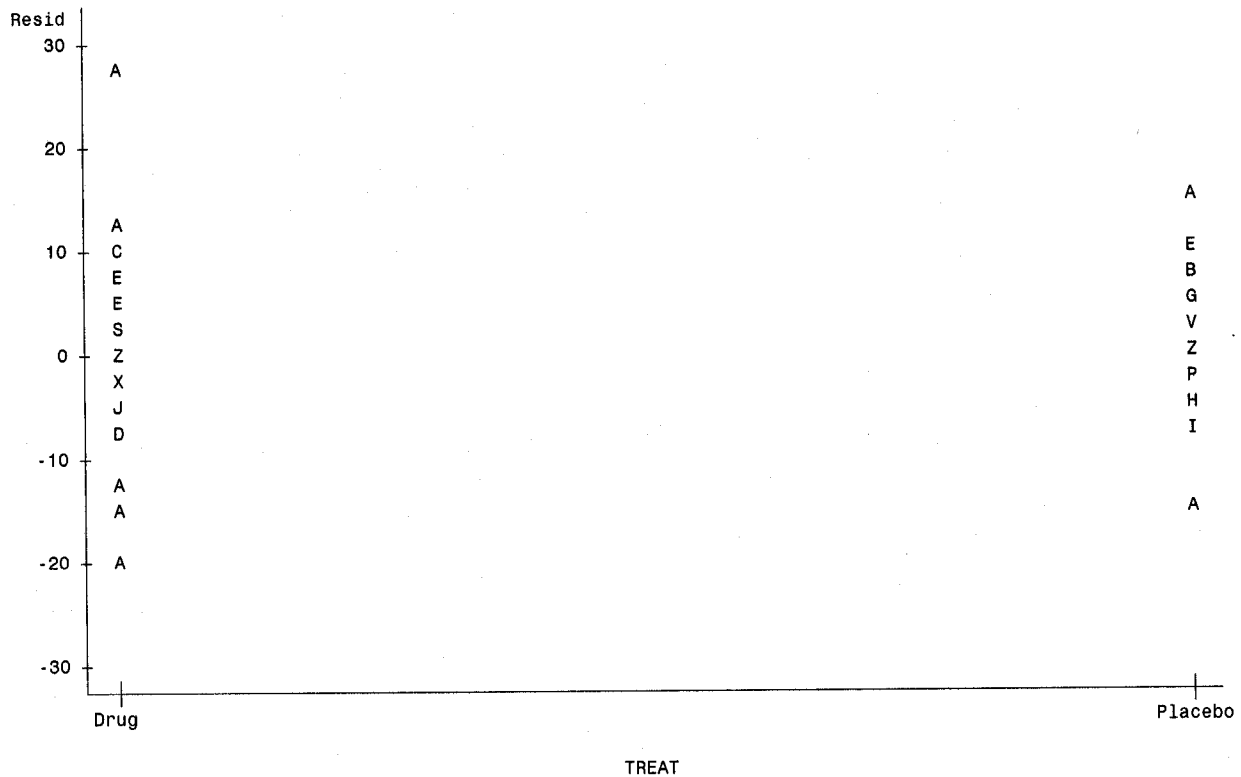
Checking the Treatment by Study Interaction Term to Test for Heterogeneity

Patient Is Random

Assuming Within Subject Variance Component Differs Across Studies

TO = Baseline (A Covariate)

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



NOTE: 28 obs hidden.

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure

Variable: Resid

Moments

N	113	Sum Weights	113
Mean	0	Sum Observations	0
Std Deviation	5.3622253	Variance	28.7534601
Skewness	0.77288202	Kurtosis	8.6916391
Uncorrected SS	3220.38753	Corrected SS	3220.38753
Coeff Variation	.	Std Error Mean	0.50443572

Basic Statistical Measures

Location		Variability	
Mean	0.00000	Std Deviation	5.36223
Median	-0.20882	Variance	28.75346
Mode	.	Range	49.58142
		Interquartile Range	3.88750

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	0	Pr > |t|	1.0000
Sign	M	-4.5	Pr >= |M|	0.4519
Signed Rank	S	-206.5	Pr >= |S|	0.5565

Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random
Assuming Within Subject Variance Component Differs Across Studies
TO = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Tests for Normality

Test	--Statistic---		-----p Value------	
Shapiro-Wilk	W	0.860134	Pr < W	<0.0001
Kolmogorov-Smirnov	D	0.145823	Pr > D	<0.0100
Cramer-von Mises	W-Sq	0.70531	Pr > W-Sq	<0.0050
Anderson-Darling	A-Sq	3.920314	Pr > A-Sq	<0.0050

Quantiles (Definition 5)

Quantile	Estimate
100% Max	28.393135
99%	13.516216
95%	7.928551
90%	6.068506
75% Q3	1.666112
50% Median	-0.208816
25% Q1	-2.221386
10%	-4.367632
5%	-6.954663
1%	-15.008352
0% Min	-21.188289

Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

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
-21.1883	7016	49	9.44865	3018	73
-15.0084	3001	67	9.79328	5027	90
-13.4115	7020	52	10.10436	7002	43
-8.0928	6003	17	13.51622	6046	30
-7.5459	5013	85	28.39314	7042	63

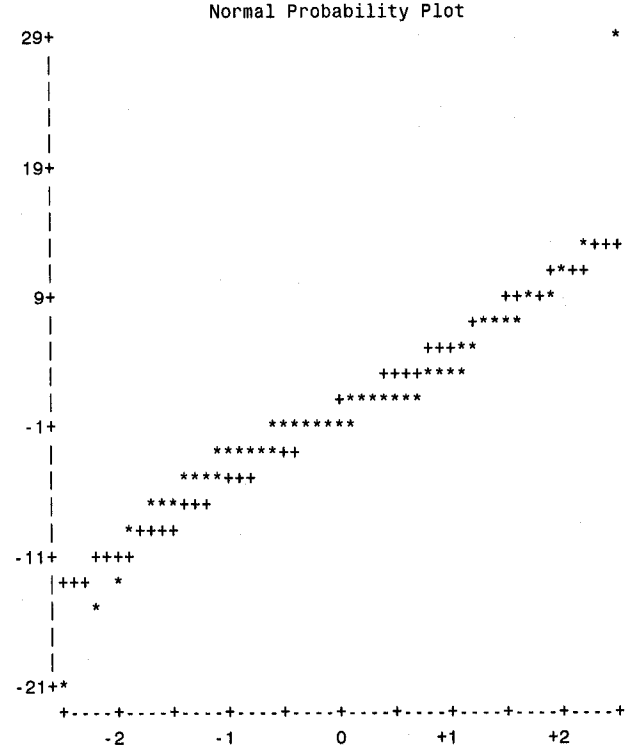
Appendix 3
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 Minutes
Model 1: Fixed Effects Model to Test Heterogeneity, Adjusting for Baseline NAR (Nasal Airflow Resistance and Study with Treatment by Study Interaction
Checking the Treatment by Study Interaction Term to Test for Heterogeneity
Patient Is Random
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

Stem	Leaf	#	Boxplot
28	4	1	*
26			
24			
22			
20			
18			
16			
14			
12	5	1	*
10	1	1	0
8	48	2	0
6	1236799	7	0
4	415	3	|
2	11333781457	11	|
0	112233444567802222345667 99	26	+--+--+
-0	98866665543221199977666432211 10	31	*-----*
-2	884332877654321	15	+-----+
-4	6654221	7	|
-6	5081	4	|
-8	1	1	0
-10			
-12	4	1	0
-14	0	1	*
-16			
-18			
-20	2	1	*

Normal Probability Plot



Appendix 3

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random

Assuming Within Subject Variance Component Differs Across Studies

T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure

Variable: Resid

Moments

N	113	Sum Weights	113
Mean	0	Sum Observations	0
Std Deviation	4.33221279	Variance	18.7680676
Skewness	-0.0176924	Kurtosis	2.13033341
Uncorrected SS	2102.02357	Corrected SS	2102.02357
Coeff Variation	.	Std Error Mean	0.4075403

Basic Statistical Measures

Location		Variability	
Mean	0.000000	Std Deviation	4.33221
Median	0.072559	Variance	18.76807
Mode	.	Range	30.33569
		Interquartile Range	4.28856

Tests for Location: Mu0=0

Test	-Statistic-		-----p Value------	
Student's t	t	0	Pr > |t|	1.0000
Sign	M	1.5	Pr >= |M|	0.8509
Signed Rank	S	42.5	Pr >= |S|	0.9037

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random
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	0.958776	Pr < W	0.0015
Kolmogorov-Smirnov	D	0.115951	Pr > D	<0.0100
Cramer-von Mises	W-Sq	0.298624	Pr > W-Sq	<0.0050
Anderson-Darling	A-Sq	1.608978	Pr > A-Sq	<0.0050

Quantiles (Definition 5)

Quantile	Estimate
100% Max	14.1277165
99%	10.4955598
95%	9.1006421
90%	4.4469323
75% Q3	2.1425837
50% Median	0.0725585
25% Q1	-2.1459792
10%	-5.1458352
5%	-7.0753927
1%	-8.3469562
0% Min	-16.2079758

Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random
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
-16.20798	7002	43	9.19496	4037	13
-8.34696	7030	57	9.25642	6017	22
-8.29710	7025	54	10.28894	7028	56
-7.93614	6046	30	10.49556	6026	24
-7.28821	3044	80	14.12772	3026	75

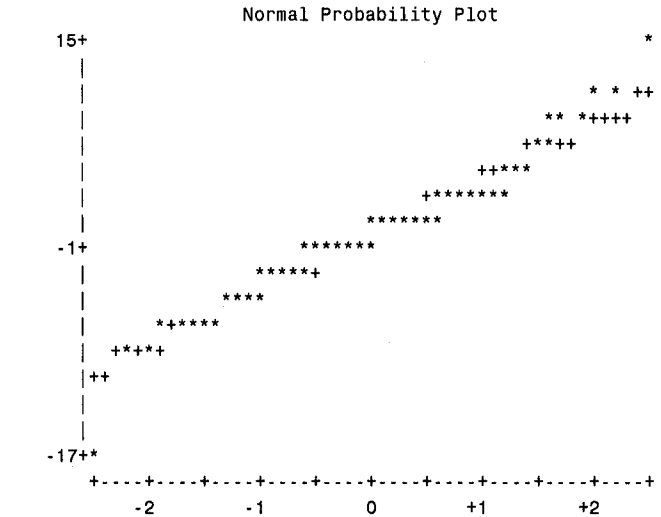
Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 Minutes
Model 1: Fixed Effects Model to Test Heterogeneity, Adjusting for Baseline NAR (Nasal Airflow Resistance and Study with Treatment by Study Interaction
Checking the Treatment by Study Interaction Term to Test for Heterogeneity
Patient Is Random
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

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

The UNIVARIATE Procedure
Variable: Resid

```
Stem Leaf                          #             Boxplot
  14 1                             1                0
  12                                                 |
  10 35                            2                0
   8 123                           3                0
   6 56                            2                |
   4 04696                         5                |
   2 011123888012225789           18             +-----+
   0 111222344555666779990334578  27             *--+--*
  -0 874410777765544443322211     25             |     |
  -2 421000986310                 12             +-----+
  -4 61099611                      8                |
  -6 9311097                       7                |
  -8 33                            2                |
 -10                                                 |
 -12                                                 |
 -14                                                 |
 -16 2                             1                *
     ----+----+----+----+----+--
```

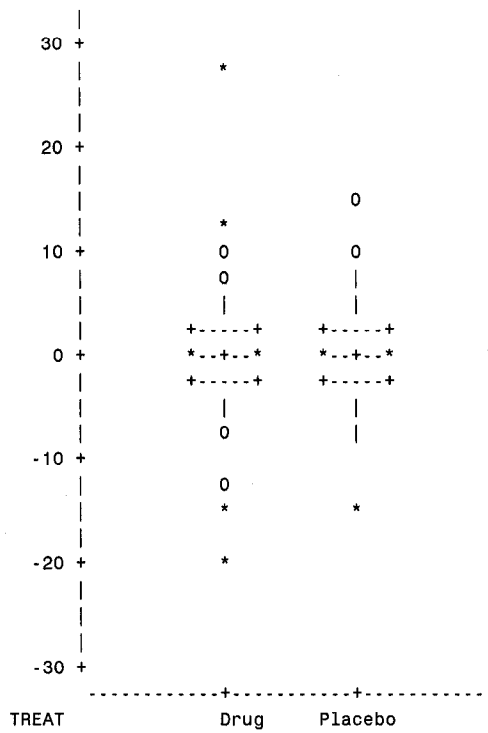
Normal Probability Plot



Meta-Analysis of Phenylephrine vs. Placebo
Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 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 Random
Assuming Within Subject Variance Component Differs Across Studies
T0 = Baseline (A Covariate)

The UNIVARIATE Procedure
Variable: Resid

Schematic Plots



Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 Minutes

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

Patient Is Random

Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Model Information

Data Set	WORK.TEN_MG
Dependent Variable	T60CHG
Covariance Structure	Compound Symmetry
Subject Effect	PATIENT(STUDY)
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	7	1 2 3 4 5 6 7
TREAT	2	Drug Placebo

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 Minutes

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

Patient Is Random

Assuming Within Subject Variance Component and Between Subject Variance Component Differ Across Studies

T0 = Baseline (A Covariate)

The Mixed Procedure

Class Level Information

Class	Levels	Values
PATIENT	113	1002 1007 1008 1011 1013 1016 1017 1018 1020 1026 1030 1031 1034 1035 1037 1038 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 5001 5010 5013 5015 5021 5022 5025 5027 5029 5030 5032 5034 5035 5043 5046 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	14
Columns in X	11
Columns in Z	0
Subjects	113
Max Obs Per Subject	2
Observations Used	226

Meta-Analysis of Phenylephrine vs. Placebo

Performing Analysis of Covariance by Time Point: Change from Baseline Nasal Airflow Resistance (NAR) at 60 Minutes

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The Mixed Procedure

Dimensions

Observations Not Used	0
Total Observations	226

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	1365.03609436	
1	2	1264.09771253	0.00608440
2	1	1261.99140904	0.00192447
3	1	1258.32679278	0.00182830
4	1	1257.47928766	0.00011379
5	1	1257.42790616	0.00000087
6	1	1257.42753092	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
Variance	PATIENT(STUDY)	STUDY 1	5.3699
CS	PATIENT(STUDY)	STUDY 1	-1.1513
Variance	PATIENT(STUDY)	STUDY 2	0.6824
CS	PATIENT(STUDY)	STUDY 2	0.009895
Variance	PATIENT(STUDY)	STUDY 3	31.6596
CS	PATIENT(STUDY)	STUDY 3	-4.2806
Variance	PATIENT(STUDY)	STUDY 4	17.4861