Researchers investigated the effect of new medication in patients with high blood pressure in a two-armed, placebo controlled, double-blinded, multisite Phase III clinical trial. Patients are randomized in a 1:1 allocation ratio to both treatment arms. The primary objective of this study is to see how the treatments differ on "change from baseline (month 0) to final systolic blood pressure (SBP)" at the end of the study (month 4). The sponsor is concerned that there may be some treatment-by-site interaction. As the lead biostatistician on the team, you are asked to assess any potential effect modification that may be present in the trial.

Variable	Label	Decode
age	Age at baseline, years	
change	Change from baseline to month 4 in systolic blood pressure (mmHg)	
cvd	Indicator of cardiovascular disease	0=No, 1=Yes
dbp0	Diastolic blood pressure at baseline (mmHg)	
dbp4	Diastolic blood pressure at month 4 (mmHg)	
patid	Patient ID number	
sbp0	Systolic blood pressure at baseline (mmHg)	
sbp4	Systolic blood pressure at month 4 (mmHg)	
sex	Indicator of sex	0=woman, 1=man
site	Indicator of site	1=site 1, 2=site 2, 3=site 3
trtgrp	Indicator of treatment	0=Placebo, 1=new medication

Summarize the descriptive statistics (N, mean, and standard deviation) in each treatment group for change in SBP (overall and stratified by study site). Round to 1 decimal place (in PROC MEANS, you can use NDEC=1). Without performing any formal statistical testing, do you observe any potential interaction effect due to study site? Please provide numeric evidence.

Change in Systolic Blood Pressure by Treatment

The MEANS Procedure

Analysis Variable : change Change in SBP from Baseline			
Treatment	N Obs	Mean	Std Dev
Placebo	80	-13.8	14.9
Treatment	80	-20.9	19.0

Change in Systolic Blood Pressure by Study Site and Treatment

The MEANS Procedure

Analysis Variable : change Change in SBP from Baseline				
site	Treatment	N Obs	Mean	Std Dev
1	Placebo	17	-17.8	19.3
	Treatment	17	-10.1	12.9
2	Placebo	27	-14.1	11.1
	Treatment	26	-15.0	17.9
3	Placebo	36	-11.8	15.0
	Treatment	37	-30.1	18.1

There appears to be some potential effect modification from study center because the treatment effect greatly differs between study sites. The average SBP decrease at center 3 was three times as much as the decrease at center 1 and twice as much as the decrease at center 2.

Perform an unadjusted analysis of the effect of treatment on change in SBP. Do the results change when you adjust for site?

An unadjusted linear regression analysis was used to test whether change in SBP from baseline was linearly associated with treatment. The F-statistic was 6.91 with 1 and 158 degrees of freedom, and the resulting p-value was 0.0094. With a p-value less than the α=0.05 significance level, the null hypothesis of there being no linear association between change in SBP and treatment was rejected. There is evidence suggesting that the linear association is

$$SBPchange = -13.8375 - 7.0875trtN$$

An adjusted multiple linear regression analysis was used to test whether change in SBP from baseline was linearly associated with treatment and study center. The F-statistic was 4.42 with 2 and 157 degrees of freedom, and the resulting p-value was 0.0052. With a p-value less than the α=0.05 significance level, the null hypothesis of there being no linear association between change in SBP and treatment was rejected. There is evidence suggesting that the linear association is

$$SBPchange = -17.4753 - 7.0082trtN + 7.0382site1 + 6.3472site2$$

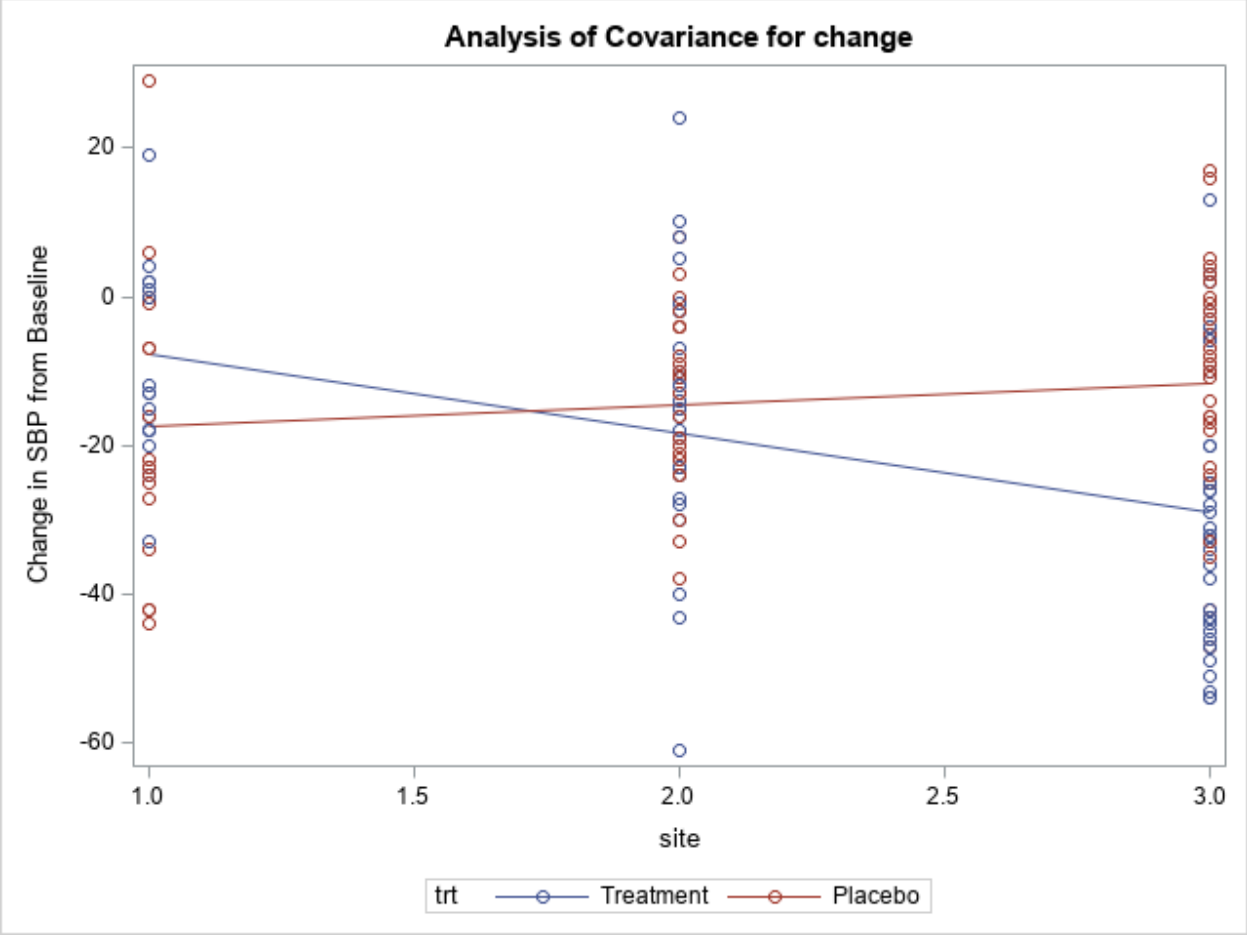
The results do not change significantly when adjusting for study center. Both regression analysis show that the new treatment decreases SBP by at least 7 mmHg.

Use PROC GLM to assess if there is a significant treatment-by-site interaction on change in SBP using a 0.15 level of significance. Report the null and alternative hypotheses, the test statistic, and the p-value from the interaction test. Use an appropriate tabulation or graph to support your conclusion. If the interaction is significant, is it quantitative or qualitative? Summarize your conclusion in a sentence.

H_0: $\beta_4 = \beta_5 = 0$ There is no interaction between treatment and study center.
H_A: $\beta_4 \neq 0, \beta_5 \neq 0$ There is interaction between treatment and study center.

A multiple linear regression analysis was used to test whether change in SBP from baseline was linearly associated with the interaction between treatment and study center. The F-statistic was 9.06 and the resulting p-value was 0.0002. With a p-value less than the α=0.15 significance level, the null hypothesis of there being no linear association between change in SBP and the interaction between treatment and study center was rejected. There is evidence suggesting that the linear association is

$$SBPchange = -11.7500 - 18.3041trtN - 6.0147site1 - 2.3981site2 + 25.9511trtNsite1 + 17.4522trtNsite2$$



The interaction is significant and is qualitative.

Re-code site with dummy variables and use PROC REG to test for treatment-by-site interaction. Report the test statistic and the p-value from the interaction test – they should match the previous output.

H_0: $\beta_4 = \beta_5 = 0$	There is no interaction between treatment and study center.
H_A: $\beta_4 \neq 0, \beta_5 \neq 0$	There is interaction between treatment and study center.

A multiple linear regression analysis using dummy variables was used to test whether change in SBP from baseline was linearly associated with the interaction between treatment and study center. For the interaction between treatment and study center 1, the F-statistic was 15.20 and resulting p-value was 0.0001. For the interaction between treatment and study center 2, the F-statistic was 9.10 and resulting p-value was 0.0030. With p-values less than the α=0.15 significance level, the null hypothesis of there being no linear association between change in SBP and the interaction between treatment and study center was rejected. There is evidence suggesting that the linear association is

$$SBPchange = -11.7500 - 18.3041trtN - 6.0147site1 - 2.3981site2 + 25.9511trtNsite1 + 17.4522trtNsite2$$

Write the linear regression model relating expected change from baseline to final SBP and treatment for site 1, site 2, and site 3. Briefly explain how these results support your previous conclusion.

treatment and site 1	$E[Y] = -11.7500 - 18.3041 - 6.0147 + 25.9511$	-10.1177
treatment and site 2	$E[Y] = -11.7500 - 18.3041 - 2.3981 + 17.4522$	-15
treatment and site 3	$E[Y] = -11.7500 - 18.3041$	-30.0541
placebo and site 1	$E[Y] = -11.7500 - 6.0147$	-17.7647
placebo and site 2	$E[Y] = -11.7500 - 2.3981$	-14.1481
placebo and site 3	$E[Y] = -11.7500$	-11.7500

These predicted values are exactly the same as the mean values calculated in question 1, which makes sense because the regression analysis came up with the best parameters that fit the inputted data. The interaction term between treatment and study center was significant because the treatment effect differed between study centers.

What is your final recommendation regarding treatment-by-site interaction? If interaction is not significant, please provide the overall measure of treatment effect and associated p-value. If the interaction is significant, please perform a subgroup analysis and report the stratified results (treatment effects and p-values).

Three linear regression analyses were used to test whether change in SBP from baseline was linearly associated with treatment at each of the three study centers.

For study center 1, the F-statistic was 1.85 with 1 and 32 degrees of freedom, and the resulting p-value was 0.1835. For study center 2, the F-statistic was 0.04 with 1 and 51 degrees of freedom, and the resulting p-value was 0.8353. With p-values less than the α=0.05 significance level, the null hypothesis of there being no linear association between change in SBP and treatment was not rejected. There is insufficient evidence to suggest the new treatment is more effective than the placebo at decreasing SBP at study centers 1 and 2.

At study center 3, the F-statistic was 21.99 with 1 and 71 degrees of freedom, and the resulting p-value was <0.0001. With a p-value less than the α=0.05 significance level, the null hypothesis of there being no linear association between change in SBP and treatment was rejected. There is evidence suggesting that at study center 3, the linear association is

$$SBPchange = -11.7500 - 18.3041trtN$$

It is recommended that those with hypertension go to study center 3 to get effective treatment.

The sponsor is also interested in knowing if this medication reduces the risk of CVD in the population under study. As a secondary analysis, you will investigate the effect of treatment on CVD. Previous Phase II trials have suggested that the medication may affect men and women differently. The sponsor would like you to explore possible effect modification due to sex.

Summarize the descriptive statistics (frequency and percent) of CVD in each treatment group (overall and stratified by sex). Do you observe any potential interaction effect due to sex?

Overall Sample	**No CVD**	**CVD**	Total
Placebo	64 (80%)	16 (20%)	80
Treatment	75 (95%)	4 (5%)	80
Total	140	20	160

Male	**No CVD**	**CVD**	Total
Placebo	34 (80.95%)	8 (19.05%)	42
Treatment	39 (97.50%)	1 (2.5%)	40
Total	73	9	82

Female	**No CVD**	**CVD**	Total
Placebo	30 (78.95%)	8 (21.05%)	38
Treatment	37 (92.50%)	3 (7.50%)	40
Total	67	11	78

There doesn't seem to be potential interaction due to sex because the percentage of those who developed CVD in the placebo and treatment group appear to be similar among males and females.

Use PROC FREQ to evaluate treatment-by-sex interaction by performing a Breslow-Day test, adjusting the test if appropriate. Report the null and alternative hypotheses, the test statistic, degrees of freedom, and p-value. Interpret the results using a 0.15 significance level.

A Breslow-Day-Tarone test was used to test whether there was interaction between treatment and sex on cardiovascular disease. The chi-squared score was 0.6485 with 1 degree of freedom, and the resulting p-value was 0.4206. With a p-value greater than the α=0.05 significance level, the null hypothesis of no interaction between treatment and sex on cardiovascular disease was not rejected. There is insufficient evidence to conclude that the effect of treatment on cardiovascular disease differs between male and females.

If the interaction is not significant, please report the overall, unadjusted treatment effect OR and p-value. If the interaction is significant, please provide the stratified ORs for men and women separately. Provide a sentence interpreting whichever OR(s) you report.

A chi-squared test was used to test whether there was an association between treatment and cardiovascular disease. The chi-squared statistic was 8.2286 with 1 degree of freedom and the resulting p-value was 0.0041. With a p-value less than the α=0.05 significance level, the null hypothesis of there being no association between treatment and cardiovascular disease was rejected. There is evidence suggesting that those who received the new treatment had 0.2105 times the odds of the cardiovascular disease compared to those who received the placebo (95% confidence interval: 0.0670, 0.6616).

Using PROC LOGISTIC, evaluate interaction due to sex using a 0.15 significance level. Interpret the results and report the appropriate p-value.

A multiple logistic regression analysis was used to test whether the risk of cardiovascular disease was associated with the interaction between treatment and sex. From the Wald test, the F-statistic was 0.6196 and resulting p-value was 0.4312. With a p-value greater than the α=0.15 significance level, the null hypothesis of there being no association between cardiovascular disease and interaction between treatment and sex was not rejected. There is insufficient evidence to conclude that the effect of treatment on cardiovascular disease differs between male and females.

When might you need to use PROC LOGISTIC instead of PROC FREQ?

The proc logistic performs a logistic regression while the proc freq function performs a chi-squared test. A logistic regression will perform a likelihood ratio test to see if the overall model is useful. If at least one parameter is not 0, then there is an association between the outcome variable and at least one of the predictors. A chi-squared test can only handle one categorical predictor variable, while a logistic regression can incorporate multiple covariates, some of which can be continuous. A logistic regression will also perform Wald tests for each predictor, not just the interaction term, so you can see the significance of each covariate.