NCT Number: NCT02536963

Study Title: Improving Quality Vision Outcomes in Managed Care Setting While Reducing Cost by Use of Accurate, Automated Screening

Document: Statistical Analysis Plan

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Statistical Analysis Plan
The analysis will be conducted under a Statistical Analysis and Report Plan (SAP) that is based on comparing the observed sensitivity and specificity to derived performance goals. The negative and positive predictive values will also be compared to performance goals as a secondary analysis.

Descriptive Analyses
The demographic characteristics for the population of children enrolled in the study will be presented descriptively. The continuous variables such as age will present the mean, standard Deviation (SD), number evaluated, median, minimum and maximum. For categorical variables such as gender, the number with the characteristic, the number evaluated, the percent, and the exact binomial 95% two-sided confidence interval will be provided. Continuous variables like age will be evaluated by either analysis of variance or the Kruskal-Wallis test. For categorical variables, the Fisher-Freeman-Halton test will be used. This assessment is not a justification for pooling the data, but will identify possible covariates that may be used to adjust estimates of sensitivity and specificity.

Co-Primary Endpoints
There are co-primary endpoints in this study, the sensitivity and specificity of the PVS for the detection of amblyopia or strabismus. The sensitivity and specificity will be compared to performance goal (PG) because there are no comparable evaluation systems currently approved to assist in the detection of amblyopia or strabismus. The null and alternative hypotheses for sensitivity are given below.

H_0: $Se_{PVS} \leq PG_1$

Versus

H_a: $Se_{PVS} > PG_1$

where Se_{PVS} is the sensitivity of the PVS for amblyopia or strabismus and PG_1 is a performance goal that depends on the total number of amblyopia or strabismus cases diagnosed in the study.

With 300 total children enrolled, 5% prevalence would yield 15 cases, 10% would yield 30 cases, and 15% prevalence would yield 45 cases. From the literature, the rate of sensitivity is based on small numbers of cases with high variability. Three possible performance goal estimates were derived: 66.1%, 81.7% or 83.5%. Since the low and high values appear to come from limited information, the LCL of 81.7% will allow the performance goal to be set at 80% = PG_1.

The null and alternative hypotheses for specificity are presented below.

H_0: $Sp_{PVS} \leq PG_2$

Versus

H_a: $Sp_{PVS} > PG_2$

where Sp_{PVS} is the specificity of the PVS for amblyopia or strabismus and PG_2 is a performance goal that depends on the total number of non-amblyopia cases diagnosed in the study.

If the prevalence is 5%, 10%, or 15% in the 300 children enrolled, the expected number of non-cases is 285, 270, or 255, respectively. Three values were reviewed from the literature and all had specificity of about 95%. To be conservative, a specificity of 90% is assumed and a target number of negative cases of 243 and a specificity of about 90% yields a lower one-sided confidence limit of 83.6% allowing a performance goal slightly lower at 82%= PG_2.

Secondary Endpoints

There are two secondary endpoints in this analysis. The first is the positive predictive value (PPV) defined as the ratio (or percentage) of the total number of true cases among all subjects with a positive PSV evaluation. The second secondary endpoint is negative predictive value (NPV), the number of non-cases among the children with a negative evaluation under the PVS.

The null and alternative hypotheses for PPV are presented below.

H_0: $PPV_{PVS} \leq PG_3$

Versus

H_a: $PPV_{PVS} > PG_3$

where PPV_{PVS} is the PPV of the PVS instrument and PG_3 is the prevalence dependent performance goal.

The null and alternative hypotheses for NPV are presented below.

H_0: $NPV_{PVS} \leq PG_4$

Versus

H_a: $NPV_{PVS} > PG_4$

where NPV_{PVS} is the NPV of the PVS instrument and PG_4 is the prevalence dependent performance goal.

Prior studies had large numbers of negative subjects and small numbers of positive subjects so it is difficult to predict LCL values for PPV and NPV. However, it is estimated that the study will have about 15-30 positive cases and about 270-285 negative cases. Using conservative estimates of about 90% sensitivity and 90% specificity, using the formulas below the corresponding PPV and NPV would be about 90% for each. Recognizing the uncertainty of the sample size and estimation process, a conservative lower limit for each performance goal will be chosen to be 75%.

Analysis of Sensitivity and Specificity

The sensitivity for the PVS will be computed as the percentage of subjects with a positive PVS evaluation divided by the total number of children determined by the intensive examination to have amblyopia. All of the data will be pooled and the statistical test will be done comparing the exact one-sided 95% lower confidence interval from the binomial distribution. If that lower limit is higher than PG_1, then the sensitivity will be determined to exceed the performance goal by a one-sided 0.05 interval test.

If the difference in sensitivity is determined to be different by study site, the sensitivity for study site i (Yi) will be computed and its variance determined (σ_i^2). The weight for each sensitivity at each site is the inverse of the variance of the estimate at that site (Fleiss, 1993). The study wide estimate of the sensitivity will be obtained by the following formula.

$$\overline{Y} = \frac{\sum_{i=1}^{3} Y_i W_i}{\sum_{i=1}^{3} W_i}$$

where

$$W_i = 1/\sigma_i^2 \ .$$

The standard error of the study site weighted estimate is given by

$$SE\left(\overline{Y}\right) = \left(\sum_{i=1}^{3} W_i\right)^{-1/2}$$

and the test is an interval test done by normal approximation. The lower one-sided 95% CL is obtained from the following formula.

$$LCL = \overline{Y} - 1.645 * SE\left(\overline{Y}\right).$$

If LCL > PG_1 then the null hypothesis will be rejected and the alternative hypothesis will be accepted.

The specificity will be obtained by taking the total number of children with negative PVS evaluations divided by the number of children determined by the extensive examination not to have amblyopia. If the study site specificities are not different by the pooling analysis above, then the exact binomial lower one-sided 95% confidence interval will be computed and compared to PG_2. If the lower confidence limit exceeds PG_2, then the null hypothesis for specificity above will be rejected and the alternative accepted.

If the specificity values from the sites are statistically heterogeneous by the pooling test, then the method of Fleiss will be used as described above for sensitivity. The test statistic is the LCL computed by substitution of specificity for sensitivity in the formulas above. If LCL > PG_2 then the null hypothesis for specificity above will be rejected and the alternative accepted.

Analysis of the PPV and NPV

If neither sensitivity nor specificity differ by study site, the PPV (as a percentage) for the study will be computed by taking the number of children with amblyopia from among all children with positive PVS evaluations. The exact 95% one-sided lower confidence limit will be computed and compared to PG_3. If that value is greater than PG_3 then the null will be rejected in favor of the alternative hypothesis. If sensitivity or specificity differ by study site, the site weighted PPV by method of Fleiss (1993) will be used to form the LCL to be compared to PG_3. This is accomplished by substituting PPV for sensitivity in the formulas above. If LCL is greater than PG_3 then the null will be rejected in favor of the alternative hypothesis. The PPV for different prevalence values presented and will be computed by the following formula.

$$\text{PPV} = \text{Sens}*\text{Prev}/(\text{Sens}*\text{Prev}+(1-\text{Spec})*(1-\text{Prev})).$$

Similarly, NPV (as a percentage) will be obtained by taking the number of children without amblyopia from among the children with a negative PVS evaluation. The exact 95% one-sided lower confidence limit will be computed and compared to PG_3. If that value is greater than PG_4 then the null will be rejected in favor of the alternative hypothesis. If sensitivity or specificity differ by study site, the site weighted PPV by method of Fleiss (1993) will be used to form the LCL to be compared to PG_4. This is accomplished by substituting PPV for sensitivity in the formulas above. If LCL is greater than PG_3 then the null will be rejected in favor of the alternative hypothesis. The NPV for different prevalence values presented and will be computed by the following formula.

$$NPV= Spec*(1-Prev)/(\ Spec*(1-Prev)+(1-Sens)*Prev)$$