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Statistical Considerations for Small Lung Nodule Profile Conformance

This document describes the situations where a site wants to show conformance with the Profile claims when i) the Profile has not reached the Claim Confirmed Stage, and ii) the Profile has reached the Claim Confirmed Stage. For the former, the confirmation assessment uses the conventional 95% confidence criterion, whereas the latter assessment is based on a 50% confidence criterion. Note that QIBA has not yet discussed the latter scenario since none of its profiles have reached the Claim Confirmed stage.

I. Profile is Not at Claim Confirmed Stage:

The three assumptions underlying the claims are 1) the measurement precision is specified by the repeatability estimates in Table 1 of the Profile, 2) the measurements have negligible bias, and 3) the measurements demonstrate the property of linearity with the true values with a slope of one. Each assumption is evaluated as follows:

1. Testing a Site's Precision:

The Profile lists seven wCV estimates based on nodule size. The site will assess two of these estimates, corresponding to smallest (6mm diameter) with a claimed wCV of 29% and largest (12mm) nodules with a claimed wCV of 11%, using a test-retest design with 25 6mm nodules and 25 12mm nodules. The following analyses apply to each nodule size range. **If the site's wCV estimate is ≤0.222 for the 6mm nodules and is ≤0.084 for the 12mm nodules, then the site has successfully passed the precision conformance requirement** (based on the 95% upper confidence bound for the wCV).

2. Testing a Site's Bias:

Claim 1 of the Profile assumes negligible bias, defined as <5%. Using a phantom nodule dataset with 40 simulated lesions, the site will take 1-2 measurements on each lesion. They will estimate the bias and construct a 95% CI, as follows: For each case, calculate the nodule volume (denoted Y_i), where *i* denotes the *i*-th case. Calculate the % bias: $b_i = [(Y_i - X_i)/X_i] \times 100$, where X_i is the true value of the nodule's volume. Over N cases estimate the bias: $bias = \sqrt{\sum_{i=1}^{N} b_i \,/N}$. The estimate of variance of the bias is $\widehat{Var}_b = \sum_{i=1}^{N} (\%b_i - \hat{b})^2 \,/(N-1)$. The 95% CI for the bias is $\hat{b} \pm t_{\alpha=0.025,(N-1)df} \times \sqrt{\widehat{Var}_b}$, where $t_{\alpha=0.025,(N-1)df}$ is from the Student's t-distribution with α=0.025 and (N-1) degrees of freedom. **The lower 95% confidence bound must be >-5% and the upper 95% bound <5% in order to be conformant with the bias assumption underlying the claim.** The sample size is based on meeting the bias conformance criterion even if the site's bias is as large as 4% and between-nodule variance as large as 10%.

3. Testing a Site's Measurement Linearity and Slope:

The longitudinal claims assume that measurement linearity holds. The site will measure 6 simulated nodules of different sizes ranging from 6 to 12mm. The nodules will each be measured 8 times for a total of 48 measurements. For each nodule, calculate the nodule volume (denoted Y_i), where *i* denotes the *i*-th case. Let X_i denote the true value for the i-th case. Fit an ordinary least squares (OLS) regression of the Y_i's on X_i's. A quadratic term is first included in the model to rule out non-linear relationships: $Y = \beta_o + \beta_1 X + \beta_2 X^2$. If $\beta_2 = 0$, then a linear model should be fit: $Y = \beta_o + \beta_1 X$, and R^2 estimated. **The estimate of β_2 should be <|0.50| and R-squared (R^2) should be >0.90 to demonstrate the property of linearity.** Let $\widehat{\beta_1}$ denote the estimated slope. Calculate its variance as $\widehat{Var}_{\beta_1} = \{\sum_{i=1}^{N}(Y_i - \widehat{Y_i})^2 / (N-2)\} / \sum_{i=1}^{N}(X_i - \bar{X})^2$, where $\widehat{Y_i}$ is the fitted value of Y_i from the regression line and $\bar{X}$ is the mean of the true values. The 95% CI for the slope is $\widehat{\beta_1} \pm t_{\alpha=0.025,(N-2)df}\sqrt{\widehat{Var}_{\beta_1}}$. **The 95% CI for the slope needs to be completely contained in the interval 0.95 to 1.05**.

II. Profile has reached Claim Confirmed Stage:

The three assumptions underlying the claims are 1) the measurement precision is specified by the repeatability estimates in Table 1 of the Profile, 2) the measurements have negligible bias, and 3) the measurements demonstrate the property of linearity with the true values with a slope of one. In a multi-site study, it has been shown that the Profile specifications lead to measurements with bias and precision equivalent or better than the assumptions underlying the claims, with 95% confidence. Moving forward, sites can show conformance with the Profile assumptions by showing consistency with two assumptions, defined at a 50% confidence level, as follows:

1. Testing a Site's Precision:

The Profile lists seven wCV estimates based on nodule size. The site will assess two of these estimates, corresponding to smallest (6mm diameter) and largest (12mm) nodules, using a test-retest design with 6 6mm nodules and 6 12mm nodules. The following analyses apply to each nodule size range. **If the site's wCV estimate is <u><</u>0.222 for the 6mm nodules and is <u><</u>0.084 for the 12mm nodules, then the site has successfully passed the precision conformance requirement** (based on the 50% upper confidence bound for the wCV).

2. Testing a Site's Bias:

Claim 1 of the Profile assumes negligible bias, defined as <5%. Using a phantom nodule dataset with 7 simulated lesions, the site will take 1-2 measurements on each lesion. They will estimate the bias and construct a 95% CI, as follows: For each case, calculate the nodule volume (denoted Y_i), where *i* denotes the *i*-th case. Calculate the % bias: $b_i = [(Y_i - X_i)/X_i] \times 100$, where X_i is the true value of the nodule's volume. Over N cases estimate the bias: $bias = \sqrt{\sum_{i=1}^{N} b_i /N}$. The estimate of variance of the bias is $\widehat{Var}_b = \sum_{i=1}^{N}(\%b_i - \hat{b})^2 /(N-1)$. The 95% CI for the bias is $\hat{b} \pm t_{\alpha=0.25,(N-1)df} \times \sqrt{\widehat{Var}_b}$, where $t_{\alpha=0.25,(N-1)df}$ is from the Student's t-distribution with α=0.25 and (N-1) degrees of freedom. **The lower 50% confidence bound must be >-5% and the upper 50% bound <5% in order to be conformant with the bias assumption underlying the claim.** The sample size is based on meeting the bias conformance criterion even if the site's bias is as large as 4% and between-nodule variance as large as 10%.