

## “Statistical Considerations for Planning a Clinical Trial”

The Profile Claims describe the technical performance of the quantitative imaging biomarker and its interpretation for the individual patient. The purpose of this section is to provide recommendations for translating the Profile claims to clinical trial planning where the results of a sample of subjects is of interest.

The Profile’s technical performance claim (Claim 1) provides an estimate of the within-subject coefficient of variation ( $wCV$ ) achievable if the Profile is followed.  $wCV$  is the within-subject standard deviation ( $wSD$ ) divided by the mean of the subject’s measurements.  $wSD$  is the standard deviation of repeated measurements (i.e. replicates) from a single experimental unit.  $wSD$  may include biological and physiological variability in the subject, as well as variability due to patient repositioning, scanner calibrations, software segmentation differences, etc [1,2].

In planning a clinical trial, regardless of the trial’s endpoint, the variance in the measurements is a key element in sample size calculations. The variance of quantitative imaging biomarker measurements is a function of both the between-subject variance ( $bVar$ ) and the within-subject variance ( $wVar = wSD^2$ ). The total variance of a subject’s measurement might be expressed as

$$Var_{subject} = bVar + wVar.$$

For a clinical trial, we might be interested in the variance of the mean over a group of  $N$  subjects

$$Var_{mean} = (bVar + wVar)/N.$$

It is important to incorporate  $wVar$  in the estimate of the variance so as not to underestimate the sample size requirements for the trial. The magnitude of  $bVar$  depends on factors affected by the design specifications of the clinical trial (e.g. inclusion and exclusion criteria). In contrast, the magnitude of  $wVar$  will vary with the magnitude of the measurements. This relationship between  $wVar$  and the magnitude of the measurements is given by

$$wVar = [wCV \times \bar{y}_{hypothesis}]^2,$$

where  $wCV$  is from the technical performance Claim (usually Claim 1) in the Profile and  $\bar{y}_{hypothesis}$  is the hypothesized mean of the measurements (either null or alternative hypothesis). Note that  $wVar$  will take on different values under the null and alternative hypothesis because the expected mean of the measurements will differ under the null and alternative hypotheses [3].

In a clinical trial where the mean change in biomarker values is assessed over time, the variance of the mean change for a sample of  $N$  subjects is

$$Var_{mean\ change} = (2 \times bVar + 2 \times wVar_{null}) \times (1 - r)/N$$

under the null hypothesis, and

$$Var_{mean\ change} = (2 \times bVar + wVar_{null} + wVar_{alternative}) \times (1 - r)/N$$

under the alternative hypothesis.  $r$  is the correlation coefficient; it describes the degree to which the first and second measurements on the same subject change together. It is important to note that  $wVar$  impacts  $r$ , such that large values of  $wVar$  attenuate  $r$  [3]. The magnitude of  $wVar$  should be considered when hypothesizing the value of  $r$  in sample size calculations.

Lastly, in some clinical trials the quantitative imaging biomarker might be used to identify who is eligible/ineligible for the study. For example, an inclusion criterion might specify that the biomarker value be in the range of  $z_1$  to  $z_2$  for subject inclusion into the trial. Subjects with biomarker values  $<z_1$  or  $>z_2$  are excluded from the trial. Since this is a cross-sectional measurement, refer to the corresponding cross-sectional claim of the Profile. Establishing a cross-sectional claim involves accounting for both the measurement bias and imprecision; it provides a formula for calculating a 95% confidence interval (CI) for the subject's true value,  $x$ , given a single measurement from the subject. For example, if the subject's measurement is  $y$ , then the cross sectional claim provides a formula to obtain a range of possible values of  $x$  based on the measurement  $y$ . The 95% CI means that if the subject was measured multiple times and the corresponding confidence intervals calculated, we would expect that 95% of the intervals would include the subject's true value,  $x$ .

In a clinical trial setting, a potential study subject would be measured and the 95% CI would be constructed. If the CI falls entirely inside the range of  $z_1$  to  $z_2$ , then the subject meets the eligibility criterion; otherwise, we are not sufficiently confident that the subject meets the eligibility criterion. Note that some Profiles do not include a cross-sectional claim. Usually this occurs when the bias of the measurements could not be estimated reliably. These Profiles are not currently able to identify subjects' trial eligibility based on the biomarker value because an accurate correspondence between the measurement ( $y$ ) and the true value ( $x$ ) has not been established [1].

#### References:

[1] Kessler LG, Barnhart HX, Buckler AJ, et al. The emerging science of quantitative imaging biomarkers: terminology and definitions for scientific studies and for regulatory submissions. SMMR 2015; 24: 9-26.

[2] Raunig D, McShane LM, Pennello G, et al. Quantitative imaging biomarkers: a review of statistical methods for technical performance assessment. SMMR 2015; 24: 27-67.

[3] To do publication