III. STATISTICAL TERMS COMMONLY USED IN SAMPLE SIZE CALCULATIONS

As stated previously, a statistician can translate the discussions surrounding the six questions posed previously into sample size calculations. In order to demonstrate this process, it is important to introduce a few statistical concepts and their relationship to the questions above.

IV. NULL AND ALTERNATIVE HYPOTHESES

In the case of the CEL-SCI Multikine study discussed earlier, the primary research question to be tested is "Is the survival rate of subjects treated with Multikine plus SOC ($p_{\text{Muilikine+SOC}}$) better than the survival rate of subjects treated with SOC only (p_{SOC})?" This statement in statistical terms would be, "Is $p_{\text{Muilikine+SOC}} > p_{\text{SOC}}$?" Certainly, the company believes that it is, or it would not be initiating a large phase III study. In statistics, hypotheses are constructed to evaluate the likelihood of such statements. These hypotheses can then be tested using statistical techniques. Each hypothesis test requires the statement of a null hypothesis (H_0) and the alternative hypothesis (H_1). These hypotheses are opposites of one another. The null hypothesis is the statement of what a researcher believes to be untrue and is commonly stated in terms including equality. In our example, the null hypothesis could be stated as H_0: $p_{\text{Muilikine+SOC}} \leq p_{\text{SOC}}$. The alternative hypothesis is a statement of what a researcher believes to be true. For our example, the alternative hypothesis is H_1: $p_{\text{Muilikine+SOC}} > p_{\text{SOC}}$. It is worth noting that this example is of a one-sided set of hypotheses. Here, the researcher is only interested if the new treatment is better than SOC. In regulatory settings, we typically are concerned with two-sided hypotheses. Here, the two-sided statement of this same example would be: H_0: $p_{\text{Muilikine+SOC}} = p_{\text{SOC}}$ and H_1: $p_{\text{Muilikine+SOC}} \neq p_{\text{SOC}}$.

Statistical methods commonly utilized in clinical trials test these hypotheses using an appropriate statistical technique. The outcome of this test can be either to reject the null hypothesis or fail to reject the null hypothesis. It should be noted that failing to reject the null hypothesis is not the same as accepting the null hypothesis. That is to say, in our two-sided example above, if we fail to reject the null hypothesis, H_0: $p_{\text{Muilikine+SOC}} = p_{\text{SOC}}$, we have not proved that the survival rate of subjects treated with Multikine + SOC is the same as the survival rate of subjects treated with SOC (standard of care) alone. Instead, we do not have conclusive evidence to support that the survival rate of subjects treated with Multikine + SOC is different than that of subjects treated with SOC alone. Similarly, if we reject the null hypothesis, we accept the alternative hypothesis. This does not represent proof of the alternative hypothesis, but rather provides evidence supporting the alternative hypothesis. As stated above, Standard of Care is defined in Chapter 7 (6,7).

The rationale for this distinction is grounded in the discussion of degree of certainty which can be visualized using Table 10.1.

[6]Moffet P, Moore G. The standard of care: legal history and definitions: the bad and good news. Western J. Emergency Med. 2011;7:109–12.

[7]Straus DC, Thomas JM. What does the medical profession mean by "standard of care?" J. Clin. Oncol. 2009;27: e192–3.