blood pressure, reduction in HIV-1 RNA levels), clinically meaningful differences are based on evaluation of published data and discussion through research working groups and other committees tasked with evaluating results from clinical trials. For example, the American Society of Clinical Oncology (ASCO) working group on pancreatic cancer recently suggested that a clinically meaningful survival benefit for a new treatment in folfirinox-eligible pancreatic cancer patients may be 4–5 months (4). It is important to understand what constitutes a clinically meaningful difference as there are situations where a very small, but clinically trivial difference can be detected using statistical techniques. Recall that to establish effectiveness, a trial must provide, "highly reliable and statistically strong evidence of an important clinical benefit" (5).

## d. What Treatment Effect Is Expected?

Treatment effect is the effect or benefit of getting one treatment over another. In preliminary trials, the treatment effect in humans may not be known. For later-phase studies, assumptions of treatment effect are normally based on the results of previously completed studies, if available. In the absence of data from an earlier trial, researchers are tasked with the problem of how to estimate the treatment effect. Typically, one of two common approaches are used: estimate treatment effect according to available information with the clinically meaningful difference or using available published data from similar studies to provide a best guess of treatment effect. For example, in phase I trials for anti-HIV compounds, it is commonly expected that at least a 1 $\log_{10}$ copies/mL drop in HIV-1 RNA is expected following a 14-day treatment in HIV-infected subjects. Given that the size of trial is inversely related to the treatment effect size, it is easy to see the importance of making informed assumptions of treatment effect in the process of calculating sample sizes.

## e. What Data Analysis Technique Is Appropriate for Determining a Difference Between Treatments?

The data analysis technique utilized will depend on the design of the study and the type of endpoint being utilized for the measure of the primary objective, and, potentially, regulatory precedence. Common data analysis techniques are tests of proportions for differences in binary data, *t*-tests, Wilcoxon rank sum tests, and analysis of variance models for the assessment of differences in continuous endpoints, and logrank tests for differences in time to event data. Most often the data analysis technique will be determined by a statistician during preliminary planning of the Protocol.

## f. What Degree of Certainty Is Expected or Required for Ascertaining Treatment Difference?

The degree of certainty or power is defined as the probability of detecting the stated treatment effect, if such an effect truly exists. Commonly, power is set at 80% or 90%, but setting power as 95% or 99% may be advisable in cases where a single study may constitute the evidence of effectiveness for a drug candidate.

[5]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Providing clinical evidence of effectiveness for human drug and biological products; May 1998 (23 pp.).