ADAPTIVE CLINICAL TRIAL DESIGN[47]

As previously mentioned, clinical trials, especially phase III clinical trials, are the largest contributor to the overall cost of drug discovery and development. It should come as no surprise that there has been a concerted effort over the last few decades to identify more efficient methods of conducting clinical trials. The concept of adaptive clinical trial designs has been developed in response to the need to decrease the overall cost of new drug development. In an adaptive clinical trial, interim analysis time points are defined within the course of the overall study. When these time points are achieved, analysis of the data collected up until this point is used to determine how the remaining portion of the clinical trial will be conducted. In other words, the adaptive clinical trials are prospectively planned to include opportunities for modification of certain aspect of the trial (e.g., sample size, treatments, population, choice of outcomes, etc.) based on data collected during the trial itself.

The ability to monitor and change aspects of an ongoing clinical trial can have a significant impact on the time, costs, and risk to patients when compared to conventional clinical trials. In a conventional clinical trial, the methods and protocols are set prior to the start of the trial and are typically not altered as the trial proceeds. Although every effort is made to design efficient clinical trials, it is important to keep in mind that study designs represent the best estimate of various parameters (e.g., number of patients required, dosing schedule, variability in response rate, etc.) that may not be fully characterized at the beginning of the trial. If the estimates turn out to be inaccurate for any reason, the study could produce false negative or false positive results, both of which would be problematic. By incorporating an interim analysis step, adaptive trial designs allow the study to be modified based on data developed through the course of the study. If, for example, an interim analysis of the data determines that one of the study arms is having no impact on the patients (i.e., the dose is too low to produce an effect), this arm of the study could be terminated. Similarly, if it were determined that the study was highly successful, futile, or causing harm to the subjects, an interim analysis would provide an opportunity to end the study earlier than anticipated based on the original study design. Event rates can also be monitored to determine if the number of subjects is appropriate. If the event rate is higher than anticipated in the general population, it may be possible to recruit a smaller number of patients. On the other hand, if the event rate is lower, it may be necessary to recruit a larger than anticipated number of patients. These and other types of changes can significantly increase the efficiency of a clinical trial, decreasing the risk to patients and the overall cost of clinical development, provided the regulatory authorities are in agreement with the adaptive trial design.