analyses that are best accomplished in consultation with a statistician and one of several commercial software packages designed to estimate sample size requirements.[45]

Irrespective of the study size necessary to meet efficacy requirements, phase III clinical trials must also be large enough to provide an adequate safety package to support regulatory approval. Given the large number of disease states and conditions that require short term administration (e.g., cumulative exposure of less than 6 months), it is difficult to provide general guidance on the population size required to provide an adequate safety assessment. For longer term treatments that are designed to treat non-life-threatening conditions (e.g., cumulative exposure of greater than 6 months), however, there are some generally accepted guidelines. The number of patients exposed to the candidate compound at therapeutically relevant doses should be greater than 1500. Of this set, 300–600 should be studied for a minimum of 6 months, and at least 100 patients should reach the 1-year mark. If, however, the candidate compound is intended to treat a life-threatening disease, a debilitating condition, or a disease with a small patient population, a smaller number of subjects may be sufficient (Regulatory approval for this deviation from the norm would be required.). On the other hand, if animal studies, similar compounds, or other data indicate that a safety issue may exists, regulatory agencies may require a larger patient population in the safety database. Similarly, if the expected benefit is small (e.g., symptomatic improvement in the mild medical condition) or a safe alternative is already available, additional subjects may be required in order to establish an appropriate safety package for a new drug application.[46]

PHASE IV CLINICAL TRIALS

Once a candidate compound has successfully completed two adequate and well-controlled studies, a new drug application can be prepared and submitted to the appropriate regulatory body. If the regulators are satisfied with the information provided, then marketing approval will be granted. In many cases, however, there may be additional question about the candidate compound that, while not critical to initial approval, are considered important enough to warrant additional examination in a clinical setting. As a result, postmarketing surveillance studies, also referred to as phase IV clinical trials, are commonly required as a condition of marketing approval.

There are a number of possible objective of a phase IV clinical trial. In some cases, it may be necessary to determine the safety and efficacy of a compound relative to a competitor compound. These studies may be