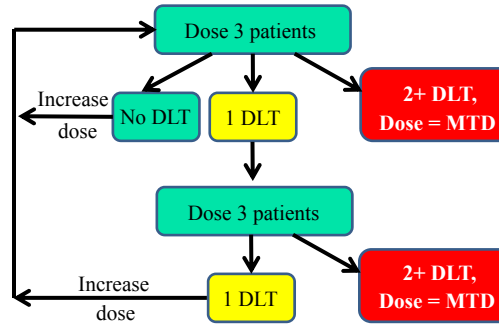

FIGURE 9.13 A typical phase I trial exposes a small group of patients to increasing amounts of clinical candidate while monitoring for adverse events. The trial is ended when the MTD is determined. The data from phase I trials are used to set dose levels for subsequent trials. DLT, dose limiting toxicities; MTD, maximum tolerated dose.

exposure. It may also be necessary to perform a separate study in which the subjects receive multiple doses that increase in each stage of the study. This is often referred to as multiple ascending dose (MAD) study and can provide a significant amount of information on the pharmacokinetics of a candidate compound. In this scenario, patient groups receive multiple doses of the candidate compound at fixed time intervals. The dose is escalated with each successive round of exposures until a predetermined maximum (often set by the MTD of the SAD studies) is reached.

In practice, all of the patients must be carefully monitored through a variety of means. Full physical exams and monitoring of cardiovascular function (e.g., BP, heart rate) and other vital signs are conducted through the course of the study. In addition, multiple types of biological specimens (e.g., blood, urine) are collected. The biological samples are used to determine the *in vivo* ADME properties of the candidate compound, as well as monitor for any safety issues that might not be apparent from physical observations (e.g., hematologic, hepatic, or renal toxicities). Depending on the PK parameters of the candidate compound, patient follow-up could be necessary for days or even weeks after the initial exposure.

Although the majority of phase I clinical trials employ healthy volunteers, there are some notable exceptions. When the proposed therapeutic agent has a known degree of toxicity, such as potential cancer chemotherapies[38] or new antiviral agents for the treatment of HIV,[39] healthy volunteers are not used. In this instance, patients with the disease or condition are used in phase I clinical trials. Also, in many cases the phase I and phase II trials are merged in order to minimize the number of patients that are exposed to a candidate compound of unknown safety and efficacy. PK studies are also minimized for the same reason.

In general, phase I clinical trials, including patient follow-up after exposure, take approximately 1–1.5 years to complete. At a minimum, the studies must demonstrate that the candidate compound is safe for use in humans in order for a clinical program to proceed to phase II trials. PK studies conducted in the phase I trial, combined with the MTD and DLTs that are observed in this round of clinical study, are used to set the doses for phase II clinical trials.