single studies should be highly statistically significant and the drug being evaluated should have a clinically meaningful superior treatment effect based on the primary endpoint of the study and **corroborative treatment effect must be observed** in secondary endpoints" (4).

a. Phase I Clinical Trial Endpoints

Phase I clinical trials are primarily conducted for arriving at an optimal dose, for use in phase II and III clinical trials, but only secondarily, if at all, for acquiring data on efficacy. In comments about phase I trials in the context of oncology, Llovet et al. (5), find that, "[i]n current oncological practice, phase I studies are intended to define appropriate dosage by using endpoints such as dose-limiting toxicity, maximum tolerated dose, pharmacokinetic profile, and pharmacodynamic profile. The primary endpoint of these studies is the safety profile or change in measures that reflect relevant biologic processes."

b. Clinical Endpoints

The endpoints that are most relevant to the study subject are events of which the study subject is aware or afraid of, such as death, a heart attack, loss of vision, or the arising need for a liver transplant due to viral infection (6). These endpoints are classified as *clinical endpoints*. In clinical trials on life-threatening disorders, the most common clinical endpoint is overall survival (OS). But, according to Le Tourneau et al. (7), "[t]he main drawback of overall survival is that it usually requires larger patient numbers and longer follow-up than surrogate time-to-event end points."

c. Surrogate Endpoints

Another class of endpoints is *surrogate endpoints*. Where the natural time course of a particular disease is extremely long, or where the window of drug therapy is extremely long, trial design may include one or more surrogate endpoints. When included in trial design, surrogate endpoints can reduce the cost and duration of the trial. According to Fleming and DeMets (8), a surrogate endpoint is a laboratory measurement or a clinical sign used as a substitute for a clinically meaningful endpoint. The surrogate endpoint measures how a patient functions, survives, or feels. The surrogate endpoint is supposed to operate as follows. Changes induced by a therapy on the surrogate endpoint reflect changes in the clinically meaningful endpoint.

Examples of surrogate endpoints include tumor size and number, or time to detection of tumor metastasis in clinical trials in oncology, LDL-cholesterol in clinical trials with drugs for atherosclerosis, and reduction in brain lesions in

[4]Sridhara R, et al. Review of oncology and hematology drug product approvals at the US Food and Drug Administration between July 2005 and December 2007. J. Natl Cancer Inst. 2010;102:222–35.

[5]Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J. Natl Cancer Inst. 2008;100:698–711.

[6]Fleming RT, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann. Intern. Med. 1996;125:605–13.

[7]Le Tourneau C, Michiels S, Gan HK, Siu LL. Reporting of time-to-event end points and tracking of failures in randomized trials of radiotherapy with or without any concomitant anticancer agent for locally advanced head and neck cancer. J. Clin. Oncol. 2009;27:5965–71.

[8]Fleming RT, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann. Intern. Med. 1996;125:605–13.