cholesterol-lowering agent, Berthold et al. (38) included a 6-week run-in period where all subjects took placebo only. Of the 215 enrolled subjects, 75 were excluded during the run-in phase for various reasons. Potential subjects were excluded for a number of reasons, including failure to meet all of the inclusion criteria. Before incorporating this kind of run-in period into the study design, statisticians need to ensure that it will not introduce bias into the results of the clinical trial. As explained in this textbook, in the chapter on ITT analysis, excluding subjects because they deviate from certain requirements in the Clinical Study Protocol can introduce bias into the results.

k. Detecting potential study subjects who show a predetermined desired response to the study drug, with the goal of including only these subjects

In a review, Stadler (39) describes a type of run-in period that screens for and retains potential subjects who exhibit a desired, predetermined response to a study drug. During this type of run-in period, all potential subjects receive the study drug. The duration of the run-in period must not be too short, otherwise influence of the study drug may not be detected. Moreover, duration of the run-in period must not be too long, at least in the context of anti-cancer drugs, because the (usually) inevitable event of death may occur. In detail, the run-in period detects and then excludes subjects where the drug is ineffective, and where the tumors increase in size. The same run-in period detects and then excludes subjects where the tumors shrink. The only subjects who are kept in the study, after the run-in period, are those where the tumors are stable. This group of subjects is then randomized, and allocated to receive placebo, or to continue receiving the study drug. The clinical trials described by Stadler (40) involve a class of drugs that inhibit tumor growth, but do not kill tumors. This class of drugs is further described below in the methodology tip.

In an article on renal cancer, Rosner et al. (41) used the term *randomized discontinuation design* to refer to a trial that contains a run-in period, where the run-in period selects a subset of enrolled patients who are relatively homogeneous with respect to important prognostic factors and where the trial randomizes only these patients. This kind of run-in period takes the form of a short clinical trial, where efficacy is measured, and where only subjects who respond with predetermined criteria are kept in

[38] Berthold HK, Unverdorben S, Degenhardt R, Bulitta M, Gouni-Berthold I. Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia. *J Am Med Assoc*. 2006;295:2262–2269.

[39] Stadler WM. The randomized discontinuation trial: a phase II design to assess growth-inhibitory agents. *Mol Cancer Ther*. 2007;6:1180–1185.

[40] Stadler WM. The randomized discontinuation trial: a phase II design to assess growth-inhibitory agents. *Mol Cancer Ther*. 2007;6:1180–1185.

[41] Rosner GL, Stadler W, Ratain MJ. Randomized discontinuation design: application to cytostatic antineoplastic agents. *J Clin Oncol*. 2002;20:4478–4484.