metastatic progression. In the absence of metastatic progression, patients were randomly assigned to one of two different … regimens." The particular type of trial design used by Hanna et al. (89) and by Belani et al. (90) is called, "randomized discontinuation" (91). A run-in period in a clinical trial that has a randomized discontinuation feature serves to enrich the study population for patients likely to respond positively to the study drug.

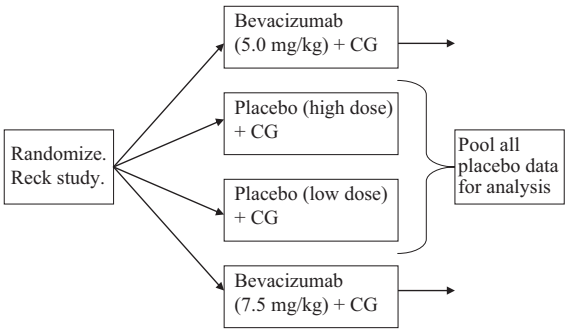

FIGURE 2.16 Study schema with four arms.

p. How to Maintain Blinding of the Treatment When the Study Drug and the Control Treatment Are Provided by Different-Sized Pills (or by Different Volumes of Solutions)—The Reck Schema

The following concerns studies requiring a "double dummy" design, such as the study of Reck et al. (92) (Fig. 2.16). This concerns trials with two different study arms. Subjects in each study arm are assigned to receive a different number of pills (or a different injected volume). For example, subjects in arm A may receive 1 pill/day and subjects in arm B receive 4 pills/day. To provide another example, subjects in arm A receive an injection of 5 mL/day, and subjects in arm B receive an injection of 20 mL/day. This poses the vexing problem of designing the placebo arm.

The problem can be articulated as follows. What approach should be used for arm C (placebo arm) of the study?

The FDA has specifically recognized this situation, writing, "[s]ome trials may study more than one dose of the test treatment … [i]n these cases, it may be easier for the investigator to use more than one placebo (double-dummy) than to try to make all treatments look the same." Thus, the best solution might be for arm C (placebo) to receive an injection of 5 mL/day of placebo and arm D (also placebo) to receive an injection of 10 mL/day of placebo (93). Thus, for maintaining blinding in this situation, a common approach is to use a double dummy.

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[90]Belani CP, Wang W, Johnson DH, et al. Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small-cell lung cancer. J. Clin. Oncol. 2005;23:3760−7.

[91]Fu P, Dowlati A, Schluchter M. Comparison of power between randomized discontinuation design and upfront randomization design on progression-free survival. J. Clin. Oncol. 2009;27:4135−41.

[92]Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J. Clin. Oncol. 2009;27:1227−34.

[93]Dept. of Health and Human Services. Food and Drug Administration. Guidance for Industry. E10. Choice of control group and related issues in clinical trials; May 2001.