In the clinical trial of Reck et al. (94), the formulation of the study drug, bevacizumab, was in liquid form, and was injected in patients in two different study arms, one arm receiving a smaller dose and the other arm receiving a larger dose. The two different doses were 7.5 mg/kg body weight and 15 mg/kg body weight.

The problem facing the investigators was how to configure the placebo. The study drug was available in a vial of only one size, and was available at only one concentration. Thus, some of the study drug patients needed to receive the contents of one vial, and the other study drug patients needed to receive the contents of two vials. To avoid bias in the trial, two different placebos were used, one with a small volume and the other with a larger volume, where the volumes corresponded to those of the study drug.

The end-result was that any physician administering a large volume would not likely be capable of guessing whether the large volume dose contained placebo or study drug. Bevacizumab or placebo was administered intravenously and concurrently with chemotherapy every 3 weeks on day 1.

Patients in all four arms of the trial received cisplatin and gemcitabine (CG). Cisplatin was administered on day 1, and gemcitabine was administered on days 1 and 8, of each 21-day cycle. Drug administration was continued for six cycles. Regarding the two placebo groups, Reck et al. (95), stated that, "[p]atients assigned to high- and low-dose placebo were pooled into one placebo group for all analyses."

Another example of using two different placebos, each corresponding to a lower dose and higher dose of study drug, comes from the example of cladribine for treating multiple sclerosis (96).

The following provides two situations where a double-dummy design can be used. In all cases, the double-dummy design is a technique for retaining the blind when administering supplies in a clinical trial, when the two treatments cannot be made identical (97).

The first design, which is from an example from the ICH Guidelines (98), involves a two-arm study where the first arm receives a study drug and the second arm receives another drug, that is, an active control drug. (This study design does not involve any placebo group.)

- *Arm A.* All subjects in arm A receive a round pill that is the active control drug plus a flat pill that is the placebo.
- *Arm B.* All subjects in arm B receive a flat pill that is the study drug plus a round pill that is the placebo.

The second design, also shown below, is a four-arm study, where two arms receive only drugs, and where the remaining two arms receive only placebo.

- *Arm A.* Round pill study drug.
- *Arm B.* Round pill placebo.
- *Arm C.* Flat pill active control drug.
- *Arm D.* Flat pill placebo.

[94]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.

[95]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.

[96]Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. New Engl. J. Med. 2010;362:416–26.

[97]ICH Harmonised Tripartite Guideline Statistical Principles for Clinical Trials E9; February 1998 (46 pp).

[98]ICH Harmonised Tripartite Guideline Statistical Principles for Clinical Trials E9; February 1998 (46 pp).