

required for a unique type of clinical study, that is, studies that characterize the placebo effect. Clinical trials that are configured to study the placebo effect can use three arms: (1) study drug arm; (2) placebo arm; and (3) no-treatment arm. In a survey of 3-arm clinical studies of this type, Krogsboll et al. (10) arrived at the conclusion that, at least for some disorders, it might be erroneous to ascribe improvement to a “placebo effect.” This conclusion is supported by the fact that, at least for some disorders, the degrees of improvement in the placebo arm and no-treatment arm were similar to each other. Disorders where spontaneous improvement (no-treatment arm) and improvement in the placebo arm were similar are nausea, depression, acute pain, cigarette smoking, and phobia. Nausea, depression, and pain are common adverse events in oncology clinical trials. Hence, in evaluating data on these adverse events, the medical writer might consider refraining from concluding that there was a “placebo effect.”

IV. PHYSICAL ASPECTS OF THE PLACEBO

Where the study drug is a pill, liquid, powder, solution, slurry, suspension, suppository, topical cream, aerosol, and the like, the placebo (or active control drug) should always be manufactured in a way that impairs the ability of the patient, medical personnel, and clerks from telling the difference between the two. This statement also applies to degradation products of the drug and placebo. With storage over the course of many months, the study drug or placebo may acquire an altered color or physical characteristic. In a study of pills, including placebo pills, Camarco et al. (11) disclose the properties of mouth feel and friability. Mouth feel encompasses a gritty feeling resulting from large particles used to manufacture the pill, and a gummy feeling resulting from a gel-like consistency upon contact of the pill with water.

The placebo and study drug should be indistinguishable in terms of packaging, labels, size, shape, opacity, coatings, viscosity, color, smell, flavor, and route of administration (12).

V. ACTIVE PLACEBO

Some drugs have obvious side effects. Thus, where an investigator or study subject has some knowledge of the expected side effects, it will be easy to guess whether the administered material is a drug or a placebo. For this reason, the pharmaceutical

¹⁰ Krogsboll LT, Hróbjartsson A, Gotzsche PC. Spontaneous improvement in randomised clinical trials: meta-analysis of three-armed trials comparing no treatment, placebo and active intervention. *BMC Med Res Methodol.* 2009;9:1.

¹¹ Camarco W, Ray D, Druffner A. Selecting superdisintegrants for orally disintegrating tablet formulations. *Pharm Technol.* 2006 (October Suppl.); 5 pages.

¹² Monkhouse DC, Rhodes CT. *Drug Products for Clinical Trials: An International Guide to Formulation, Production, Quality Control.* New York: Marcel Dekker, Inc.; 1998.