

journal, mandated that the CONSORT guidelines for reporting clinical trials be used in his journal. The CONSORT guidelines (42) provide a reasonable list of parameters for including in publications relating to clinical trials.

Where side effects specifically associated with the study drug are known by the subjects or by clinical trial personnel, the presentation of these side effects can result in unintentional unblinding. Masking of these side effects can be undertaken, before the study, by using a placebo that causes the same type of side effects. As discussed in this textbook in the placebo chapter, an active placebo is a placebo with properties that mimic side effects such as dry mouth, or sweating, that might otherwise reveal that a subject is in the study drug group or placebo group (43,44). Another approach for preventing unblinding caused by known side effects of the study drug is shown by the following example. In a clinical trial on spironolactone, which produces the adverse drug reaction of feminization (of male subjects), the investigators maintained blinding by mandating that this adverse event, and others, be represented by letters of the alphabet (45).

Unintentional unblinding can also occur where the study drug requires continual dose adjustments during the course of the trial. Thus, physicians who are compelled to adjust the doses of some subjects, but not of other subjects, may be able to guess that the adjusted subjects are in the study drug arm, and that non-adjusted subjects are in the placebo arm. This type of unblinding can be prevented by requiring some of the placebo subjects to have adjustments of placebo (46,47,48).

VIII. INTERACTIVE VOICE RESPONSE SYSTEMS

An Interactive Voice Response System (IVR system; IVRS) can be used to screen and register study subjects, to ensure that only persons signing the consent form are registered, and for managing data from study subjects during the entire clinical trial. IVR systems enable remote site randomization of new subjects. IVR systems are a tool where the telephone, or internet, is used to input information. In subject recruitment through an IVR system, potential subjects can telephone a toll-free number, and answer a series of questions to determine their potential eligibility, for example

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⁴³ Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. *Ann Intern Med.* 2002;136:254–259.

⁴⁴ Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. *Cochrane Database of Systematic Reviews.* 2004;(1). Art. No.: CD003012. doi: 10.1002/14651858.CD003012.pub2.

⁴⁵ DeMets DL, Furbert CD, Friedman LM. *Data Monitoring in Clinical Trials.* New York, NY: Springer; 2006;150–151.

⁴⁶ Hertzberg V, Chimowitz M, Lynn M, et al. Use of dose modification schedules is effective for blinding trials of warfarin: evidence from the WASID study. *Clin Trials.* 2008;5:25–30.

⁴⁷ Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. *Lancet.* 2008;350:389–396.

⁴⁸ Friedman LM, Furbert CD, DeMets DL. *Fundamentals of Clinical Trials.* 4th ed. New York, NY: Springer; 2010;123.