Internet-based systems of allocation and randomization are also available, for example, a vendor called, Sealed Envelope, Ltd, located in London, England. Clinical trials that have used this vendor are cited in footnotes (38,39,40). Swingler and Zwarenstein (41) describe a technique similar to the above-described envelope technique, but it is not as secure. Their method uses sealed envelopes, but no carbon paper. Berger and Weinstein (42) document a number of clinical trials where the sealed envelopes were tampered with, for example, by holding the envelopes up to the light. Use of aluminum foil can prevent this particular tampering problem.

Clinical trials on human subjects may include an independent organization, called an IDS, whose members are the only ones to receive and know the study arm assignment. In other words, the IDS is the only party that opens the envelope. Bottles of pills or vials are coded with symbols that only the IDS understands, that is, the bottles of pills would not be labeled as, "Treatment A" and "Treatment B." Study investigators, physicians taking care of patients, statisticians, monitoring boards, would have no information about what arm a participant is in, until there is a formal decision to unblind specific subjects, subgroups, or the entire study population.

A pharmacist can be informed of patient assignment by code in order to dispense placebo or the appropriate dose of study drug to each subject, as used, for example, in the cited study (43).

e. Allocation by Coin-Toss Versus Allocation by Sealed Envelope

While enrolling subjects in a clinical trial, it is possible to allocate each subject, as they are enrolled, to either Treatment A or Treatment B, by flipping a penny. Heads means Treatment A, while tails means Treatment B. As mentioned above, a problem with this technique, is that it is statistically possible to have all subjects allocated to receive Treatment A (and none receiving Treatment B). Thus, the coin-toss method must not be used. Allocation by sealed envelope absolutely ensures that equal numbers of subjects receive Treatment A and Treatment B.

III. BLOCKED RANDOMIZATION

For most clinical trials, subjects are enrolled one by one, over the course of many months. The simplest allocation procedure is complete randomization (analogous to repeated coin-tossing in the case of two arms), where each

[38]Kapoor R, Furby J, Hayton T, et al. Lamotrigine for neuroprotection in secondary progressive multiple sclerosis: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Neurol. 2010;9:681–8.

[39]Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, et al. Early insulin therapy in very-low-birth-weight infants. New Engl. J. Med. 2008;359:1873–84.

[40]Brady AR, Gibbs JS, Greenhalgh RM, et al. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. J. Vasc. Surg. 2005;4:602–9.

[41]Swingler GH, Zwarenstein M. An effectiveness trial of a diagnostic test in a busy outpatients department in a developing country: issues around allocation concealment and envelope randomization. J. Clin. Epidemiol. 2000;53:702–6.

[42]Berger VW, Weinstein S. Ensuring the comparability of comparison groups: is randomization enough? Control Clin. Trials 2004;25:515–24.

[43]Romine JS, Sipe JC, Koziol JA, Zyroff J, Beutler E. A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. Proc. Assoc. Am. Physicians 1999;111:35–44.