In an emergency, the investigator will first contact the [XXXX] CRA or medical monitor prior to revealing the code for a particular patient. If the [XXXX] CRA or medical monitor cannot be reached, the treating physician or designee may break the double-masked code by opening the envelope and revealing the code for that particular patient. The person breaking the code must not reveal the information to the evaluating physician. The person breaking the code will note the date, time and reason for unmasking, and document the procedure with his/her signature. This information will be noted on the envelope in the section provided and the envelope will be resealed. All sealed and unsealed envelopes will be returned to [XXXX] to verify that masking was maintained.

IV. SUMMARY

A serious adverse event or an emergency in a particular study subject can trigger the decision to unblind that subject. Clinical Study Protocols differ in their disclosure of which persons will receive information on the unblinded subject, that is, should only the safety monitor receive unblinded information, or should the sponsor also receive unblinded information. Another concept is that only selected personnel, for example a pharmacist, possess the randomization code. To understand the event that can trigger unblinding, namely, the *serious adverse event*, the reader may review the chapters in this textbook on drug safety and on package inserts.

V. SUBJECTS ARE ENROLLED INTO CLINICAL TRIALS, ONE BY ONE, OVER THE COURSE OF MANY MONTHS

For most clinical trials, subjects are enrolled one by one, over the course of many months. Let us assume that allocation is accomplished by using a hat containing 50 red balls and 50 green balls. Each person that enters the enrollment office, puts a hand into the hat, takes out a ball, and takes it to the pharmacy to receive Treatment A or Treatment B. With use of this method, it is possible for the first 30 or 50 subjects to receive only Treatment A (none receiving Treatment B). It is only after every single ball is taken from the hat that we can be assured that equal numbers of subjects are receiving Treatment A and Treatment B (34). But a reality of clinical trials is that efficacy and safety are continually monitored. Please contemplate the following hypothetical. Assume that the trial is still in its early phases, and only 30 balls have been taken from the hat, and that nearly all of the subjects are receiving Treatment A. Let us further assume that Treatment A is an active control, for example methotrexate (a very toxic anti-cancer agent), and let us assume that Treatment B is the antibody, trastuzumab (not particularly toxic). Now, returning to the hypothetical, it can be seen that most of the subjects in the early phases of the clinical trial may be experiencing severe toxic reactions, due to the methotrexate. As a consequence of the high prevalence of toxic

[34] Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet*. 2002;359:515–519.