be used. Allocation by sealed envelope absolutely ensures that equal numbers of subjects receive Treatment A and Treatment B.

III. INFORMATION ON RANDOMIZATION, BLINDING, AND UNBLINDING MAY BE INCLUDED IN THE CLINICAL STUDY PROTOCOL

a. Introduction

The medical writer should include information on randomization when drafting Clinical Study Protocols. The ICH Guidelines (26) specifically recommend that the sponsor identify methods of randomization, and situations where it is permissible to break the code:

> *A description of the specific procedures used to carry out blinding should be provided (e.g., how bottles were labeled, labels that reveal blind-breakage, sealed code list/envelopes, double dummy techniques), including the circumstances in which the blind would be broken for an individual or for all patients, e.g., for serious adverse events, the procedures used and who had access to patient codes.*

The following excerpts from a variety of Clinical Study Protocols provide instructions on randomization codes, persons possessing the randomization code, and conditions under which the code may be broken. The "[XXXX]" indicates the redacted name of the sponsor.

b. When to break the randomization code – clinical study protocol for trial on Alzheimer's disease (27)

> *Patients participating in the trial will be assigned a sequential trial number. The computer-generated list of trial numbers is linked to a randomized list with medication numbers, equivalent to 80 batches of indomethacin and 80 batches of placebo. The participating pharmacist will retain the randomization code.*
>
> *In case of an adverse event with a possible causal relationship to the use of indomethacin, the medical attendant (e.g. family physician, physician) will discontinue the trial medication. The trial ends, however the trial code will not be broken and the patient's data will be analyzed. The medical attendant will be asked to report this decision to the investigators as soon as possible.*
>
> *The medical attendant is allowed to lower the dose of the study medication, in case of a dubious causal relationship between the adverse event and the study medication. The trial code will not be broken and the patient will be considered a normal participator of the trial.*
>
> *In case of a serious adverse event, the patient's medical attendant will ask the pharmacist to announce the nature of trial medication. The code will then be broken, the medication will*

[26] ICH Harmonised Tripartite Guideline. Structure and content of clinical study reports E3. Step 4 version, November 1995; 43 pages.

[27] Clinical Study Protocol. Effect of indomethacin on the progression of Alzheimer's disease. A randomized double blind, placebo-controlled, multicenter clinical trial. Kremer HPH, Jansen RWMM. Radboud University Medical Center Nijmegen.