Approximately 900 patients will be randomized in a 2:2:1 ratio to Treatment Arm 1, Treatment Arm 2, or Treatment Arm 3, respectively. Randomization will be accomplished using Impala (an automated web/telephone randomization system provided by the sponsor) ... At the Screening Visit, the investigative site will contact Impala (online or by telephone call). The site will enroll the patient into the Impala by indicating minimal information sufficient to distinguish one patient from another (e.g., date of birth and initials) and receive the Patient ID number. At the Baseline Visit, the system will associate that patient with the next available treatment on the randomization schedule and provide the randomization number. The system will then give the investigative site a code which corresponds to study drug that was previously shipped to the site and is in the site's inventory ready to be dispensed. This code corresponds to the study drug of that period in the treatment sequence in which the patient has just been randomized.

V. INSTRUCTIONS FOR UNBLINDING

a. Introduction

In addition to instructions on randomization and blinding, the Clinical Study Protocol can include instructions for unblinding. ICH Guidelines (51) 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 (52)

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 be discontinued and the patient's data will not be included in the analysis of the final outcome measures. However, the data of patients discontinuing the trial will analyzed according to the intention to treat" principle.

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

[52]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.