stratified blocked randomization can be reduced, when the number of strata is large, or the block sizes are too large in relation to the number of patients enrolled (48).

IV. CLINICAL STUDY PROTOCOL RANDOMIZATION INSTRUCTIONS

This provides examples of randomization instructions from two Clinical Study Protocols. The Protocols were published as supplements to articles appearing in the *New England Journal of Medicine*.

a. Randomization Procedure From a Clinical Study Protocol for a COPD Study

This provides an example of randomization instructions from a Clinical Study Protocol. The Protocol concerned chronic obstructive pulmonary disease (COPD). The study drug was the antibiotic, *azithromycin*. The excerpt states that the user inputs information at a website. The user chooses a study site. The website's software stratifies study subjects by study sites, that is, study sites that are within a given clinical center. The software responds by providing a "treatment assignment number." This number, in turn, is coupled with a "schedule" that is kept at a pharmacy. The excerpt from the Protocol reads (49):

> Randomization will be carried out by linking to the Data Coordinating Center through a website, (http://www.copdcrn.org) using a ... User ID and password. After securing entry a menu listing the clinical sites appears. The user must choose one of these ... [clinical sites] ... Randomization is stratified by each designated site in each clinical center. As an example, the Minneapolis clinical center has three sites: the VA Hospital in Minneapolis, Health Partners, and the Mayo Clinic ... If all eligibility criteria are met the randomization program will issue a treatment assignment number such as '113'. This number matches a schedule that is retained in each site's clinical pharmacy, where separate supplies of capsules containing the active drug and the placebo are also kept. The only person knowing this schedule will be the pharmacist and the DCC. When the clinic coordinator requests pills for treatment assignment #113, the pharmacist will check the schedule and distribute the assigned drug from the appropriate pharmacy supply. The actual assignment will only be revealed in cases of emergencies.

b. Randomization Procedure From Clinical Study Protocol for an Arthritis Study

This provides another example of a randomization procedure from a Clinical Study Protocol. The clinical trial concerned *tofacitinib* for treating rheumatoid arthritis. The procedure refers to the fact that the potential subject visits the investigative site for screening, and that during the visit, an employee at the site contacts an automated randomization system. The procedure states that information on the subject is inputted, and that the system responds by providing a "Patient ID number." The procedure also refers to a subsequent visit to the investigative site (the "Baseline Visit"), where the subject gets assigned a code that corresponds to a drug, for example, the study drug or a placebo. The procedure read (50):

[48]Kundt G, Glass A. Evaluation of imbalance in stratified blocked randomization. Methods Inf. Med. 2013;51:55–62.

[49]Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. New Engl. J. Med. 2011;365:689–98.

[50]Phase 3 randomized, double-blind study of the efficacy and safety of 2 doses of CP690,550 compared to methotrexate in methotrexate-naive patients with rheumatoid arthritis. Compound Name: tofacitinib. US IND No: 70,903. Protocol No: A3921069; November 2012.