Question 1

Researchers are interested in testing tenofovir as a treatment for hepatitis B virus infection. They need to create a randomization list for a two-group randomized clinical trial comparing "Arm A: tenofovir" to "Arm B: placebo". The random allocation will be 1:1 with trial participants overall having a 50% chance of being randomized to "Arm A: tenofovir" and a 50% chance of being randomized to "Arm B: Placebo."

Part A

You have decided to implement the randomization using permuted blocks. The permuted blocks will be of size 6. Each block will have 3 allocations to "Arm A: tenofovir" and 3 allocations to "Arm B: placebo" in a random order. The study will recruit approximately 2,000 participants. **How many permuted blocks do you need?** Create the randomization list (include patient ID and treatment assignment) for this trial. Print the first 20 random allocations for review.

334 permuted blocks are needed.

Part B

Another investigator would like to stratify the randomization by age group categories (<23 years, 23-28 years and >30 years) as well as by hepatitis B DNA level (<8 log10 IU/ml and ≥8 log10 IU/ml). The randomization will still use permuted blocks of size 6. The investigator wants to recruit approximately 500 participants per stratum. **How many permuted blocks do you need in each stratum?** Create new stratified randomization lists for the trial. Print the first 10 random allocations in each stratum.

84 permuted blocks are needed in each of the 4 strata.

Part C

Based on the set-up in the previous question with a block size of 6, what is the minimum number of randomizations you have to make in a single block to ensure at least two participants are randomized to "Arm A: tenofovir" AND at least two participants are randomized to "Arm B: placebo"?

For a given stratum, you would need a minimum of 5 participants in a single block to guarantee at least 2 participants are randomized to both arms.

Obs 1 trt A
Obs 2 trt A
Obs 3 trt A
Obs 4 trt B
Obs 5 trt B
Obs 6 trt B

Part D

Age and hepatitis B DNA level are the two most important variables to balance the randomization by, however another investigator suggests additionally stratifying by the 10 centers that plan to recruit participants into the clinical trial. If you do this, how many randomizations lists will there be? Describe a benefit and a concern of additionally stratifying the randomization by center.

Additionally stratifying by centers will create 60 strata with 34 participants each. Too many small strata will cause imbalances in randomization that cancel out the intended beneficial effects of blocking. It is suggested to use a limited number of strata by only stratifying on the important variables, age, and hepatitis B DNA level.

Question 2

A Phase II dose-finding clinical trial will be conducted assessing the effect of a new medication on reducing glucose level in diabetics. There will be four treatments in the clinical trial, three doses of the experimental new drug (called GLU-001) and Placebo. The randomization will be 2:2:2:1 (into the treatment doses of 10 mg/day of GLU-001, 20 mg/day of GLU-001, 50 mg/day of GLU-001, and Placebo) and will be stratified by study center. Patients will have their glucose level measured at baseline, then they will be randomized, and then they are to take their randomized medication daily for 28 days, after which their glucose will be measured again.

The study requires 210 evaluable patients (i.e., 210 patients who are randomized and complete the 28-day follow-up) across 4 study centers (the 4 study centers have been chosen, and the number of study centers will not deviate from 4), with the ideal plan being that each study center will enroll approximately 50-55 patients each (though the number of subjects that end up being enrolled at each study center does not necessarily go according to plan, and often varies widely; please keep this fact in mind when you generate the randomization schedule outlined below).

Generate a formatted, labeled randomization schedule for this upcoming study. Use block randomization and choose a fixed block size you feel is appropriate (there is more than one correct answer here). The randomization schedule should include site, patient number and treatment group. The patient numbers should be 3 digits, and start with “1” for study center 2, “2” for study center 2, etc.