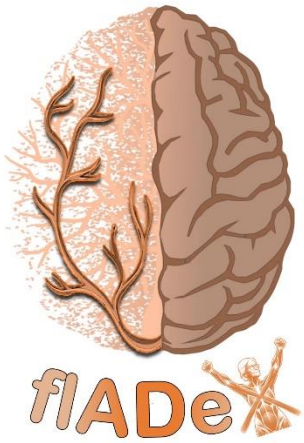

Manual of Procedures FLADEX Project

MOP Chapter 4.1: Randomization

Promoting Fitness & Health through Physical Activity

UNIVERSIDAD DE GRANADA

Chapter 4.1: Randomization

Index

1. Introduction

Following a counterbalanced crossover design, each participant will be included in all study conditions. The three study conditions are: (A) aerobic exercise, (B) resistance exercise, and (C) resting control. The order of each condition will be randomized for each participant to achieve a counterbalanced design. The following document describes the required steps to perform the randomization process and how to address potential issues in the randomization in the flADex project.

2. Randomization description

After collecting all basic participant data in the familiarization session, the order of the conditions will be randomly assigned. Before randomization, it must be verified that all participant data are entered in REDCap (Research Electronic Data Capture). To prevent the one of the three conditions from being applied to different participants on a same day, the order of the conditions was randomly allocated using a Latin square design (Keedwell & Dénes 2015). The 3x3 Latin square design indicates that each treatment appears only once in each row (participant) and column (visit) (Figure 1).

Participant Number	Block	Visit 1	Visit 2	Visit 3
1	1	B	A	C
2	1	A	C	B
3	1	C	B	A

Figure 1. 3x3 Latin square design.

The 3x3 Latin square randomization was set using the function "*rlatin*" of the "*magic*" package of Rstudio (Hankin 2005). Then, a randomization dashboard (https://javier-sanchez3.shinyapps.io/latin_square_design/) was created for execution of the randomization for each wave of participants. The randomization will be performed by a blinded researcher, Dr. Verónica Cabanas-Sánchez, who is completely external to the project.

The order of condition allocation will follow one of the following six combinations:

- **Order 1:** Condition A, Condition B, Condition C
- **Order 2:** Condition A, Condition C, Condition B
- **Order 3:** Condition B, Condition A, Condition C
- **Order 4:** Condition B, Condition C, Condition A
- **Order 5:** Condition C, Condition A, Condition B
- **Order 6:** Condition C, Condition B, Condition A

The principal investigator (PI) and research staff (who do not conduct the exercise sessions) will remain blinded to the condition assignment. The PI will only break this 'blinding' condition in the event of an adverse event occurring with any participant.

3. Previous procedure

Schedule

The ideal maximum time window allowed from signing informed consent in the familiarization session until the randomization process is conducted is 1 week. Then, the participant must complete each weekly condition during the following 3 weeks; therefore, the ideal time frame from the 1st condition to the 3rd condition is 3 weeks, but this can be extended up to 6 weeks if there is need to reschedule or repeat any condition.

Verification

Randomization can only occur after it has been verified in REDCap that the basic data from the familiarization session of each participant is completed and accurate. The assessment lead (*Beatriz Fernandez Gámez*) must confirm that the data is filled out correctly and stored appropriately. Once verified, the assessment lead must change the final tab in REDCap to "complete" for all instruments. Once the quality of all data is confirmed, the participant will be ready for randomization. At this point, an email will be sent to the external person in charge of randomizing the participants.

4. Randomization procedure

The randomization procedure will be carried out by a person completely external to the project *(Dr. Verónica Cabanas-Sánchez)* and will follow these steps:

4.1. Email notification to the external researcher

Once the basic data from the familiarization are verified for all participants in the respective wave, the project manager, Dr. Isabel Martínez-Fuentes, will send an email to the external researcher in charge of randomization. The email must include the dashboard link to perform the randomization.

4.2. Execution of the randomization

Upon accessing the website, the randomization dashboard will have preestablished values for “number of blocks”, “block size”, and “burn-in” (Figure 2). This information must not be modified, as it is based on the design of the randomization.

- The “Number of blocks” (or groups), set to “3”, will generate three blocks of 3x3 Latin squares, thus 9 participants will be randomized for each wave.
- “Block size” refers to the number of conditions in the Latin-square. In this case, there are 3 conditions (A, B, and C), and the order will be randomly assigned to 3 participants.
- “Burn-in” refers to the warm-up period for generating randomization numbers. That is, the first 10 iterations are considered a "burn-in" period and are discarded.

Figure 2. Randomization dashboard with preestablished values.

Dr. Cabanas-Sánchez will access the dashboard link, click "*Randomize*", and then click "*Download Randomization file*". Upon clicking "*Randomize*", the randomization results will appear on the right side of the screen (Figure 3).

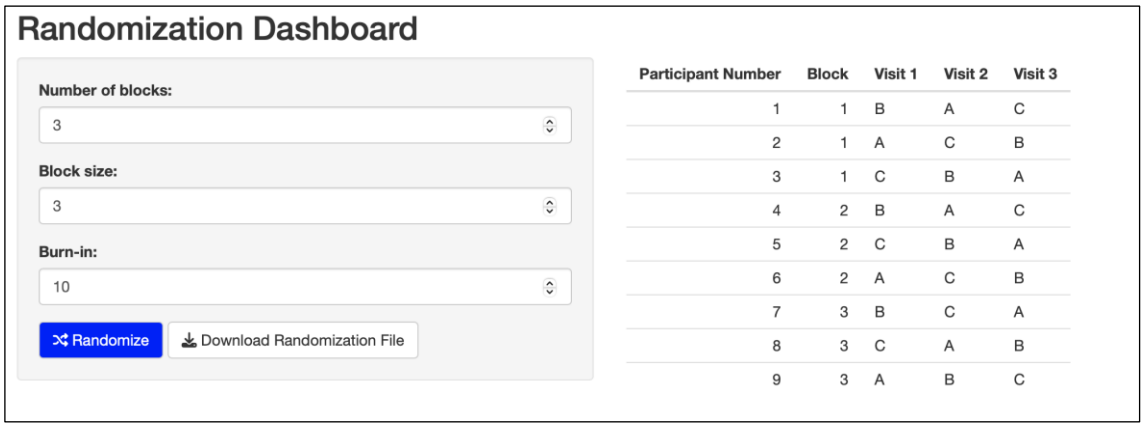

Figure 3. Randomization results.

4.3 Sending the Randomization file

Dr. Cabanas-Sánchez will email the randomization file to the project manager, Dr. Isabel Martín-Fuentes.

4.4 Entering the Randomization in REDCap

Dr. Isabel Martín-Fuentes will enter the condition allocation in the "*Randomization FLADEX study*" instrument for each participant in REDCap, as well as the randomization date and any necessary comments (Figure 4). Once the process is completed, the Project Manager must set the instrument to "*Complete*" status.

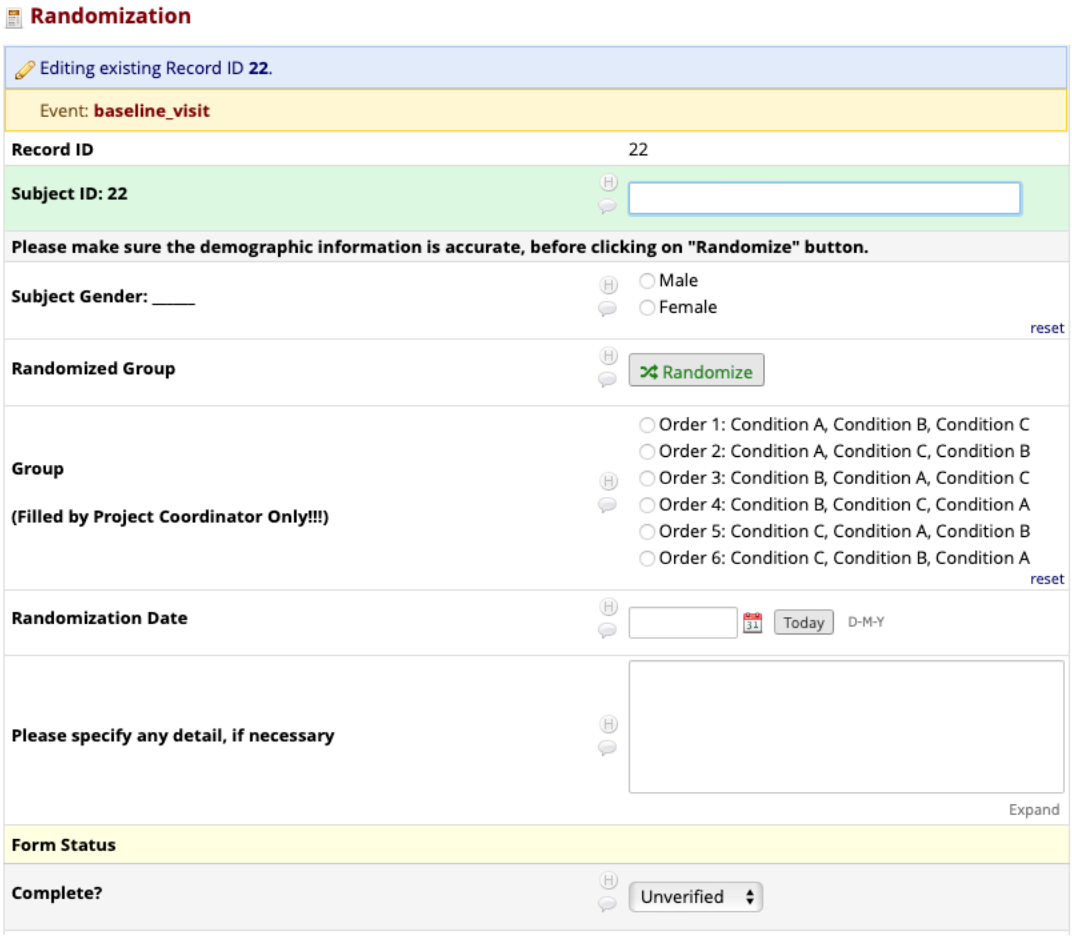

Figure 4. Randomization instrument and participant's data.

4.5 The coordinator will inform the exercise program manager of the condition assignment for each participant, and the manager will be responsible for informing the randomized participant of their randomly assigned condition.

4.6 Study participants **will begin their intervention at the beginning of the following week** unless there is a scheduling conflict for the participant. All new participants will start the intervention at the beginning of the following week in which they are randomly assigned.

5. Potential issues

It is unexpected but possible that a participant may be randomly assigned when they are not eligible. This could happen if the participant does not disclose certain medical information or if there is an error in data entry leading to an incorrect eligibility assessment.

If a randomization error occurs, a protocol deviation should be initiated and reported to the principal investigator as soon as the situation is discovered. In such a situation, the principal investigator and project coordinator must convene to discuss the appropriate approach for the participant.

Once a participant is randomized, no changes can be made to the elements determining eligibility. If an error is discovered in any instrument, only the REDCap Data Administrator can make these changes. It is crucial to contact the project coordinator promptly.

If a participant decides to withdraw from continuing to participate in the study, or if there are still openings in the strata to fill to reach the target number of participants, new participants will be randomized into these slots until this number is achieved.

6. References

1. Hankin RK. Recreational mathematics with R: introducing the “magic” package. R News. 2005;5(1):48-51.

2. Keedwell AD, Dénes J. Latin Squares and Their Applications: Latin Squares and Their Applications. Elsevier; 2015.