RANDOMISATION IN CLINICAL TRIALS

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Background

Randomization is a procedure in experimental studies when assigning participants to treatment groups before a clinical trial start. Randomization ensures that each subject has an equal chance of receiving any of the interventions under the study. It produces study groups that are comparable in terms of both known and unknown risk variables, eliminates investigator bias in participant allocation (i.e., allocation concealment), minimizes the variability of the evaluation, provides an unbiased evaluation of the intervention, and ensures that statistical tests have valid false positive error rates (Friedman, Furberg, & Demets, 2010).

The important roles of randomization are as follows:

i. It eliminates the possibility of allocation/selection bias in study sampling involving a selection of participants who may not represent the study population. Such allocation/selection bias can easily occur when a researcher or participant influences group selection spontaneously or involuntarily which may lead to imbalance of prognostic factors at baseline. The direction of the allocation/selection bias can be positive or negative, which can invalidate comparisons between groups. The researcher would have to control for covariates in the analysis to obtain an unbiased outcome caused by the indistinguishable between treatment effects due to the influence of risk imbalance (Friedman et al., 2010).

ii. Effective randomization produces comparable groups in term of a balance in the known and unknown confounding or unmeasured prognostic variables/factors. Although some of the baseline variables or covariates may not be a perfect balance, the overall magnitude and direction of the differences will tend to be equally divided between the two groups. In relatively small study and in the present of strong risk factors, randomization with balanced groups can be achieved using stratified randomization (Friedman et al., 2010).

iii. Randomization provides a basis for the statistical methods to be used when analyzing the data. If randomizations are not used, additional assumptions about group comparability and the appropriateness of statistical models must be made before the comparison are valid. Although group comparison is never perfectly balanced for all covariates in any single experiment, the randomization process allows us to assign a probability distribution to the difference in outcome between treatment groups. Another benefit of randomization is fulfilling the statistical tests assumption (Byar et al., 2009).

What needs to be avoided when dealing with randomization?

During a randomization process, a researcher should avoid two types of biases:

Selection bias might occur when the researcher questions on what types of intervention that participants should receive if the allocation is predictable or known (Altman & Doré, 1990, Williams & Davis, 1994). Randomization procedures should be done in an unpredictable situation where the best is to blind the researchers. (i.e., allocation concealment). According to Schulz & Grimes, 2002, trials with insufficient or unclear randomization procedures tend to exaggerate treatment effects by up to 40% when compared to trials with proper randomization. This insufficient randomization may harm the research's outcome.

Accidental bias can occur if the randomization procedure does not achieve balance on risk factors or prognostic covariates, particularly in a small study (Lachin, 1988). Accidental bias is associated with covariates imbalances when comparing the treatment groups. However, larger sample size and using right randomization procedure can avoid accidental bias.

METHODS OF RANDOMIZATION

Many procedures can be used for the random assignment of participants in treatment groups depending on scientific arguments reflecting the special aspects of the trial setting (Hilgers et al., 2017). The common randomizations method used to generate the random allocation sequence is Fixed Allocation Randomization, in which allocation to intervention and control groups should be in equal probability and is not altered as the study progresses (Lachin, 1988). It includes main types of randomizations but is not limited to simple, mixed blocks and stratified. There are researchers such as Peto, 1978 that used unequal allocation ratios such as 2:1,

for intervention and control groups to gain more information about participants' responses towards new interventions, such as toxicity and side effects, but the study may loss some power. However, the topic will not be discussed here.

Type of Randomisation	Usage and technique
Simple Randomization	▪ Known as complete randomization, it is based on a single sequence of random assignments (Altman & Bland, 1999). ▪ Simple and easy approach and works well for a large sample size in clinical trials (n>100) in which it can generate similar numbers of subjects among groups. ▪ In a small sample size clinical trial, simple randomization may be resulting in an unequal number of participants among groups (Lachin, 1988). For example, using a coin toss with a small sample size (n = 10) may result in an imbalance such that 7 participants are assigned to the control group and 3 to the treatment group. ***Technique used:*** - Flipping a coin is the most common and basic method of simple randomization. With two treatment groups (control versus treatment), for example, the side of the coin (heads – control, tails - treatment) determines each subject's assignment. - Using a shuffled deck of cards (e.g., even - control, odd - treatment) or throwing dice are two other options (e.g., below, and equal to 3 - control, over 3 - treatment). - A random number table found in a statistics book or computer-generated random numbers can be used. - Advanced random strategies to allocate participants in more than two groups where algorithms and online statistical computing web programs were used.
Block Randomization	• Block randomization is designed to randomly allocate subjects into groups with equal sample sizes. • Each block is small in size and has balanced predetermined group assignments, which each block has the same number of subjects at all times during the trials. • Block randomization procedure produces a balanced study arm in small to moderate clinical trials (n<100) without covariates. • If certain covariates happen to be in the groups at different quantity, they need to be controlled to avoid bias in the statistical analysis. ***Technique used:*** • The researcher will determine the size of the blocks in a multiple of the number of groups (i.e., with two treatment groups, block size of either 4, 6, or 8) and all possible balanced combinations of assignment within the block (i.e., an equal number for all groups within the block) will be calculated. The patients are then assigned to groups based on a random selection of blocks. (Altman & Bland, 1999)
Stratified Randomization	▪ The stratified randomization method addresses the need to control and balance the possible influence of covariates that would jeopardize the conclusions of the clinical trial. The stratified randomizations are performed by creating a separate block for each combination of covariates and all subjects are assigned to the appropriate block of covariates. Simple randomizations are applied within each block to assign participants to one of the groups. ▪ This type of randomization is useful in a smaller clinical trial but can be complicated when dealing with many covariates (Weir & Lees, 2003). ▪ The researchers need to identify all subjects at baseline before group allocation is done which each influence of identified covariate has on the dependent variable. ***Technique used:*** ▪ For an example, 2 groups involving 40 participants, with the covariates of sex (2 levels: male, female) and body mass index (3 levels: underweight, normal, overweight) between study arms. With these 2 covariates, possible block combinations total 6 (eg, male, underweight). A simple randomization procedure, such as flipping a coin, is used to assign the participants within each block to one of the treatment groups (Weir & Lees, 2003).

Recommendation of the methodology for randomization.

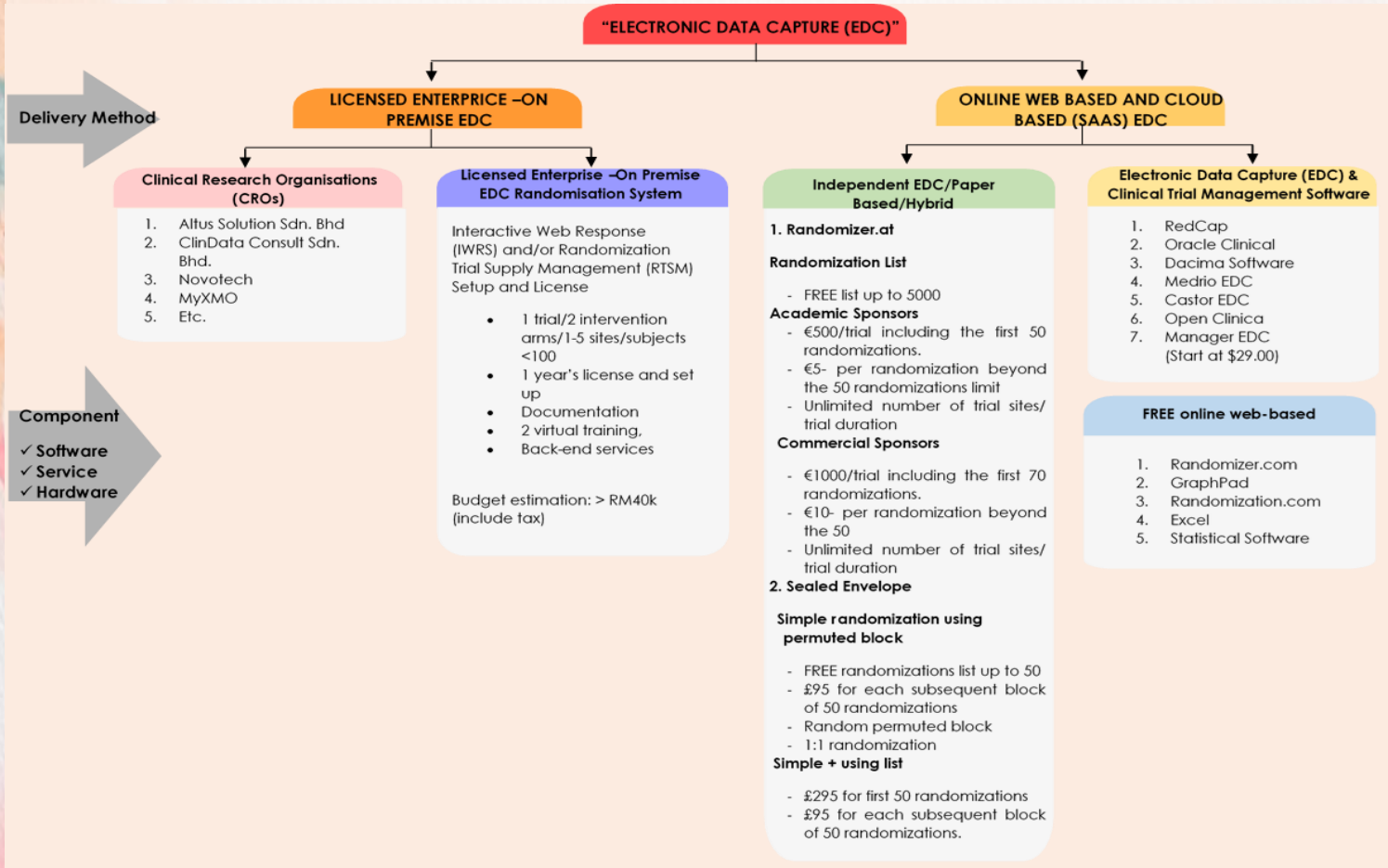
It is critical to consider how the randomization procedure is applied (Pocock S.J. & Simon, 1975). It is advised that an independent unit/body be responsible for establishing the randomization procedure and assigning participants to the appropriate group to achieve reliable randomization. In the independent unit/body, there could be a statistician or physician, or knowledgeable research personnel who is not involved in the research or participants' treatment. In the larger clinical trial scale that involved multicenter trials, the coordinating center is normally in charge of the randomization process. They are usually known as Clinical Research Organization (CRO).

In a normal situation where fixed proportion randomization is used, the randomization is done before the study begins. The researcher will call the independent unit/body to get the treatment assigned for the next subjects, where for the situation not available, the sequenced and sealed envelope containing information about the treatment will be provided to the researchers beforehand. In several double-blind drug studies, medication bottles labeled with small, perforated tabs have been used to identify the treatment to the subjects. In the multicenter trial, a central randomization operations process might be used. The systems, referred to as Interactive Voice Response Systems (IVRS) or Interactive Web Response Systems (IWRS) are effective and can be used to not only assign intervention but can also capture basic eligibility data. The use of IWRS becoming common due to its ease of use where the researchers need to log in to a central computer via the internet or dial into a central computer and enter data via touchtone, with a voice response (Krischer et al., 1991).

What is available in Malaysia? What is your option? Should you try do-it-yourself randomization, or should you use a professional clinical trials unit?

- You could do it yourself if you have:
  - a small trial
  - AND it is under personal control
  - AND you have the skills
- You should use an independant unit if you have:
  - a large trial
  - OR a multicenter trial
  - OR more than one person recruiting participants
  - OR you need experienced support

Randomization Service below summarizes options for what is available in Malaysia.



RANDOMISATION SERVICES as used by Clinical Research Organizations (CROs), Hospital, Clinics and Academic Research Centre

FREE ONLINE WEB-BASED AND CLOUD

Services	Types of Services	Fee	Requirement	Owner/ Country of Origin	Establishment	Features and extra applications added	Limitation
Randomizer.org https://randomizer.org/	Simple	Free	Standard web browser connected to the Internet (e.g., Chrome, Safari, Firefox, Internet Explorer) No specialized software, plugins, or extensions	Wesleyan Uni, Connecticut, England	Science.org American Psychological Association Web of Science Cited >500 publications	Very simple and easy to implement	Only run Simple Random number
GraphPad https://www.graphpad.com/quickcalcs/index.cfm	Simple Block	Free	Standard web browser connected to the Internet (e.g., Chrome, Safari, Firefox, Internet Explorer)		1. Widely used in the scientific community 2. Cited more than >100 citations	Very simple and easy to implement	• Once the randomization plan is generated, the same randomization plan cannot be generated as this uses the seed point of the local computer clock and is not displayed for further use. • A maximum of only 10 treatments can be assigned to patients.
Randomization.com http://www.jerrydallal.com/random/randomize.htm	Simple Block	Free	Standard web browser connected to the Internet (e.g., Chrome, Safari, Firefox, Internet Explorer)		Cited more than >100 citations	Up to 20 treatments can be specified	Available only for simple and block randomization.

PAID ONLINE WEB-BASED AND CLOUD

Services	Types of Services	Fee	Requirement	Owner	Establishment	Features and extra applications added	Limitation
Randomizer.at https://randomizer.at	Permuted blocks, minimization, biased coin, urn randomization, other algorithms, etc.	**Randomization List** FREE list up to 5000 **Academic Sponsors** €500/trial including the first 50 randomizations. €5- per randomization beyond the 50 randomizations limit Unlimited number of trial sites Unlimited trial duration **Commercial Sponsors** €1000/trial including the first 70 randomizations. €10- per randomization beyond the 50 Unlimited number of trial sites Unlimited trial duration	Online web-based	Medical University of Graz Institute for Medical Informatics, Statistics, and Documentation (IMI)	Most cited in medical and health sciences journal	Within six months after trial activation - no more than 10 subjects have been randomized into a trial and the trial coordinator confirms trial termination, the full basic fee will be refunded.	Randomization is limited to 10 randomizations per trial for FREE randomization list
Sealed Envelope **https://www.sealedenvelope.com/**		**Simple randomization using permuted block** FREE randomizations list up to 50 £95 for each subsequent block of 50 randomizations Random permuted block	Online web-based		Most cited in medical and health sciences journal	• Web-based online • Randomization by text message. • Code Breaking Costume: blinding, rescue medication, maintenance therapy and dose	

		1:1 randomization **Simple + using list** **£295 for first 50 randomizations** £95 for each subsequent block of 50 randomizations. Random permuted block 2:1 or other unequal allocations Randomize by text message Stratification Named randomization groups Eligibility criteria checks **Fully Featured Randomisation for blinded and unblinded trials** From £1,800 Set-up Unblinded trial for public sector/academic/non-profit customers From £60 per month - **Up to 100 randomizations. et-up by Sealed Envelope Minimization Expert technical support Customized randomization form Role-based user accounts Reports Comprehensive audit log Code list management Maintenance and rescue codes Unblinding Change request process Validation documentation Price exclude Value Added Tax (VAT)				calculations as appropriate, Eligibility criteria, randomization protocol, and patient characteristics	

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