Randomization Procedures in Randomized Clinical Trials

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Overview

Brief Introduction of Clinical Trials

The following are several **definitions of a clinical trial** that were found in different textbooks and articles.

- A clinical trial is a study in human subjects in which treatment (intervention) is initiated specifically for therapy evaluation.
- A prospective study comparing the effect and value of the treatment against a control in human beings.
- A clinical trial is an experiment testing medical treatments in human subjects.

In most clinical trials, one objective is to provide an unbiased comparison between treatments.

Phases of Clinical Trials

Phases of clinical trials

Clinical trials are classified into four phases.

- **Phase I:** To explore possible toxic effects of drugs and determine a maximum tolerated dose for further experimentation. Also during Phase I the pharmacology of the drug may be explored.
- **Phase II:** A dose finding study is sometimes conducted to identify a lowest dose level with good treatment effects. Further assessment of drug safety is conducted.
- **Phase III:** We compare the new treatment (drug or therapy) to the current standard of treatment (placebo) with respect to treatment efficacy and safety.
- **Phase IV:** (post marketing) An observational study of adverse effects is conducted.

Randomization Procedures

- In phase III, randomized clinical trials are conducted to evaluate the treatment effect of an new drug by comparing it with the control group (placebo).
- In the context of a two-armed randomized clinical trial, treatments are assigned to patients based on a randomization procedure.

Why Randomize?

At the end of a trial, we may observe a difference between treatment effects. There are several possible explanations for the difference:

- The new treatment is more/less effective comparing with the placebo.
- The difference in treatment effects is solely due to chance.
- There is a systematic difference (or bias) between treatment groups due to factors other than treatments.

Randomization aims to obviate the third possibility.

- Procedures promoting the comparability between two groups of patients who receive different treatments without introducing human factors, are essential to protect the comparison between treatment effects from bias.

Randomization Procedures Continue

- Two Treatments: A and B
- n patients enter the trial sequentially and must be randomized immediately to either A or B.
- Randomization sequence:

$$\boldsymbol{T} = (T_1, \ldots, T_n)'$$

where $T_j = 1$ if the patient j received treatment A and $T_j = 0$ if treatment B.

We focus on reviewing randomization procedures in the following.

- Complete randomization
- Random allocation rule
- Truncated binomial design
- Permuted block design
- Random block design
- Biased coin design
- Big stick design

Complete Randomization (CR)

Complete randomization(CR)

The treatment assignments $\boldsymbol{T} = T_1, \ldots, T_n$ are independent and identically distributed Bernoulli random variables where

$$P(T_j = 1) = 1/2, \quad \text{for } j = 1, \ldots, n.$$

Pros: CR is easy to implement in practice.

Cons: This procedure is less attractive since there is a non-ignorable probability of obtaining unbalanced treatment assignments, i.e., significantly more patients receive one treatment compared to another treatment.

Random Allocation Rule (RAR)

Random allocation rule (RAR)

The RAR relies on the previous treatment assignments of $j-1$ patients when allocating a treatment to the jth patient. Let $\mathcal{F}_n$ be the treatment assignments for first n patients, where $\mathcal{F}_n = \{T_1, \ldots, T_n\}$. The RAR is defined by the following rule - the probability that the jth patient receives treatment A is given by

$$E(T_j|\mathcal{F}_{j-1}) = \frac{\frac{n}{2} - N_A(j-1)}{n-(j-1)}, \quad j = 2, \ldots, n$$

where $P(T_1) = 1/2$ and $N_A(j-1)$ is the number of patients who received treatment A after $j-1$ patients have been assigned.

Pros: The number of treatment assignments in A and B are equal.
Cons: The treatment assignments are predictable at some stages in the trial, which may result in selection bias. For instance, if $n/2$ patients have already received treatment A, the remaining patients who have not received treatments must receive treatment B; thus, a significant imbalance also occurs midway through the trial. The influences of imbalance under the RAR are discussed for large n by Rosenberger and Lachin (2015).

Truncated Binomial Design (TBD)

Truncated binomial design (TBD)

The rule for allocating patients under the TBD is summarized as the following, when n is even:

$$
\begin{aligned}
E(T_j|\mathcal{F}_{j-1}) &= \frac{1}{2}, && \text{if } \max\{N_A(j-1), N_B(j-1)\} < n/2 \\
&= 0, && \text{if } N_A(j-1) = n/2, \\
&= 1, && \text{if } N_A(j-1) = n/2.
\end{aligned}
$$

Pros: The number of treatment assignments in A and B are equal.
Cons: Similar to the problems in the RAR, the randomization assignments are predictable at some stages, and imbalances in the assignments are expected to occur during the trial.

Permuted Block Design (PBD)

Severe imbalances may occur during the trial if a design discussed previously are adopted. However, the PBD better controls on imbalances.

Permuted block design (PBD)

For PBD, M blocks are established, and each block has $m = n/M$ patients. Within each block, $m/2$ patients receive one treatment, and the rest receive another treatment. The RAR or the TBD are implemented when allocating the patients within each block.

Pros: The maximum value for the possible imbalance is $m/2$ during the trial; thus the extent of the imbalance can be alleviated.
Cons: Selection bias can not be prevented because of the predictability in the randomization sequences.

Random Block Design (RBD)

Unlike the PBD, the block size varies in the random block design (RBD).

Random block design (RBD)

Define B_j, $j = 1, \ldots, n$, as one half of the block size of the block containing the jth patient, so that B_j is a random variable from a discrete uniform distribution, and $B_{\max}$ is the largest possible value for B_j. The position of a jth patient within its block is defined as R_j, and this depends on the block size B_j. The RAR or the TBD are used to allocate treatments within a block. For instance, if the RAR was adopted, we have

$$E(T_j|\mathcal{F}_j, B_j, R_j) = \frac{\frac{B_j}{2} - \sum_{l=j+1-R_j}^{j-1} T_l}{B_j - R_j + 1}$$

Pros: The variability in block sizes reduces the adverse effects of selection bias comparing to PBD.

Cons: There is a high probability that the last block is unfilled since n is not known in advance. Thus the final imbalance can be as large as B_{max} if the last block is unfilled.

Biased Coin Design (BCD)

Biased coin design (BCD)

The BCD was proposed by Efron (1971). The allocation rule is described as the following:

$$
\begin{aligned}
E(T_j|\mathcal{F}_{j-1}) &= \frac{1}{2}, && \text{if } D_{j-1} = 0,\\
&= p, && \text{if } D_{j-1} < 0,\\
&= 1-p, && \text{if } D_{j-1} > 0,
\end{aligned}
$$

where D_n measures the differences of treatment assignments between treatment A and B (e.g., $D_n = N_A(n) - N_B(n) = 2N_A(n) - n$), and p is a constant, $p \in (0.5, 1]$. Efron recommended $p = 2/3$ in his original paper.

The BCD attempts to build the trade-off between imbalance and predictability by introducing parameter D.

Big Stick Design (BSD)

Big stick design (BSD)

Soares and Wu (1983) introduced the big stick design (BSD). Define an imbalance tolerance parameter b, which is a positive integer. The level of imbalance is controlled within an acceptable range by b, which is fixed in advance. The rule for the BSD described as the following:

$$
\begin{aligned}
E(T_j|\mathcal{F}_{j-1}) &= \frac{1}{2}, && \text{if } |D_{j-1}| < b \\
&= 0, && \text{if } D_{j-1} = b \\
&= 1, && \text{if } D_{j-1} = -b.
\end{aligned}
$$

Unlike the BCD, the level of imbalance in BSD is further controlled in an acceptable range by imposing a deterministic treatment assignment (by setting p=0).

Conclusion

In conclusion, adopting a randomization procedure in clinical trials helps eliminate conscious bias from physicians' and patients' perspectives; it balances unconscious bias between treatment groups resulting from unknown factors affecting treatment effects.

Except for these randomization procedures we discussed previously, there are other randomization techniques are proposed to control potential factors or from the ethical consideration, such as

- Stratification
- Covariate-Adaptive Design
- Response-Adaptive Design
- ...

References

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Thank you!