Measurement, Design, and Analytic Techniques in Mental Health and Behavioral Sciences

Lecture 4 (April 9, 2009): Different Designs on Behavioral Sciences

XH Andrew Zhou

azhou@u.washington.edu

Department of Biostatistics, University of Washington

Two types of randomization

- Unrestricted randomization: having no constraints imposed on the random allocation of treatments.
- Restricted randomization: imposing "balancing" restrictions on the probability of treatment allocation, e.g. equal numbers of patients per treatment group.
  - Balance restrictions impose balance on treatment assignment throughout the length of the trial in order to achieve equal numbers of subjects within each treatment assignation.
  - those that impose covariate balance between treatment groups, e.g. an equal distribution of males and females across treatment groups.

Stratification

- To obtain balanced treatment distributions within a covariate, we can stratify subjects into groups, and then randomize them to treatment within these groups.
- For example, in clinical trials of depression gender may affect outcome independently of treatment; therefore, gender may be used as a stratifying covariate.
- Specifically, a randomization schedule will be done for males, and a separate one will be done for females, to ensure treatment balance exists for each gender stratum.
- Hence, within each gender, the desired treatment balance is maintained. More generally, stratification

Stratification, continued

- Stratification is a technique which partitions patients into mutually exclusive subsets defined by some covariates that are believed to influence response and is used to reduce accidental bias .
- Accidental bias is defined as bias that occurs when nuisance factors that may be known or unknown to the experimenter systematically affect the experimental units [12].
- Therefore, stratification is a method used to achieve distributional balance of covariates between treatment groups (or balanced treatment assignments within each level of a stratum) that are expected a priori to influence outcome.

Reducing Type I error

- Type I error is the error we make by declaring a difference in outcomes between treatment groups when in fact no difference exists.
- In trials with up to 400 patients, statistical studies demonstrate that stratification helped in reducing the probability of type I error (Kernan et al., 1999, Journal of Clinical Epidemiology; Feinstein and Landis, 1976, Journal of Chronic Diseases).

Increasing power of statistical tests

- Power is the ability to detect a difference in outcomes between treatments when a difference does exist.
- In statistical studies of 100 subjects, power increases of up to 12% have been demonstrated when both stratified randomization with adjusted analysis were utilized (Kernan et al, 1999, Journal of Clinical Epidemiology; Green and Byar, 1978, Journal of Chronic Disease).

Disadvantages of stratification

- It is important to limit stratification variables to represent only the most important variables and levels.
- Over-stratification can lead to imbalances in overall treatment allocations because large numbers of strata can produce small patient numbers within strata.

Simple randomization

- Randomization with no restrictions imposed on the nature of the allocation sequence with the exception of pre-specification of the total sample size is referred to as simple randomization.
- As an example, simple randomization occurs when the total sample size is exactly pre-specified whereby a randomly chosen subset of n/2 out of n subjects is allocated to treatment 1 and the remaining n/ 2 subjects are allocated to treatment 2.
- Simple randomization is the only scheme without restrictions; that is, treatment assignments are unbiased or random.
- An important property of simple randomization is the minimization of the determinism of the treatment selection process.

Imbalance

- Completely randomization can lead to large imbalances. For example, if treatment 1 or treatment 2 is to be assigned to each of 12 patients, the probability of perfect balance (6 subjects assigned to treatment one and 6 subjects assigned to treatment 6) is only .0.23.
- That is, the probability of having 3 assigned to treatment one and 9 assigned to treatment two is 0.05.

Restricted randomization

- Certain methods of restricted randomization attempt to correct for the probability of treatment imbalance by imposing the restriction that the final allocation is exactly equal between treatment groups.
- Simple randomization, mentioned previously, has the restriction that the total number of people assigned to each treatment within a particular stratum is equal. However, the balance in treatment numbers is not obtained until the total sample size is reached.
- Randomizing participants within sequential blocks is an example of a design, which improves balance in the number of treatment assignments throughout the length of the study.

Blocked randomization

- The block design consists of M blocks containing n = N/M participants where N is the total sample size.
- Within each block given two treatment arms, n/2 participants are assigned to treatment 1 and n/2 are assigned to treatment 2.
- A random allocation rule is utilized in each block to ensure balance throughout the course of the trial. The maximum amount of imbalance that can occur at any point in time during a trial is limited to n/2.

Permuted block randomization

- By imposing balance restriction at interval periods, this block design ensures that the number of subjects assigned to treatment is balanced throughout the course of the trial.
- However, block designs may appear deterministic in an un-blinded setting due to the periodic balance invoked at the end of each block.
- Although treatment balance is achieved using the block design, selection bias may occur due to deterministic nature of every even randomization. For example given a three treatment clinical trial with a block size of six where the first five subjects have a treatment assignment sequence of ’2,3,1,1,2’ then the next assignment of 3 is known and therefore deterministic.

Permuted block randomization, continued

- A variable block design, where block size itself randomly selected, can reduce selection bias.
- Finally, the blocked randomization scheme does not provide restrictions for covariate. balance.
- Using a stratified permuted block design can produce covariate balance and treatment balance, where a permuted block randomization scheme is preformed within each stratum.

Permuted block randomization, continued

- A major advantage of the permuted block design is its ease of implementation.
- Once stratifying factors, block size and number of treatment arms have been determined a schedule of treatment assignment may be produced before the clinical trial begins.
- The treatment assignment then remains static throughout the course of the trial.
- A proper analysis that includes all stratifying factors and block can then be performed to ascertain whether treatment effect differences exist.

Urn randomization

- A permuted block design keeps the probability of treatment assignment constant during a trial, a non-adaptive one.
- Adaptive randomization scheme makes the probability of allocation change as the trial progresses.
- It is a dynamic process for treatment assignment as enrollment accrues.
- At any accrual point at which an imbalance occurs, the adaptive randomization scheme adjusts the allocation probability so that the probability of assigning treatment is higher for the arm with fewer treated subjects. So treatment imbalance is corrected as the trial progresses.

Wei's urn design

- Choose an urn containing a set number of balls of two types 1 and 2.
- For a particular subject, a ball is drawn. If the ball is of type 1, the subject receives treatment 1, and a set number of type 2 balls are added to the urn; otherwise, the subject receives treatment 2, and a set number of type 1 balls are added to the urn.
- Hence, the composition of the urn is such that the probability of assignment is larger for the treatment type, which has been selected less often at any point in the trial.

Wei's urn design, continued

- For two treatment arms we can let $N_1(j)$ and $N_2(j)$ be the proportion of participants randomized to treatment arm 1 and 2 out of the total of j participants randomized so far in the trial.
- F_j is the set of treatment assignments which have been allocated at j stage of the randomization process; $F_j = T_1, ..., T_j$.
- F_{j-1} is the set of treatment assignments which have been allocated previous to the current treatment to be assigned where T_j is the current treatment to be assigned.

Wei's urn design, continued

-
- The urn design is denoted $UD(\alpha, \beta)$ and has the following allocation:

$$P(T_j \mid F_{j-1}) = 1 - \frac{\alpha + \beta N_2(j-1)}{2\alpha + \beta(j-1)},$$

$j \geq 2$, and

$$P(T_1 \mid F_0) = 1/2.$$

An example of urn randomization

- If $\alpha = 0$ and $\beta = 1$, we have

$$P(T_j \mid F_{j-1}) = 1 - \frac{N_2(j-1)}{j-1}.$$

- For example, if there are 22 out of the first 50 assignments to treatment two, the probability of assigning the 51th subject to treatment two is then

$$P(T_{51} \mid F_{50}) = 1 - \frac{\frac{22}{50}(51-1)}{51-1} = 0.56.$$

- For the $UD(0,1)$ design, there is 56% chance that the next assignment will be treatment 2 and a 44% chance of having treatment 1.

Generalization

- Wei's $UD(0,1)$ design may be generalized to three treatment groups as follows: for the $UD(0,1)$ design the urn, the probability that the jth assignment is to treatment i given the previous $j-1$ assignments is:

$$P(T_j \mid F_{j-1,k=3}) = \frac{j-1-N_i(j-1)}{(j-1)(3-1)},$$

where $i = 1, 2, 3$ represent each of the three treatment arms.

Wei's urn design, continued

- For clinical trials with small samples, urn randomization scheme forces balance. As the sample size increases, the allocation process can be shown to approach that of complete randomization.
- The urn randomization design is a compromise between complete randomization design and the permuted block design.
- The probability of correct guess is lower for the urn design compared to the blocked design but is higher than that for complete randomization.

Implementation issues and potential drawbacks

- Implementation constraints can make the use of urn randomization impossible in some circumstances.
- If treatment assignment cannot wait for determination of the values of the covariates entry of data into the computer program and feedback of the assignment then urn randomization may be infeasible.
- Turnaround time can be a special problem in multi site trials where randomization is centrally controlled.

Implementation issues and potential drawbacks, continued

- For clinical trials with small samples, urn randomization scheme forces balance. As the sample size increases, the allocation process can be shown to approach that of complete randomization.
- The urn randomization design is a compromise between complete randomization design and the permuted block design.
- The probability of correct guess is lower for the urn design compared to the blocked design but is higher than that for complete randomization.

Covariate adaptive design

- In the case that several covariates are known a priori to influence outcome, covariate adaptive randomization methodology may be used to force balance over both treatment and prognostic factors (Pocock and Simon, 1975, Biometrics; Taves, 1974, Clinical Pharmacology & Therapeutics; Matts and Begg, 1985, Statistics in Medicine).
- Stratified randomization has the same goals of balance as the covariate adaptive scheme.
- While stratified randomization promotes parsimony in selection of stratification factors, covariate adaptive methods utilizes all covariates thought to influence response.

Sample size and number of covariates

- Sample size and number of covariates need to be considered together.
- For very small samples (e.g., group sizes 5- 12), balancing may be preferable, or urn randomization with no covariates and special permutation tests.
- With very small sample sizes, only one or two covariates should be considered.
- For intermediate sizes (e.g., groups of 20-50), urn randomization is attractive to control possible bias for a few covariates(e .g.,3 -5).
- For larger samples(e.g., 50-200), urn randomization can be useful if control over many covariates is needed.
- When samples are very large (250 +), simple randomization may be adequate.

Sample size and number of covariates, continued

- The number of covariates urn randomization can successfully handle in a given trial depends on a number of factors, including how the covariates are distributed(e .g.,skewness), how the covariates are correlated, the number of treatments and whether any of the covariates interact.
- Extensive simulation studies are needed to determine with precision how these different factors affect the performance of urn randomization.

Urn randomization in practice

- Urn randomization has been applied in several addictions and mental health studies .
- The earliest being that of McCrady et al. (1986), where five covariates were balanced across three treatment groups with a total sample o f 54.
- The largest completed alcohol treatment study to use urn randomization is that of Longabaugh et al. (1993), in which six covariates were balanced across three groups with a total sample size of 229.

Urn randomization in practice, continued

- Urn randomization was used in the MATCH trial, where each treatment site was balanced separately.
- Each Project MATCH treatment site was expected to randomize 200 subjects into three conditions, balancing eight covariates.
- The covariates were number of DSM-III-R alcohol dependence symptoms, prior inpatient treatment for drinking, prior psychiatric treatment, sociopathy marital status, employment status, gender and education. All covadates were dichotomized.

Issues in analyses

- We can base tests of statistical significance for randomized studies on either a permutation model or a population model.
- A permutation model requires no assumptions regarding the origin of the study participants or the distribution of their responses.
- The most commonly used population model assumes that participants were sampled at random from a homogenous population and their responses follow a common distribution.
- Under the assumption of a homogenous population, the method of randomization may be ignored in the analysis.
- The assumption of the homogeneous population may not hold for most clinical trials.

Issues in analyses, continued

- Permutation methods of analysis have been suggested for the urn and covariate adaptive schemes.
- The analysis becomes more complicated by these restrictions placed on the probability of assignation.
- It has been recommended to account for covariates, used in randomization techniques, in the analysis.

Analyses of urn randomization

- In the statistical literature, discussions of analysis given that urn randomization was utilized in the design stage of the study promote the use of permutation tests (Wei, 1988, Biometrika).
- The effect of ignoring the randomization in the presence of heterogeneity is not as easily illustrated as that of blocked randomization.
- Additionally, tests based on a permutation model for the urn design may differ substantially from tests based on a parametric or population model (normal distribution, variance homogeneity, etc.).

Analyses of urn randomization, continued

- Due to the inherent time heterogeneity expected in a clinical trial as well as the difficulty in quantifying the effect of urn randomization on outcome, the proper permutation tests whose variance account for randomization restrictions are suggested over the use of statistical tests based on population models (Wei and Lachin JM, 1988, Controlled Clinical Trials).
- Wei (Biometrika, 1988) demonstrated the differences in significance that can occur when the randomization is ignored in the analysis.

Analyses for covariate adaptive randomziation

- Covariate adaptive randomization utilizes the method of minimization assuring that treatment arms are balanced within various strata of predefined covariates.
- A disadvantage of covariate adaptive randomization is the complexity introduced into the analysis. Taves promoted the use of ANCOVA for analysis where all covariates used as minimization factors are also used in the analysis.
- However, the correct statistical methods for covariate adaptive randomization of analysis are still a conundrum in statistical sciences.
- Along with ANCOVA, permutation tests which take into account the particulars of the adaptive randomization scheme have been suggested for analysis.

Analysis of blocked designs

- The principal of blocking is to increase the power for treatment comparisons by dividing experimental units into homogenous strata and then pooling the treatment group differences over blocks.
- In the instance of a clinical trila where patients are gradually accrued over time, participants may be time heterogeneous. Therefore, incorporating blocking within the analysis should provide a more powerful test of the treatment effect. Data may be examined for the existence of an intrablock correlation (participant responses within blocks may be positively correlated because they are recruited closer in time) and a block-stratified analysis may be required dependent on the existence of an intrablock correlation due to time heterogeneity.

Analysis of blocked designs, continued

- In the instance of a positive intrablock correlation, an analysis ignoring block will be conservative (have higher Type II error).

Summary on analyses

- Given that all assumptions are met, the type of randomization scheme may be ignored in the analysis and the population model may be used as a method of inference.
- In the case of accrual in a clinical trial where time heterogeneity of outcome is likely, population-based tests may not be valid.
- Permutation tests on the other hand assume nothing about the data except that participants were randomized.
- Under the permutation model of inference, restrictions of the randomization scheme may be incorporated into the analysis.

Summary on Analyses, continued

- It has been shown that it is important to incorporate a permutation method of analysis for a blocked design in the presence of intra-block correlation, for the urn design where time heterogeneity is not as easily assessed and for covariate adaptive design where minimization complicates the analysis.
- In summary, failure to account for restriction in analysis may result in conservative tests of significance.