South American Journal of Clinical Research
Volume 2, Issue 2, 2015

An Overview of Basic Epidemiology Concepts, Randomization Techniques and Minimization for Clinical Trials

Article Review by Praneeth Kumar
Ph.D in Clinical Research, Texila American University
Email:- Praneethuk4@gmail.com

Abstract

This article will cover concepts of association and outcomes, introduce standard epidemiological concepts of incidence and prevalence, define and describe relative risk, absolute risk, attributable risk and the various methods for calculating those quantities in different observational research designs. Definitions of and methods for reducing bias are major components of this section.

Epidemiology is the study of disease in populations. It thus differs from the more conventional medical approaches to the study of disease that is normally concerned with the study of disease processes in affected individuals.Cohort, cross sectional, and case-control studies are collectively referred to as observational studies. Often these studies are the only practicable method of studying various problems, Cohort studies are used to study incidence, causes, and prognosis. Because they measure events in chronological order they can be used to distinguish between cause and effect. Cross sectional studies are used to determine prevalence. They are relatively quick and easy but do not permit distinction between cause and effect. Case controlled studies compare groups retrospectively. They seek to identify possible predictors of outcome and are useful for studying rare diseases or outcomes.

The crucial point of a clinical trial is the aim of investigating the difference of the patient groups caused only by the treatment procedures that are applied. If other kinds of differences exist (such as systematic differences) between the groups to be formed, then the outcomes are supposed to be biased. Forms of bias can corrupt a study at any phase, including patient selection (selection and membership bias), study performance (performance and information bias), patient follow-up (non responder and transfer bias), and outcome determination (detection, recall, acceptability, and interviewer bias).

The two common methods that are used to reduce the bias are randomization and blinding. The aim of randomization in clinical trials is the creation of groups that are comparable for any known or unknown, potentially confounding variables. Randomization, if done properly, ensures strengthening both the internal validity by minimizing selection bias and external validity by providing a correct basis for generalization. Simple randomization, weighted randomization, block randomization, stratified randomization, and minimization methods are discussed in this article.

Keywords: *Epidemiology, simple randomization, block randomization, stratified randomization, minimization and blinding.*

Introduction

Epidemiology is the study of the distribution and determinants of disease frequency [1]. In the fifth century BC, Hippocrates suggested that the development of human disease might be related to the external and internal environment of an individual [1]. In the 1600s and 1800s in England, John Graunt and William Farr quantified vital statistics on the basis of birth and death records [1]. In the 1850s, John Snow associated cholera with water contamination in London by observing higher cholera rates in homes supplied by certain water sources [1].

Epidemiological methods gradually evolved with use of the case-control study to demonstrate an association between smoking and lung cancer, use of the prospective cohort study to determine risk factors for cardiovascular disease in the Framingham Heart Study, and use of the randomized clinical trial for the poliomyelitis vaccine [1]. The evidence-based medicine and patient-derived outcomes assessment

movements burst onto the scene of clinical medicine in the 1980s and 1990s as a result of contemporaneous medical, societal, and economic influences. Pioneers such as Sackett and Feinstein emphasized levels of evidence and patient-centered outcomes assessment 2-10. Work by Weinberg and colleagues revealed large small-area variations in clinical practice, with some patients being thirty times more likely to undergo an operative procedure than other patients with identical symptoms merely because of their geographic location 11-16. Additional critical research suggested that up to 40% of some surgical procedures might be inappropriate and up to 85% of common medical treatments were not rigorously validated 17-19. Meanwhile, the costs of health care were rapidly rising to over two billion dollars per day, increasing from 5.2% of the gross domestic product in 1960 to 16.2% in 199720. Health maintenance organizations and managed care emerged. In addition, increasing federal, state, and consumer oversight was brought to bear on the practice of clinical medicine.

Observational research methods

Cohort, cross sectional, and case-control studies are collectively referred to as observational studies. Often these studies are the only practicable method of studying various problems, for example, studies of aetiology, instances where a randomised controlled trial might be unethical, or if the condition to be studied is rare. Cohort studies are used to study incidence, causes, and prognosis. Because they measure events in chronological order they can be used to distinguish between cause and effect. Cross sectional studies are used to determine prevalence. They are relatively quick and easy but do not permit distinction between cause and effect. Case controlled studies compare groups retrospectively. They seek to identify possible predictors of outcome and are useful for studying rare diseases or outcomes. They are often used to generate hypotheses that can then be studied via prospective cohort or other studies.

Cohort studies

Cohort studies describe incidence or natural history. They analyse predictors (risk factors) thereby enabling calculation of relative risk. Cohort studies measure events in temporal sequence thereby distinguishing causes from effects. Retrospective cohorts where available are cheaper and quicker. Confounding variables are the major problem in analysing cohort studies. Subject selection and loss to follow up is a major potential.

Advantages and disadvantages of cohort studies

The use of cohorts is often mandatory as a randomised controlled trial may be unethical; for example, you cannot deliberately expose people to cigarette smoke or asbestos. Thus research on risk factors relies heavily on cohort studies. As cohort studies measure potential causes before the outcome has occurred the study can demonstrate that these “causes” preceded outcome, thereby avoiding the debate as to which is cause and which is effect. A further advantage is that a single study can examine various outcome variables. This contrasts with case-control studies as they assess only one outcome variable (that is, whatever outcome the cases have entered the study with). Cohorts permit calculation of the effect of each variable on the probability of developing the outcome of interest (relative risk). However, where a certain outcome is rare then a prospective cohort study is inefficient. The efficiency of a prospective cohort study increases as the incidence of any particular outcome increases. Thus a study of patients with a diagnosis of deliberate self-harmin the 12 months after initial presentation would be efficiently studied using a cohort design. Another problem with prospective cohort studies is the loss of some subjects to follow up. This can significantly affect the outcome. Taking incidence analysis as an example (incidence =cases/per period of time)

Retrospective studies are much cheaper as the data have already been collected. One advantage of such a study design is the lack of bias because the outcome of current interest was not the original reason for the data to be collected. However, because the cohort was originally constructed for another purpose it is unlikely that all the relevant information will have been rigorously collected. Retrospective cohorts also suffer the disadvantage that people with the outcome of interest are more likely to remember certain

antecedents, or exaggerate or minimise what they now consider to be risk factors (recall bias). Where two cohorts are compared one will have been exposed to the agent of interest and one will not. The major disadvantage is the inability to control for all other factors that might differ between the two groups. These factors are known as confounding variables. A confounding variable is independently associated with both the variable of interest and the outcome of interest. For example, lung cancer (outcome) is less common in people with asthma (variable). However, it is unlikely that asthma in itself confers any protection against lung cancer. It is more probable that the incidence of lung cancer is lower in people with asthma because fewer asthmatics smoke cigarettes (confounding variable). The only way to eliminate all possibility of a confounding variable is via a prospective randomised controlled study. In this type of study each type of exposure is assigned by chance and so confounding variables should be present in equal numbers in both groups. Finally, problems can arise as a result of bias.

Cross Sectional Studies

Cross sectional studies are the best way to determine prevalence. Are relatively quick. Can study multiple outcomes. Do not themselves differentiate between cause and effect or the sequence of events.

Advantages and disadvantages

The most important advantage of cross sectional studies is that in general they are quick and cheap. As there is no follow up, less resource are required to run the study. Cross sectional studies are the best way to determine prevalence and are useful at identifying associations that can then be more rigorously studied using a cohort study. The most important problem with this type of study is differentiating cause and effect from simple association. For example, a study finding an association between low CD4 counts and HIV infection does not demonstrate whether HIV infection lowers CD4 levels or low CD4 levels predispose to HIV infection. Moreover, male homosexuality is associated with both but causes neither. (Another example of a confounding variable). Often there are a number of plausible explanations. For example, if a study shows a negative relation between height and age it could be concluded that people lose height as they get older, younger generations are getting taller, or that tall people have a reduced life expectancy when compared with short people. Cross sectional studies do not provide an explanation for their findings. Rare conditions cannot efficiently be studied using cross sectional studies because even in large samples there may be no one with the disease. In this situation it is better to study a cross sectional sample of patients who already have the disease (a case series). In this way it was found in 1983 that of 1000 patients with AIDS, 727 were homosexual or bisexual men and 236 were intravenous drug abusers.[6] The conclusion that individuals in these two groups had a higher relative risk was inescapable. The natural history of HIV infection was then studied using cohort studies and efficacy of treatments via case controlled studies and randomised clinical trials.

Examples

An example of a cross sectional study was the prevalence study of skull fractures in children admitted to hospital in Edinburgh from 1983 to 1989.7 Note that although the study period was seven years it was not a longitudinal or cohort study because information about each subject was recorded at a single point in time. A questionnaire based cross sectional study explored the relation between A&E attendance and alcohol consumption in elderly persons. A recent example can be found in the BMJ, in which the prevalence of serious eye disease in a London population was evaluated.

Case-Control Studies

In contrast with cohort and cross sectional studies, case control studies are usually retrospective. Case-control studies are simple to organise Retrospectively compare two groups. Aim to identify predictors of an outcome. Permit assessment of the influence of predictors on outcome via calculation of an odds ratio.

Useful for hypothesis generation. Can only look at one outcome. Bias is an major problem

Advantages and disadvantages of case control studies

When conditions are uncommon, case-control studies generate a lot of information from relatively few subjects. When there is a long latent period between an exposure and the disease, case-control studies are the only feasible option. With less than 300 confirmed case a cross sectional study would need about 200 000 subjects to include one symptomatic patient. Given a postulated latency of 10 to 30 years a cohort study would require both a vast sample size and take a generation to complete. In case-control studies comparatively few subjects are required so more resources are available for studying each. Inconsequence a huge number of variables can be considered. This type of study is therefore useful for generating hypotheses that can then be tested using other types of study. This flexibility of the variables studied comes at the expense of the restricted outcomes studied. The only outcome is the presence or absence of the disease or whatever criteria were chosen to select the cases. The major problems with case-control studies are the familiar ones of confounding variables and bias.

Standard Epidemiological Concepts

Incidence

Incidence is a measure of the risk of developing some new condition within a specified period of time. Although sometimes loosely expressed simply as the number of new cases during some time period, it is better expressed as a proportion or a rate with a denominator.

For example, if a population initially contains 1,000 non-diseased persons and 28 develop a condition over two years of observation, the incidence proportion is 28 cases per 1,000 persons, i.e. 2.8%.

Incidence rate

The incidence rate is the number of new cases per population in a given time period. When the denominator is the sum of the person-time of the at risk population, it is also known as the incidence density rate or person-time incidence rate.

In the same example as above, the incidence rate is 14 cases per 1000 person-years, because the incidence proportion (28 per 1,000) is divided by the number of years (two).

Using person-time rather than just time handles situations where the amount of observation time differs between people, or when the population at risk varies with time. Use of this measure implicitly implies the assumption that the incidence rate is constant over different periods of time, such that for an incidence rate of 14 per 1000 persons-years, 14 cases would be expected for 1000 persons observed for 1 year or 50 persons observed for 20 years.

Prevalence

In epidemiology, the prevalence of a disease in a statistical population is defined as the total number of cases of the disease in the population at a given time, or the total number of cases in the population, divided by the number of individuals in the population. It is used as an estimate of how common a condition is within a population over a certain period of time. It helps physicians or other health professional understand the probability of certain diagnoses and is routinely used by epidemiologists, health care providers. Government agencies and insurers.

Suppose we define a as the number of individuals in a given population with the disease at a given time, and b as the number of individuals in the same population at risk of developing the disease at a given time, not including those already with the disease. Then, we can write the prevalence as

$$\textbf{Prevalence} = \frac{a}{a + b}$$

Incidence vs. prevalence

Incidence should not be confused with prevalence, which is a measure of the total number of cases of disease in a population, rather than the rate of occurrence of new cases. Thus, incidence conveys information about the risk of contracting the disease, whereas prevalence indicates how widespread the disease is. Prevalence is the ratio of the total number of cases in the total population, and is more a measure of the burden of the disease on society. Prevalence can also be measured with respect to a relevant subgroup of a population (see: denominator data) incidence is more useful usually than prevalence in understanding the disease etiology.ie if incidence rate of population of a disease increases this means that there is a risk factor that promotes the incidence.

Example

Consider a disease that takes a long time to cure, and that was spread widely in 2002, but whose spread was arrested in 2003. This disease will have a high prevalence and a high incidence in 2002; but in 2003 it will have a low incidence, although it will continue to have a high prevalence because it takes a long time to cure so the fraction of affected individuals remains high. In contrast, a disease that has a short duration may have allow prevalence and a high incidence. When the incidence is approximately constant for the duration of the disease, prevalence is approximately the product of disease incidence and average disease duration, so

Prevalence = incidence x duration.

The importance of this equation is the relation between prevalence and incidence, for example when the incidence goes up then the prevalence must go up as well.

When studying the aetiology of a disease, it is better to analyse incidence rather than prevalence, since prevalence mixes in the duration of a condition, rather than providing a pure measure of risk.

Relative risk

In statistics and mathematical epidemiology, relative risk (RR) is the risk of an event (or of developing a disease) relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group versus a non-exposed group.

$$RR = \frac{P_{exposed}}{P_{non\ exposed}}$$

Consider an example where the probability of developing lung cancer among smokers was 20% and among non-smokers 1%. This situation is expressed in the 2 × 2 table to the right.

Risk	**Disease status**	
	Present	Absent
Smoke	a	B
Non Smoke	c	D

Here, a = 20(%), b = 80, c = 1, and d = 99. Then the relative risk of cancer associated with smoking would be

$$RR = \frac{a/(a+b)\ 20/100}{c/(c+d)\ 1/100} = \frac{}{} = 20$$

Smokers would be twenty times as likely as non-smokers to develop lung cancer.

Another term for the relative risk is the risk ratio because it is the ratio of the risk in the exposed divided by the risk in the unexposed.

Absolute risk

Absolute risk of a disease is your risk of developing the disease over a time-period. We all have absolute risks of developing various diseases such as heart disease, cancer, stroke, etc. The same absolute risk can be expressed in different ways. For example, say you have a 1 in 10 risk of developing a certain disease in your life. This can also be said a 10% risk, or a 0.1 risk - depending if you use percentages or decimals.

Attributable risk

In epidemiology, attributable risk is the difference in rate of a condition between an exposed population and an unexposed population.

The concept was first proposed by Levin in 1953.

The term population attributable risk (PAR) has been described as the reduction in incidence that would be observed if the population were entirely unexposed, compared with its current (actual) exposure pattern. In this context, the comparison is to the existing pattern of exposure, not the absence of exposure.

Population attributable risk is often simply called "attributable risk" (AR), and the later term is most often associated with the above PAR definition. However, some epidemiologists use "attributable risk" when referring to the excess risk, also called the risk difference or rate difference.

Green land and Robins distinguished between excess fraction and etiologic fraction in 1988.

Etiologic fraction is the proportion of the cases that the exposure had played a causal role in its development.

It is defined as:

$$\mathbf{EF} = \frac{\mathbf{N_e - N_n}}{\mathbf{N_e}}$$

where:

EF = Etiologic fraction

Ne = Number of exposed individuals in a population that develop the disease

Nn = Number of unexposed individuals in the same population that develop the disease.

Excess fraction, however, is the proportion of the cases that occurs among exposed population that is in excess in comparison with the unexposed.

All etiologic cases are excess cases, but not vice versa. From the standpoint of both law and biology it is important to measure the etiology fraction. In most epidemiological studies, PAR measures only the excess fraction. (Larger than etiologic fraction)

Bias

The crucial point of a clinical trial is the aim of investigating the difference of the patient groups caused only by the treatment procedures that are applied. If other kinds of differences exist (such as systematic differences) between the groups to be formed, then the outcomes are supposed to be biased. The term bias describes the systematic tendency of any factors associated with the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value.

One of the possible sources of bias may occur in the design phase of the trial. For example, assignment of the patients at lower risk to one group and there are different randomization and blinding methods.

Other sources of bias may occur during the conduct and analysis of a clinical trial. For example, protocol violations and exclusion of patients from analysis based upon knowledge of subject outcomes are possible sources of bias that may affect the accurate assessment of the treatment.

Methods for Reducing Bias

The most common design techniques for avoiding bias in clinical trials are
1) *Randomization and*
2) *Blinding.*

1. Randomization

Randomization aims to obviate the systematic differences (or bias) between groups due to the factors other than the intervention. It gives each patient a known (usually equal) chance of being assigned to any of the groups and it is based on the premise that the group assignment cannot be predicted. It also tends to provide treatment groups with similar distributions of prognostic factors (known and unknown).

Simple randomization

Randomization based on a single sequence of random assignments is known as simple randomization. This technique maintains complete randomness of the assignment of a person to a particular group. The most common and basic method of simple randomization is flipping a coin. For example, with 2 treatment groups (control versus treatment), the side of the coin (i.e., heads = control, tails = treatment) determines the assignment of each participant. Other methods include using a shuffled deck of cards (e.g., even = control, odd = treatment) or throwing a die (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 also be used for simple randomization of participants.

This randomization approach is simple and easy to implement in a clinical trial. In large trials (n > 200), simple randomization can be trusted to generate similar numbers of participants among groups. However, randomization results could be problematic in relatively small sample size clinical trials (n < 100), resulting in an unequal number of participants among groups. 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 (Figure 1).

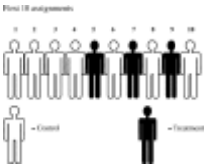

Figure 1 Imbalance of sample size between treatment arms due to simple randomization (coin toss) in a small trial (n = 10).

Weighted Randomization

Assignments may be weighted by making small changes in simple randomization procedures. For example, if the number of patients that shall be assigned to treatment A is desired to be double the number of patients assigned to treatment B, then choosing the numbers between 01 - 66 for treatment A and numbers between 67 - 99 for treatment B from the table of random numbers would be sufficient.

Block Randomization

As may be easily concluded from the explanations and examples of simple randomization, in such ways of randomization the number of the patients assigned to groups generally differs. On the other hand, in most of the studies the number of the patients is desired to be very close or equal in the different

groups. With the help of block randomization, the number of patients in different groups is balanced as much as possible

In block randomization, the blocks may be in any size. However, a multiple of the number of treatments is usually preferred for the block size. For example, if there are two treatment procedures, then it is better to use blocks of size 2, 4, 6... and if there are three treatment procedures, blocks of size 3, 6, 9 ... are preferred.

Two-Sized Block Randomization for Two Treatments

There are two possible block types when there are two treatment procedures and when the block size is supposed to be 2:

1. AB	2. BA

When we use the 14th column of the table of random numbers and ignore the numbers different from 1 and 2 then we have the below sequence for the blocks 3 and ignore the numbers different from 1 and 2 then we have the below sequence for the blocks:

1 2 2 2 2

When we make the block assignment according to this sequence, the assignment of the treatments will be as shown in Table 6. As can be seen, there will be five patients in both treatments A and B in the final assignment.

Table 6. Allocation scheme in two-sized block randomization

Block	**1**		**2**		**2**		**2**		**2**	
No. of patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Treatment procedure	**A**	**B**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	**A**

Four-sized Block Randomization for Two Treatments

When we consider blocks of size four for two treatment procedures, then there will be six different combinations in which two patients would be assigned to treatment A and two to treatment B,

AABB	1. BBAA	2. ABAB	3. BABA	4. ABBA	5. BAAB

If we use only these six different combinations in the assignment process of the treatments, then the number of the patients in one group may differ at most by two patients from the other group at any given time; however, the difference would not usually be more than one. When we select the 13th column of the table of random numbers and ignore the numbers different from 1 - 6, we get the below sequence,

5 4 3 2 4 6 1 3 2 3

The assignments of the patients when the first four numbers of this sequence are used are shown in Table 7:

Table 7. Allocation in four-sized blocks

Block	5				4				3				2			
No. of patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Treatment	A	B	B	A	B	A	B	A	A	B	A	B	B	B	A	A

Block sizes are not restricted. For example, for a block of six, possible combinations would be in the form of AAABBB, ABABAB, ABAABB, ... However, large blocks should not be used since such design would make the groups more unbalanced.

Six-sized Block Randomization for Three Treatments

The large sized blocks are not preferred in the studies where block design is used. For example, when there are three different treatment procedures and the block size is considered to be six, then we get different block structures (Table 8), and this may cause trouble for the researcher.

For example, assume that 30 patients will be assigned in this trial. As each block consists of six patients, it is enough to select five blocks. When we select the first two columns of the table of random numbers, the sequence will be as follows;

23 05 14 38 97 11

In this sequence, we ignore 97 as we have 90 blocks. Thus, five blocks (blocks 23, 05, 14, 38 and 11) consisting of 30 patients have the assignments below:

1. ACCBAB 2. AACBBC 3. CCBBAA 4. ABCBAC 5. BBCAAC

By this sequence, the 1st patient will be assigned to treatment A, the 2nd to treatment C, the 14th to treatment C and the 30th to treatment C. At the end of the research there will be 10 patients in each group.

In clinical trials it is generally desired to keep the randomization sequence hidden from the people who actually determine the treatment procedures. For this reason, sometimes two-sized, four-sized and six-sized blocks may be needed to be used together.

Stratified Randomization

While simple randomization methods eliminate the bias caused by allocation procedures, it does not strictly guarantee an unbiased structure. For example, it does not guarantee that the patients in each group show similar age characteristics. Especially in small studies, it is more likely that some differences will occur between groups due to the chance factor and this may cause trouble in interpreting the results. Even in the studies with more than 100 patients, there may be some significant variations especially for rare characteristics 3,4,7,11,13.

In many clinical trials, it is pre-known that sub-groups of patients respond differently to the treatment. For this reason, the patients in each group should have similar characteristics in such cases

Table 8. 9 Block combinations for three different treatment procedures

1.AABCBC	11.BBCAAC	21.ABBCCA	31.CAACBB	41.ABCCAB	51.BCABCA
2.AABBCC	12. BBACCA	22. ACCABB	32. CAABCB	42.ABCCBA	52. BCAACB
3.AACCBB	13.CCBABA	23.ACCBAB	33.CAABBC	43.BACABC	53.BCACAB
4.AACBCB	14.CCBBAA	24.ACCBBA	34.CBBCAA	44.BACBAC	54.BCACBA
5. AACBBC	15.CCAABB	25.BAABCC	35.CBBACA	45.BACBCA	55.ACBABC
6.AABCCB	16.CCABAB	26.BAACBC	36. CBBAAC	46.BACACB	56.ACBBAC
7.BBACAC	17.CCABBA	27.BAACCB	37.ABCABC	47.BACCAB	57.ACBBCA
8.BBAACC	18.CCBAAB	28.BCCBAA	38.ABCBAC	48.BACCBA	58.ACBACB
9.BBCCAA	19.ABBACC	29.BCCABA	39.ABCBCA	49.BCAABC	59.ACBCAB
10.BBCACA	20.ABBCAC	30.BCCAAB	40.ABCACB	50.BCABAC	60.ACBCBA

With the help of stratified randomization, patients' characteristics that are important and prognostic can be balanced without sacrificing the advantages of randomization. Briefly, the aim of stratified randomization is to make the chosen prognostic characteristics or other patient factors as similar as possible for each treatment group. Stratified randomization may also prevent the imbalances that may occur by chance. In stratified randomization, block randomization is used for each strata. Simple randomization should not be preferred because of the possible imbalances among strata.

The first step in stratified randomization is to form block sets for all combinations of prognostic factors. For example, if it is necessary to balance the groups according to gender, then two block sets are formed for each gender (Table 9).

Table 9. Stratified randomization for two treatment groups (Block size = 4)

Male	Female
ABAB	BAAB
AABB	BABA
BBAA	ABAB
AABB	BBAA

According to this assignment sequence, the male patients will be assigned to treatment A, B, A, ... and female patients will be assigned to treatment B, A, A, ..., respectively. If the study is stopped at the fourth block, then eight females and males will be assigned to treatments A and B. Thus, the groups will be balanced according to gender.

Similarly, in a trial for breast cancer with two different drugs, one of the suitable stratification factors may be the menopausal status of the patient. A similar plan for pre- and post- menopausal women may be prepared as below.

Stratified randomization may also be used for two or more stratification variables. Assume that the tumour size is an additional stratification variable for the above breast cancer example. If we categorize the tumour size in two groups such as £ 4 and > 4, we get a 4-strata (2 for menopausal status, 2 for tumour size; 2 × 2=4) study. An example for this allocation is given in Table 10. Here, block randomization is applied for each stratification factor.

As opposed to block randomization, it is necessary to form a different block sequence for all stratification factors in stratified randomization. When we choose the first four columns of the table of random numbers for the stratification factors in our example and ignore the numbers not in the range 1 - 6 we get the sequences: (2, 1, 3, 1) for the first stratification factor, (3, 5, 4, 1) for the second, (1, 5, 3, 3) for

the third and (5, 4, 1, 4) for the last. These number sequences represent the six blocks given in the example of block randomization and generate the assignment sequence shown in Table 10:

Table 10. Stratified randomization for two factors

Menopausal status	Tumor size	BLOCKS
Pre-menopausal	≤ 4	ABAB ABBA AABB BABA
	>4	ABBA BBAA AABB AABB
Post-menopausal	≤ 4	AABB BABA BABA BBAA
	>4	ABBA AABB ABBA BBAA

In other words, the first pre-menopausal patient with tumour size ² 4 will be assigned to treatment A and the first post-menopausal patient with tumour size >4 will be assigned to treatment B.

We may add the node involvement as a third stratification variable to our example. If we categorize node involvement in three groups such as 0, 1 - 4 and 5+, we get a 12-stratum (2x2x3=12) study. However, to study with more strata may result in imbalanced assignment of treatments to the groups. For this reason, especially in small studies, it is not practical to use more than two stratification factors. When it is really essential to stratify for more than two groups.

Minimization

Minimization may be viewed parallel to stratified randomization; Minimization is an effective method that ensures a perfect balance between groups for many prognostic factors even in small samples. It has some definite advantages over simple and stratified randomization when the sample size is small[3].

Minimization is based on a completely different principle from randomization. For example, if the order of being accepted to the trial is taken into consideration in a clinical trial, the first patient is allocated randomly. After wards, the treatment that provides a better balance between the groups is evaluated according to the concerned prognostic characteristics for each subsequent patient[1]. The patient is then allocated to a treatment group according to whichever minimizes the imbalance between the groups with a probability greater than 0.5. The probability is generally taken to be 1 to make the design more balanced and easy to handle.

For example, suppose we extend the example given in stratified randomization and add another stratification factor such as node involvement (0, 1 - 4 or 5+). In such trials with more than two stratification factors (or prognostic characteristics), especially when a small-scaled study is planned, it is not practical to apply stratified randomization since it would be much harder to achieve a good balance between the groups. Especially when one of the stratification factors is very rare, it is inevitable that there will be some imbalances between the groups. For these reasons, the best method to be used in such trials is minimization. Now assuming that there are two groups (control and treatment) in this trial and that the trial is supposed to cover 30 patients, our stratification factors will be as shown in Table 11:

Table 11. The stratification factors for breast cancer example

Menopausal Status	Tumor size	Node Involvement
Pre-menopausal	≤ 4	0 1–4 5+
	≥ 5	0 1–4 5+
Post-menopausal	≤ 4	0 1–4 5+
	≥ 5	0 1–4 5+

The sub-totals of each factor are as shown in Table 12 after 29 patients are accepted for this trial.

Table 12. The distribution of the first 29 patients by their characteristics in a clinical trial using minimization approach

Factors	Factor levels	Treatment groups	Control group
Menopausal status	Pre Post	7 8	7 7
Tumour size	≤ 4 ≥ 5	9 6	8 6
Node Involvement	0 1–4 5+	1 9 5	1 8 5

Assume that the next patient (30th patient) is postmenopausal with tumour size 3 and node involvement 5. The imbalance totals for women with same characteristics are shown in Table 13. Since our aim is to balance the groups to the extent possible, the most suitable treatment for the next patient is the group with the smallest total. Thus, as the totals (total of highlighted characteristics) in our groups are 22 and 20 for experiment and control groups, respectively, we assign this patient to the control group to provide a better balance.

Table 13. Calculation of imbalance in patient characteristics for allocating the treatment to the 30th patient

Factor	Factor levels	Treatment group (Total # of patients = 15)	Control group (Total # of patients = 14)
Menopausal status	Post	8	7
Tumour size	≤4	9	8
Node involvement	5+	5	5
Imbalance totals	22	20	

After a patient is allocated to a treatment, the totals in the table are updated and the process is repeated for the next patient. In case of equality of totals between groups the patient is allocated randomly (by simple randomization) as is the case for the first patient.

Blinding

Blinding embodies a rich history spanning over two centuries. Most researchers worldwide understand blinding terminology, but confusion lurks beyond a general comprehension. Terms such as single blind, double blind, and triple blind mean different things to different people. Moreover, many medical researchers confuse blinding with allocation concealment. Such confusion indicates misunderstandings of both. The term blinding refers to keeping trial participants, investigators (usually health-care providers), or assessors (those collecting outcome data) unaware of the assigned intervention, so that they will not be influenced by that knowledge. Blinding usually reduces differential assessment of outcomes (information bias), but can also improve compliance and retention of trial participants while reducing biased supplemental care or treatment (sometimes called co-intervention). Many investigators and readers naively consider a randomised trial as high quality simply because it is double blind, as if double-blinding is the sine qua non of a randomised controlled trial. Although double blinding (blinding investigators, participants, and outcome assessors) indicates a strong design, trials that are not double blinded should not automatically be deemed inferior. Rather than solely relying on terminology like double blinding, researchers should explicitly state who was blinded, and how. We recommend placing greater credence in results when investigators at least blind outcome assessments, except with objective outcomes, such as death, which leave little room for bias. If investigators properly report their blinding efforts, readers can judge them. Unfortunately, many articles do not contain proper reporting. If an article claims blinding without any accompanying clarification, readers should remain sceptical about its effect on basis reduction.

As mentioned before, there are various possible sources of bias that may influence the results of the study in a clinical trial. One of these sources is possible preconceived notions of the patient receiving the treatment or of the assessor of the response to the treatment about the superiority of one treatment over another. If one of the patients or the assessors knows the treatment applied to the patient, this might influence the evaluation of response and lead to a biased result. Although such a biased assessment is generally made unconsciously and unintentionally, it may also be made intentionally. Such biased assessments are more likely to occur when the response to the treatment is subjective rather than objective.

One way of avoiding these biased assessments is to design the trial in such a manner that neither the patient nor any of the research staff in a clinical trial has any knowledge about the treatment given to the patient. Such trial designs are termed double-blind trials. In double-blind trials, the different treatments or drugs given to the patient must obviously be identical in shape and taste. The trial is said to be a single-blind trial if only the researcher or his/her staff knows which treatment is being applied to the patient, or very rarely vice versa. In an open-label trial the applied treatment is known by both patient and researcher.

It is desirable to use the maximum degree of blinding in clinical trials. This requires that the treatments to be applied during the trial should be completely indistinguishable by their characteristics (such as shapes, tastes etc. for drugs) either before or during administration, and that the blinding is maintained appropriately during the whole trial. Some difficulties may arise in applying the double blind procedure. For example, the treatments may have a completely different nature such as surgery and drug therapy. In such cases where a double blind trial is not feasible, the single-blind method may be considered.

In single-blind trials, although it is easy to design the study and to make a decision about whether the patient should be excluded from the trial or not since the researcher knows the treatment being applied to

the patient, there is a possibility of bias because of the knowledge of the applied treatment. On the other hand, in some cases only an open-label trial is practically or ethically possible. Single-blind and open-label trials surely provide an additional flexibility, but in such trials the researcher or the patient himself may be a possible source of bias. It is thus very important that the researcher's knowledge of the next treatment should not affect his decision to enter the patient or his evaluation of the response of the patient.

Double blinded versus single blinded

For single-blind and open-label trials, central randomization by telephone, interactive voice response system, fax or Internet may be considered to avoid possible bias in accepting the patients to the trial. In addition, the clinical assessments should be made by medical staff who are not actually involved in treating the patients and who remain blind to treatment.

The blinding should be considered to be broken (for a single patient) only when knowledge of the applied treatment is deemed essential by the patient's physician for the patient's care.

Conclusion

Our discussion and examples above have shown that there are many possible sources for Error that can result in systematic distortions of study results. These distortions are a problem especially when the epidemiologist is estimating the association between a risk factor and a health problem. Whether a risk factor or a protective factor goes undetected, or a behaviour or condition is misidentified as a risk or protective factor, the implications can be serious for the public. A risk factor that goes unidentified is one about which information cannot be used to alter the public's behaviour and will result in sickness or death for individuals. An erroneously identified risk factor may cause unneeded pain and worry among the public or perhaps an unnecessary diversion of research funds. Epidemiologists conducting observational studies (cohort, cross-sectional and especially case–control) need to be aware of the potential for biases and exert extra care to eliminate or lessen their effect. As interpreters of studies we members of the public need to be aware of the possible biases in such studies when we evaluate their conclusions as reported by the mass media.

From this survey it was apparent that if the number of important prognostic factors and layers within these is sufficiently small, then the preferred method of randomization (agreed by most trialists and the ICH) is permuted blocks of varying random length within strata. This method reduces the problem of predictability and at the same time balances across combinations of factors. If the number of prognostic factors is large, then minimization can be used to provide treatment balance as well as balance over these factors. However, only those factors known to affect outcome should be considered.

Trialists believe that keeping the randomization method as simple as possible will reduce time, cost and programming errors. More complex algorithms may increase costs and errors, prove difficult to understand and may not prove to be less predictable. Whatever method is chosen, consideration should be given to using simulations to test the method first to ensure that the algorithm is correct, achieves balance and is not predictable.

Survey respondents stated that the method of randomization should depend on the context of the study, the objectives of the study and the resources available. One method may not be suitable for all trials.

Survey respondents predict that minimization will probably become more widely used in the future along with increased use of Web-based and telephone-based systems. However, very few respondents considered that more complex methods of randomization offer any advantages.

References

[1]. Heineken's CH, Buring JE. *Epidemiology in medicine.* May rent SL, editor. Boston: Little, Brown; 1987.
[2]. Fowkes F, Fulton P. Critical appraisal of published research: introductory guidelines. BMJ 1991; 302:1136–40.
[3]. Doll R, Peto H. Mortality in relation to smoking. 40 years observation on female British doctors. BMJ 1989; 208:967–73.
[4]. Alberman ED, Butler NR, Sheridan MD. Visual acuity of a national sample (1958 cohort) at 7 years. Dev. Med Child Neural 1971; 13:9–14.
[5]. Davey Smith G, Hart C, Blane D, et al. Adverse socioeconomic conditions in childhood and cause specific mortality: prospective observational study. BMJ 1998; 316: 1631–5.
[6]. Goyder EC, Goodacre SW, Botha JL, et al. How do individuals with diabetes use the accident and emergency department? J Accid Emerg Med 1997; 14:371–4.
[7]. Jaffe HW, Bregman DJ, Selik RM. Acquired immune deficiency in the US: the first 1000 cases. J Info Dis 1983; 148:339–45.
[8]. Lerner DJ, Kennel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26 year follow-up of the Framingham population. Am Heart J 1986; 111:383–90.
[9]. van der Pol V, Rodgers H, Aitken P, et al. Does alcohol contribute to accident and emergency department attendance in elderly people? J Accid Emerge Med1996; 13:258–60.
[10]. Reidy A, Minassian DC, Vafadis G, et al. BMJ 1998;316:1643–7.
[11]. Karjaleinen, Kujala U, Kaprio J, et al. BMJ 1998; 316:1784–5.
[12]. Kunst A, Groenhof F, Mackenbach J. BMJ 1998; 316:1636–42.
[13]. Hill AB, Hill ID. Bradford Hills principles of medical statistics. 12th edn. London: Edward Arnold, 1991. 60 Mann www.emjonline.comDownloaded from emj.bmj.com on June 22, 2013 - Published by group.bmj.com
[14]. John stone AJ, Zuberi SH, Scobie WH. Skull fractures in children: a population study. J Accid Emerge Med1996; 13:386–9.
[15]. Juni, P., Altman, D.G., and Egger, M. Assessing the quality of controlled clinical trials. *British Medical Journal*. 2001; 323: 42-46.
[16]. Checklist of items to include when reporting a randomized trial. In CONSORT statement. http://www.consort-statement.org/statement
[17]. Altman, D.G., and Bland, J.M. How to randomize. *British Medical Journal*. 1999; 319; 703-704.
[18]. Altman, D.G., and Bland, J.M. Treatment allocations by minimisation. *British Medical Journal*. 2005; 330: 843.
[19]. Singh, G. Minimisation may be viewed parallel to stratified randomisation though not equivalent. *British Medical Journal*. Rapid Responses; http://bmj.bmjjournals.com/cgi/eletters/330/7495/84, [Accessed October 30, 2005]
[20]. Department of Health Services Research, Palo Alto Medical Foundation Research Institute, Palo Alto, CA, USA.
[21]. Ingersoll C.D. It's time for evidence. J Athl Train. 2006; 41:7. [PMC free article] [PubMed]
[22]. Request for proposals: evidence-based practice and outcomes of care in athletic training. National Athletic Trainers' Association Research & Education Foundation.http://www.natafoundation.org/pdfs/Evidence-BasedPractice20and20Outcomes.pdf. Accessed December 24, 2006.
[23]. Singer J.D, Willett J.B. Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. New York, NY: Oxford University Press; 2003. pp. 3–15.

[24]. McEntegart D.J. The pursuit of balance using stratified and dynamic randomization techniques: an overview. Drug Info J. 2003; 37(3):293–308.
[25]. Altman D.G, Bland J.M. Statistics notes: treatment allocation in controlled trials. Why randomize? BMJ. 1999; 318(7192):1209. [PMC free article] [PubMed]
[26]. Hedden S.L, Woolson R.F, Malcolm R.J. Randomization in substance abuse clinical trials. Subst Abuse Treat Prev Policy. 2006; 1(1):6. [PMC free article] [PubMed]
[27]. Lachin J.M, Matts J.P, Wei L.J. Randomization in clinical trials: conclusions and recommendations. Control Cline Trials. 9 ;(4):365–374. 1988.
[28]. Schulz K.F, Grimes D.A. Generation of allocation sequences in randomized trials: chance, not choice. Lancet. 2002; 359(9305):515–519. [PubMed]
[29]. Scott N.W, McPherson G.C, Ramsay C.R, Campbell M.K. The method of minimization for allocation to clinical trials: a review. Control Cline Trials. 2002; 23(6):662–674. [PubMed]
[30]. Altman D.G, Bland J.M. How to randomize. BMJ. 1999; 319(7211):703–704. [PMC free article][PubMed]
[31]. Pocock S.J, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975; 31(1):103–115. [PubMed]
[32]. Fleiss J.L, Levin B, Paik M.C. Statistical Methods for Rates and Proportions. *3rd ed*. Hoboken, NJ: John Wiley & Sons; 2003. How to randomize. pp. 86–94.
[33]. Simon S.D. Is the randomized clinical trial the gold standard of research? J Androl. 2001; 22(6):938–943. [PubMed]
[34]. Fisher R.A. The arrangement of field experiments. J Ministry Ag. 1926; 33:503–513.
[35]. Amberson J.B, McMahon B.T, Pinner M.A. Clinical trial of sanocrysin in pulmonary tuberculosis. Am Rev Tuberc. 1931; 24:401–435.
[36]. Kalish L.A, Begg C.B. Treatment allocation methods in clinical trials: a review. Stat Med.1985; 4(2):129–144. [PubMed]
[37]. Schulz K.F, Grimes D.A. Allocation concealment in randomized trials: defending against deciphering. Lancet. 2002; 359(9306):614–618. [PubMed]
[38]. Frane J.W. A method of biased coin randomization, its implementation, and its validation. Drug INF J. 1998; 32(2):423–432.
[39]. Lomax R.G. Statistical Concepts: A Second Course for Education and the Behavioral Sciences. Mahwah, NJ: Lawrence Erlbaum Assoc; 2001. pp. 186–199.
[40]. Weir C.J, Lees K.R. Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. Stat Med. 2003; 22(5):705–726. [PubMed]
[41]. Kaptchuk TJ. Intentional ignorance: a history of blind assessment and placebo controls in medicine. *Bull Hist Med* 1998; **72:**389–433.
[42]. Devereaux PJ, Manns BJ, Ghali WA, et al. Physician interpretations and textbook definitions of blinding terminology in randomized controlled trials. *JAMA* 2001; **285:** 2000–03.
[43]. Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomized trials. *Ann Intern Med* 2002; **136:** 254–59.
[44]. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273:**408–12.
[45]. Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynaecology journals. *JAMA* 1994; **272:**125–28.
[46]. Chalmers I. What is the prior probability of a proposed new treatment being superior to established treatments? *BMJ* 1997; **314:**
[47]. Altman DG, Bland JM. Treatment allocation by minimisation. BMJ2005; 330:843.
[48]. Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. Control Cline Trials1988; 9:327-44. CrossRefMedlineWeb of Science
[49]. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. Stat Med1999; 18:1905-42.Medline Web
[50]. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med2012; 31:328-40.CrossRefMedline