

OVERVIEW OF RANDOMIZED CONTROLLED TRIALSDR. RATHAI RAJAGOPALAN¹, DR. PRIYADARSHINI M.DEODURG², DR. SRIKANTH*²¹Department of Pharmacology, M.S.Ramaiah medical college, MSR Nagar, MSRIT post, Bangalore, 560054, India, ²Department of Pharmacology, Khaja Banda Nawaz institute of medical sciences, Gulbarga, 585104, India. Email: pharmacsrikanth@gmail.com*Received:19 May 2013 , Revised and Accepted:16 June 2013***ABSTRACT**

Randomized controlled trials are considered to be the gold standard in clinical studies to establish level of evidence in medical research. But, they are not easy to conduct and various other aspects have to be looked into. Randomization offers each enrolled subject equal chance of being allocated to the intervention and the control groups. Randomized control trial (RCT) is most powerful tool in clinical research. In this, subjects are assigned to different groups of interventions by chance for comparison. RCT is only study design which can help us evaluate a new treatment. By assigning participants to different intervention groups by chance, comparison between the interventions groups is made. Purpose of randomization is to make the treatment groups comparable, eliminates the source of and it ensures that the difference in groups is only due to trial treatments. In this article, we review randomized control trial with special emphasis on various types of randomized controlled trials, their characteristics, the process of randomization, and advantages and drawbacks of randomized controlled trials.

Keywords: Randomized controlled trials, study design, randomization, clinical research**INTRODUCTION**

Randomized controlled trial is defined as "An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, maneuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups" [1].

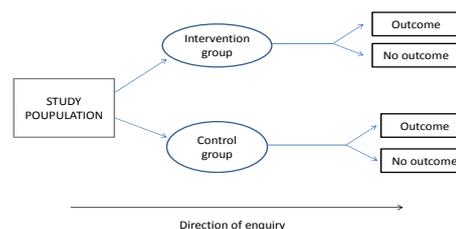
The terms "Randomized Control Trial" and "randomized trial" are often used synonymously, but some authors distinguish between "Randomized Control Trial" which compare treatment groups with control groups not receiving treatment (as in a placebo-controlled study), and "randomized trials" which can compare multiple treatment groups with each other [2].

First published RCT in medicine is credited to Sir A. Bradford Hill [3], an epidemiologist for England's Medical Research Council. Randomization as a basic principle of experimental design in the 1920s was developed by RA Fisher who presented randomization as an essential ingredient of his approach to the design and analysis of experiments, validating significance tests predominantly in agricultural research [4].

RCTs are now recognized as optimal method for "rational therapeutics" in medicine [5]. To improve the reporting of RCTs in the medical journals, Consolidated Standards of Reporting Trials (CONSORT) Statements were published regularly, the last being published in 2010 by an international group of scientists and editors which have become widely accepted to improve the reporting of RCTs [6].

Intervention trials (controlled trials)

The term "intervention" refers to treatment and in its much wider sense includes prevention strategies, screening programs, diagnostic tests, interventional procedures, educational models and the setting in which health care is provided. In an intervention trial primary exposure under study is applied by the investigator. These are the only experimental form of epidemiologic studies, though they are also observational in that subjects remain in their ordinary habitats. In an intervention trial, the investigator decides which subjects are to be exposed and which are not.

**Fig. 3: Outline of an intervention trial [7]****Nonrandomized controlled**

A study where participants have been assigned to the treatment, procedure, or intervention alternatives by a method that is not random. The investigator defines and manages the alternatives. This is an experimental study in which people are allocated to different interventions using methods that are not random. In these studies, allocation to different groups is done arbitrarily. This kind of study design may sometimes overestimate the advantages of one treatment over other [8].

Non-randomized trials are a type of quasi-experimental design. Non-randomized clinical trials are sometimes referred to as "quasi-experimental" clinical trials or "non-equivalent control group" designs because the characteristics of subjects in non-randomized groups will tend to be non-equivalent. The estimation of intervention effects in non-randomized clinical trials may be biased if group differences in subject characteristics are not controlled for in the data analysis

When is it appropriate to use a non-randomized trial design?

- When the act of random allocation may reduce the effectiveness of the intervention (Occurs when the effectiveness of the intervention depends on the participant's active participation which is influenced by their beliefs and preferences)
- When it would be unethical to do random allocation

- When it is impractical to do random allocation (e.g. cost or convenience factors)
- When there are legal or political obstacles to random allocation

Randomized controlled trial

Randomized controlled trials (RCTs) are considered the “gold standard” in medical research since they offer the best answers about the effectiveness of different therapies or interventions. The important aspect of this study design is that the patients are randomly assigned to the study all groups that help in avoiding bias in patient allocation-to-treatment that a physician might be subject to. It also increases the probability that the differences between the groups can be attributed only to the treatment(s) under study [8].

Types of Randomized Controlled Trials

- Randomized Controlled Clinical Trial: Diagnostic, Therapeutic, Prophylactic, Devices, Procedures, Regimens, Protocols
- Randomized Controlled Field Trial
- Preventive Trial
- Risk Factor Trial
- Cessation experiments
- Trial of etiologic agents
- Evaluation of health system

Randomized Controlled Clinical Trial

Includes Diagnostic, Therapeutic, Prophylactic, Devices, Procedures, Regimens, Protocols. Concerned with evaluating therapeutic agent, mainly drugs e.g. Evaluation of nitrates in reducing cardiovascular mortality. A simplified diagram of a Randomized Controlled Clinical Trial is depicted in figure 1, and the flow chart according to CONSORT statement for reporting a RCT is depicted in figure 2.

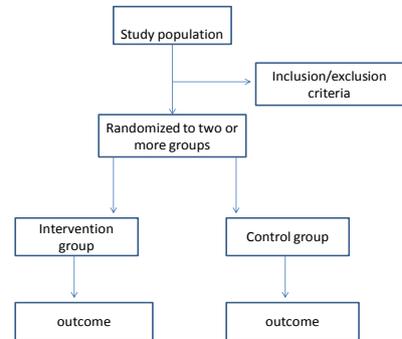


Fig. 1- Example of a Randomized Controlled Clinical Trial [7]

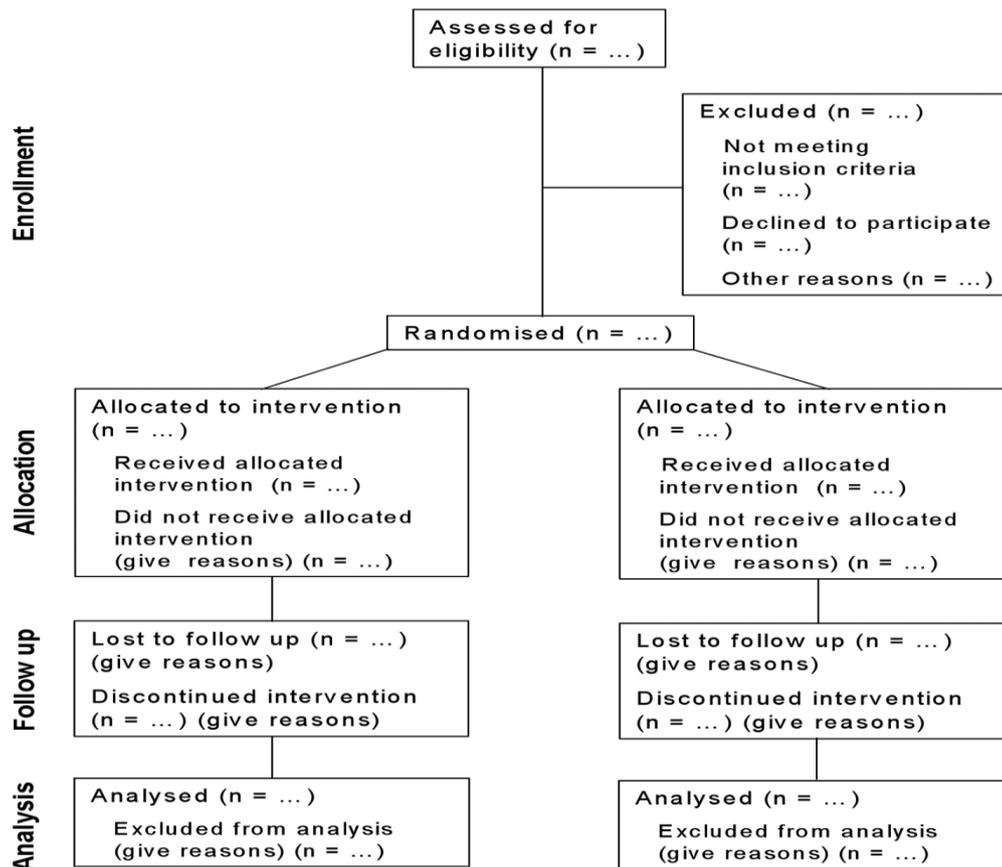


Fig. 2: Flow diagram of the progress through the phases of a parallel randomized trial of two groups [6]

Randomized Controlled Field Trial: It is similar to an Randomized Controlled Clinical Trial except that the intervention is preventive and not therapeutic. These are usually preventive trials in which the efficacy of a preventive intervention such as a new vaccine is tested in one study group and the other group receives a placebo or

standard. As they are usually conducted in the community, the term used is Randomized Controlled Field Trial.

Preventive Trials: Trial of primary preventive measures e.g. Vaccines. Analysis of preventive trials must result in clear statement about benefits to community, risk involved and cost to health

Risk Factor Trials: Investigator intervenes to interrupt the usual sequence in the development of disease for those individuals who have risk factor for developing the disease

e.g. Primary prevention of CHD using simvastatin to lower serum cholesterol

Cessation Experiment: An attempt is made to evaluate the termination of a habit which is considered to be causally related to disease

e.g. Cigarette smoking and lung cancer

Trials of Etiological Agents: To confirm or refute an etiological hypothesis

Evaluation of Health Services: Domiciliary treatment of primary pulmonary tuberculosis was as effective as more costlier hospital or sanatorium treatment

Controls in Randomized Controlled Clinical Trial

FDA classifies clinical trial control groups into six types [9].

Placebo Concurrent Control

In a placebo-controlled trial, subjects are randomly assigned to a test treatment or to an identical-appearing treatment that does not contain the test drug

No-treatment Concurrent Control

In a no treatment-controlled trial, subjects are randomly assigned to test treatment or to no (i.e., absence of) study treatment. The principal difference between this design and a placebo-controlled trial is that subjects and investigators are not blind to treatment assignment.

Dose-response Concurrent Control

In a randomized, fixed-dose, dose-response trial, subjects are randomized to one of several fixed dose groups. Subjects may either be placed on their fixed dose initially or be raised to that dose gradually, but the intended comparison is between the groups on their final dose

Active (Positive) Concurrent Control

In an active control (or positive control) trial, subjects are randomly assigned to the test treatment or to an active control treatment.

External Control (Including Historical Control)

An externally controlled trial compares a group of subjects receiving the test treatment with a group of patients external to the study, rather than to an internal control group consisting of patients from the same population assigned to a different treatment. The external control can be a group of patients treated at an earlier time (historical control) or a group treated during the same time period but in another setting

Multiple Control Groups

It is often possible and advantageous to use more than one kind of control in a single study, e.g., use of both an active control and placebo. Similarly, trials can use several doses of test drug and several doses of an active control, with or without placebo. This design may be useful for active drug comparisons where the relative potency of the two drugs is not well established, or where the purpose of the trial is to establish relative potency.

Strengths of RCT

- Most like an experiment
- The only effective method known to control selection bias
- Able to directly estimate risk
- Controls confounding bias without adjustment
- Permits the use of probability theory to express the likelihood that any difference in outcome between treatment groups merely indicates chance

- Provides strongest evidence for causality in relation to temporality and control for unknown "confounders"
- Allows comparison of multiple outcomes
- Similar distribution of baseline characteristics in comparison groups
- Fulfills the basic assumption of statistical hypothesis tests
- Protection against confounders, both known and unknown
- Similar distribution of baseline characteristics in comparison groups

Weaknesses of RCT

- Subjects are often a highly selected group (selected for willingness to comply with treatment regimen, level of health, etc.) and volunteers may differ from population of interest (i.e., generalizability may suffer).
- Not suitable for rare outcomes
- Not suitable for outcomes requiring long or extensive follow-up
- Adherence/withdrawal issues
- Limitations of external validity
- Narrowing of the studied question Sometimes impossible or impractical to conduct
- Complex, Expensive, time consuming, sometimes ethically questionable.

Examples of Experimental Studies

- Lewis EJ, Hunsicker LG, Clarke WR, et al: Renoprotective effect of the angiotensinreceptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851-860, 2001
- Brenner BM, Cooper ME, de Zeeuw D, et al: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861-869, 2001

Different types of randomized studies as follows [10-12]

Randomized Controlled Trials Classified According to the Different Aspects of Interventions Evaluated (Based on outcome of interest)

- **Explanatory or pragmatic trials** - Explanatory trials are designed to know whether new interventions work and if it works how it works. Pragmatic trials on the other hand, are designed not only to determine whether the intervention works but also to describe all the consequences of the intervention and its use under circumstances corresponding to clinical practice [13].
- **Efficacy or effectiveness trials** - Efficacy refers to whether an intervention works in people who receive it, whereas effectiveness refers to whether an intervention works in people to whom it has been offered [14].
- **Phase 1, 2, 3, and 4 trials**

Based on hypothesis

- **Superiority trials**- Here one intervention is hypothesized to be superior to another in a statistically significant way.
- **Non-inferiority trials** -They determine whether a new treatment is not worse than a reference treatment.
- **Equivalence trials** -They investigate whether two interventions are indistinguishable from each other.

According to the number of participants

- **N-of-one trials**- Randomized controlled trials with only one participant are called "n-of-one trials" or "individual patient trials". They provide individual results and not generalized results[15].
- **Mega Trial**- Mega trial is randomized clinical trial with a simple design which includes thousands of patients from multiple centers and from different countries; and limited

data collection [16]. These helps in obtaining increased statistical power and generalized results

- **Sequential trials-** A sequential trial is a study with parallel design in which the number of participants is not specified by the investigators beforehand. Instead, the investigators continue recruiting participants until a clear benefit of one of the interventions is observed or until they become convinced that there are no important differences between the interventions .
- **Fixed trials-** Alternatively, in a fixed trial, the investigators establish deductively the number of participants (sample size) that will be studied. This number can be decided arbitrarily or can be calculated using statistical methods.

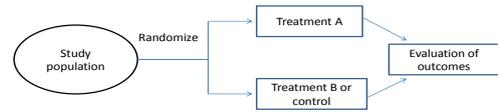


Fig. 4: Parallel design [8]

According to level of blinding

The purpose of blinding is to reduce the risk of ascertainment and observation bias. An RCT may be blinded (also called "masked"), by "procedures that prevent study data collector, participants, or data observers from knowing which intervention was received"[12].

Blinded RCTs have been classified as "single-blind", "double-blind" or "triple-blind".

- **Open RCT:** In open RCT, everybody involved in the trial knows which intervention is given to each participant
- **Single-blind:** Patient or evaluator is blinded as to treatment, but not both
- **Double-blind design:** Neither patient nor outcome evaluator knows to which treatment patient was assigned
- **Triple-blind:** Patient, Physician, and Data analyst are blinded as to treatment identity

Randomized Controlled Trials Classified According to Participants' Exposure and Response to the Intervention (RCTs based on study design)

These include parallel, crossover, cluster and factorial designs

Parallel

In parallel studies, treatment and controls are allocated to different individuals. This is unlike a crossover study where at first one group receives treatment A, followed by treatment B later, while the other group receives treatment B followed by treatment A [Figure 4]. As each participant is given only one study intervention, they do not produce statistically and clinically valid results when there are only few participants in the trial [17]. Using these studies, comparison of relative or absolute efficacy can be obtained in a short period. However, these studies generally require large number of patients for the analysis

Crossover

In these types of studies each patient serves as his own control. Each patient gets both drugs; the order in which the patient gets each drug is randomized [Figure 5]. Generally, it requires a smaller sample size. As each participant acts as his or her own control in crossover trials, they can produce statistically and clinically valid results with fewer participants [18].

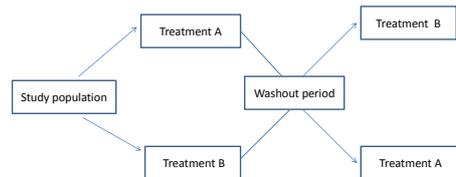


Fig. 5: Cross over design [8]

Factorial

Studies involving two or more factors while randomizing are called factorial designs [Figure 6]. Factorial design permits researchers to investigate the joint effect of two or more factors on a dependent variable (e.g. weight). The factorial design also facilitates the study of interactions, illuminating the effects of different conditions of the experiment on identifiable subgroups of subjects participating in the experiment

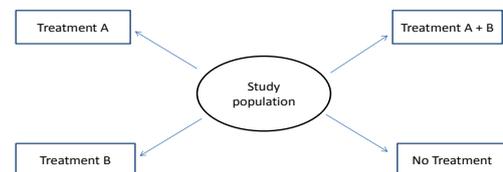


Fig. 6: Factorial design [8]

Table: difference between factorial and cross over design

Factorial	Cross over
Groups assigned different treatments	each patient receives both treatment
Shorter duration	longer duration
Large sample size	small sample size
No carryover effect	carryover effect
Robust to problems like missing data, missed visits	less variability and greater sensitivity

Cluster

It is a type of randomized controlled trial wherein groups of participants (as opposed to individual participants) are randomized [Figure 7]. Cluster randomized controlled trials are also known as cluster randomized trials, group randomized trials, and place randomized trials.

Advantages of cluster randomized controlled trials over individually randomized controlled trials include the ability to study interventions that cannot be directed toward selected individuals (e.g. a radio show about lifestyle changes) and the ability to control for "contamination" across individuals (e.g. one individual's change in behavior may influence another individual to do so too).

Disadvantages compared with individually randomized controlled trials include greater complexity in design and analysis and a requirement for more participants to obtain the same statistical power.

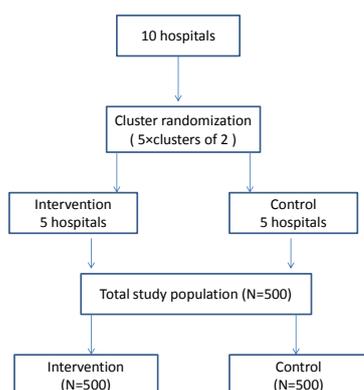


Fig. 7:Cluster randomization [19]

Traditional Designs for Clinical Trials

- Parallel-group design
- Crossover design
- Factorial design
- Add-on design
- Randomized withdrawal design
- Early-escape design /Fail

Other designs

- Add on trials
- Run in phase
- Taper phase
- Adaptive design
- Sequential design

The detailed explanation of the above designs is beyond the scope of the article

Steps in conducting a RCT

The protocol

- Rationale
- Aims and objectives, Research questions

- Design of the study: selection of patients, drugs and doses, assessment, withdrawals, data analysis, data discharge
- Ethics: patient consent, adverse events
- Documentation

Select participants

- Likely to benefit and not be harmed
- Likely to adhere
- Should be representative of the population
- Adequate sample size is key features of RCT

Measure baseline variables

Randomize

- Eliminates baseline confounding

Blinding the intervention

- As important as randomization
- Eliminates biased measurement of outcome

Follow subjects

- Adherence to protocol
- Lost to follow up
- Minimal loss to follow up is key features of RCT

Measure outcome

- Positive results/Negative results
- Clinically important measures
- Adverse events
- Specific primary & secondary outcomes

Randomization Procedure

Importance of Randomization in Randomized Controlled Trial

Randomization is the random allocation of treatment, which means all participants have the same chance of being assigned to each of the study groups. The allocation, therefore, is not determined by the investigators, the clinicians, or other study participants [20]. The effects of the treatment would be indistinguishable from the influence of the imbalance of covariates, thereby requiring the researcher to control for the covariates in the analysis to obtain an unbiased result [21].

The basic benefits of randomization include

- Eliminates selection bias.
- Balances arms with respect to prognostic variables (known and unknown).
- Forms basis for statistical tests, a basis for an assumption-free statistical test of the equality of treatments

Criteria For Randomization

Unpredictability

- Each participant has the same chance of receiving any of the interventions.
- Allocation is carried out using a chance mechanism so that neither the participant nor the investigator will know in advance which will be assigned.

Balance

- Treatment groups are of a similar size & constitution, groups are alike in all important aspects and only differ in the intervention each group receives

Simplicity

- Easy for investigator/staff to implement

Methods of Randomization

The common types of randomization include (1) simple, (2) block, (3) stratified and (4) unequal randomization. Some other methods such as biased coin, minimization and response-adaptive methods may be applied for specific purposes

Simple Randomization

Randomization based on a single sequence of random assignments is known as simple randomization [22]. The most common and basic method of simple randomization is flipping a coin. For example, with two treatment groups (placebo versus treatment), the side of the coin (i.e., heads - control, tails - placebo) determines the assignment of each subject. A random number table found in a statistics book or computer-generated random numbers can also be used for simple randomization of subjects

Advantage

- simple and easy to implement

Disadvantage

- At any point in time, there may be an imbalance in the number of subjects on each treatment
- Balance improves as the sample size n increases
- Thus desirable to restrict randomization to ensure balance throughout the trial

Stratified Randomization

The stratified randomization method addresses the need to control and balance the influence of covariates. Stratified randomization is achieved by generating a separate block for each combination of covariates, and subjects are assigned to the appropriate block of covariates. After all subjects have been identified and assigned into blocks, simple randomization is performed within each block to assign subjects to one of the groups.

Although stratified randomization is a relatively simple and useful technique, especially for smaller clinical trials, it becomes complicated to implement if many covariates must be controlled [23].

The block size should be relative small to maintain balance in small strata. Increased number of stratification variables or increased number of levels within strata leads to fewer patients per stratum. Subjects should have baseline measurements taken before randomization. Large clinical trials don't use stratification. It is unlikely to get imbalance in subject characteristics in a large randomized trial. When baseline characteristics of all subjects are not available before assignment, using stratified randomization is difficult [24].

Block Randomization

The block randomization method is designed to randomize subjects into groups that result in equal sample sizes. This method is used to ensure a balance in sample size across groups over time. Blocks are small and balanced with predetermined group assignments, which keeps the numbers of subjects in each group similar at all times [25, 26]. The block size is determined by the researcher and should be a multiple of the number of groups (i.e., with two treatment groups, block size of either 4, 6, or 8). Blocks are best used in smaller increments as researchers can more easily control balance [27].

Example: Two treatments of A, B and Block size of $2 \times 2 = 4$

Possible treatment allocations within each block are

(1) AABB, (2) BBAA, (3) ABAB, (4) BABA, (5) ABBA, (6) BAAB

Advantage

Balance between the numbers of participants in each group is guaranteed during course of randomization. Another advantage of blocking is that if the trial is terminated before enrollment is completed, balance will exist in terms of number of participants randomized to each group.

Disadvantage

Analysis of data is more complicated than simple randomization. Also with fixed blocks, people involved in the trial may be able to predict the group assignment of participants being randomized at the last in the block.

Unequal Randomization

Most randomized trials allocate equal numbers of patients to experimental and control groups. This is the most statistically efficient randomization ratio as it maximizes statistical power for a given total sample size. However, this may not be the most economically efficient or ethically/practically feasible. When two or more treatments under evaluation have a cost difference it may be more economically efficient to randomize fewer patients to the expensive treatment and more to the cheaper one. The substantial cost savings can be achieved by adopting a smaller randomization ratio such as a ratio of 2:1, with only a modest loss in statistical power. When one arm of the treatment saves lives and the other such as placebo/medical care only does not much to save them in the oncology trials. The subject survival time depends on which treatment they receive

Covariate adaptive randomization

Covariate adaptive randomization has been recommended as a valid alternative randomization method for clinical research [28]. In covariate adaptive randomization, a new participant is sequentially assigned to a particular treatment group by taking into account the specific covariates and previous assignments of participants [29].

Allocation Concealment

- Procedure for protecting randomization process so that the treatment to be allocated is not known before the patient is entered into the study
- Protects an assignment sequence before & until allocation Prevents selection bias
- Always possible to have allocation concealment

Effective Allocation Concealment

- Sequentially numbered opaque sealed envelopes
- Pharmacy controlled
- Serially arranged numbered containers (not labeled as A or B when only two assignments)
- Central randomization

Trial registration

In 2004, the International Committee of Medical Journal Editors (ICMJE) announced that all trials starting enrollment after July 1, 2005 must be registered prior to consideration for publication in one of the 12 member journals of the Committee [30].

Consort guidelines for reporting an RCT should be followed. The final report should include all relevant details like development of the protocol, ethical committee approval, sample size calculations, details of methodology with primary and secondary outcome measures, procedures of randomization, allocation concealment, blinding procedures, results and observations, analysis and statistical tests applied.

Conflict of interest: none

REFERENCES

1. Available from <http://www.cebm.net/index.aspx?o=1116>. [Last accessed on June 1st 2012 at 6.00pm].

2. Ranjith G, Interferon- α -induced depression: when a randomized trial is not a randomized controlled trial, *Psychother Psychosom* 2005;74(6):387.
3. Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. *Br Med J* 1948;2:769-82.
4. Peter Armitage. *International Journal of Epidemiology* 2003;32:925-28.
5. Meldrum ML. A brief history of the randomized controlled trial. From oranges and lemons to the gold standard. *Hematol Oncol Clin North Am* 2000;14:745-60.
6. Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
7. Anita S Acharya, Anupam Prakash, Aruna Nigam, Pikee Saxena. Scientific study designs for research: an overview. *Indian journal of medical specialities* 2012;3(2):191-94 (modified).
8. Shraddha Parab, Supriya Bhalerao. Study designs. *International Journal of Ayurveda Research* 2010;1(2):128-31.
9. Available from <http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm125912.pdf>. [Last accessed on 20th march 2013 at 4 pm].
10. Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: Comparative study of articles indexed in PubMed. *BMJ* 2010;340:c723.
11. Stolberg HO, Norman G, Trop I. Randomized controlled trials. *Am J Roentgenol* 2004;183:1539-44.
12. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;336:601-5.
13. Sackett DL, Gent M., Controversy in counting and attributing events in clinical trials, *N Engl J Med* 1979;301:410-12.
14. Fletcher RH, Fletcher SW, Wagner EH., *Clinical epidemiology: the essentials*, 3rd ed. Baltimore, MD: Williams & Wilkins;1996.
15. Guyatt G, Sackett D, Taylor DW, Chong J, Roberts RS, Pugsley S. Determining optimal therapy-randomized trials in individual patients, *N Engl J Med* 1986;314:889-92.
16. Woods KL, Mega-trials and management of acute myocardial infarction, *Lancet* 1995; 346:611-14.
17. Louis TA, Lavori PW, Bailar JC III, Polansky M., Crossover and self controlled designs in clinical research. In: Bailar JC III, Mosteller F, editors. *Medical uses of statistics*, 2nd ed. Boston, MA: New England Medical Journal Publications;1992. p. 83-104.
18. Greenland S, O'Rourke K. Meta-analysis. In: Rothman KJ, Greenland S, Lash TL, editors. *Modern Epidemiology*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins;2008. p. 652-82.
19. Donner A, Klar N: *Design and Analysis of Cluster Randomization Trials in Health Research*. London: Arnold; 2000.
20. Duffy SW. Interpretation of the breast screening trials: A commentary on the recent paper by Gotzsche and Olsen. *The Breast* 2001;20:209-12.
21. Kalish LA, Begg GB. Treatment allocation methods in clinical trials a review. *Stat Med* 1985;4:129-44.
22. Altman DG, Bland JM. Statistics notes. Treatment allocation in controlled trials: Why randomize? *BMJ* 1999;318:1209.
23. Weir CJ, Lees KR. Comparison of stratification and adaptive methods for treatment allocation in an acute stroke clinical trial. *Stat Med* 2003;22:705-26.
24. Lachin JM, Matis JP, Wei LJ. Randomizations in clinical trials, conclusions and recommendations. *Control Clin Trials* 1988;9:365-74.
25. Frane JW. A method of biased coin randomization, its implementation and validation. *Drug Inf J* 1998;32:423-32.
26. Altman DG Bland JM. How to use randomize. *BMJ* 1999;319:703-4.
27. Lachin JM, Matis JP, Wei LJ. Randomizations in clinical trials, conclusions and recommendations. *Control Clin Trials* 1988;9:365-74.
28. Zalene M. Randomized consent designs for clinical trials: An update. *Stat Med* 1990;9:645-56.
29. Kalish LA, Begg GB. Treatment allocation methods in clinical trials a review. *Stat Med* 1985;4:129-44.
30. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *New Engl J Med* 2004;351:1250-1.