

# Clinical Trials in Preventive Oral Health Care - A Review

## Abstract

Randomized controlled trials (RCTs) are considered as the golden standard for providing research evidence for interventions in evidence based health care. RCTs can be used for many purposes. They can be used for evaluating new drugs, preventive trails like vaccines, single and multi risk factor trails, cessation experiments and testing of other treatments for health care. Such trials can be used to assess new programmes for screening and early detection or new ways of organizing and delivering health services. RCTs are difficult to design, implement and translate into clinical practice or public health policy. Although Randomized clinical trials are powerful tools, their use is limited by ethical and practical concerns. Exposing patients to an intervention believed to be inferior to current treatment is often thought unethical. Apart from these constraints, it remains an ideal that all new health care interventions should be evaluated through Randomized controlled trials.

## Key Words

Randomized controlled trials; evidence based health care; intervention

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## INTRODUCTION

Dentistry has entered the era of evidence based practice in which practitioners and public health policy makers need to use the best available evidence when making decisions concerning the most appropriate methods for disease treatment and prevention.<sup>[1]</sup> Our objective both in public health and in clinical practice is to modify the natural history of a disease so as to prevent or delay disability and to improve the health of the patient or the population. The challenge is to select the best available preventive or therapeutic measures to achieve this goal.<sup>[2]</sup> Randomized controlled trials (RCTs) are considered as the golden standard for providing research evidence for interventions in evidence based health care. RCTs are regarded as the most reliable method of evaluating both the effectiveness and side effects of new interventions in health care and offer the best evidence for changing clinical practice and informing public health policy.<sup>[3,4]</sup> RCTs can be used for many purposes. They can be used for evaluating new drugs, preventive trails like vaccines, single and multi risk factor trails, cessation experiments and

testing of other treatments for health care. Such trials can be used to assess new programmes for screening and early detection or new ways of organizing and delivering health services.

## HISTORY

The history of clinical trials dates back to approximately 600 B.C.<sup>[5]</sup> In 600 B.C. Daniel of Judah conducted the earliest recorded clinical trial on a group of Children. In 1537, Ambroise pare treated his patients with a mixture of oil of rose, turpentine and egg yolk for treating open wounds compared to the traditionally used formula. On 20<sup>th</sup> May 1747, James Lind conducted first documented clinical trial on scurvy for 6 days. He was the first to introduce the use of a control group. He found that addition of citrus fruits could prevent scurvy.<sup>[6,7]</sup> The concept of randomization was first introduced by R. A. Fisher in agricultural research in 1923. The first use of randomization in a medical trial was in 1926 by J. Burns Amberson. The first trial which utilized proper randomization and blinding was performed by the British Medical Research Council in 1948 to evaluate the effects of Streptomycin in tuberculosis. Credit for the modern

randomized trial is given to Sir Austin Bradford Hill. In 1950, Hill together with Richard Doll was the first to demonstrate association between smoking and lung cancer.<sup>[8,9]</sup>

### **CLASSIFICATION OF RCTS**

According to Jadad,<sup>[5]</sup> Randomized controlled trials can be classified according to:

- i. Different aspects of interventions evaluated
- ii. Participants exposure and response to the intervention
- iii. The number of participants
- iv. The level of blinding
- v. Non randomized participant preferences.

#### **RCTs classified according to the different aspects of interventions evaluated**

It includes:

- i. Explanatory or pragmatic trials
- ii. Efficacy or equivalence trials
- iii. Phase 1, 2, 3 and 4 trials

#### **RCTs classified according to participants exposure and response to the intervention**

It includes:

- i. Parallel
- ii. Cross over
- iii. Factorial

#### **RCTs classified according to the number of participants**

It includes:

- i. N-of-one trials.
- ii. Sequential trials
- iii. Fixed trials

#### **RCTs classified according to the level of blinding**

It includes:

- i. single blinded RCT
- ii. double blinded RCT
- iii. triple blinded RCT
- iv. quadruple blinded RCT

#### **RCTs classified according to Nonrandomized participant preferences**

It includes:

- i. Preferential trials

### **DESIGN OF RCT**

Randomized controlled clinical trials are considered to be the highest quality of evidence for the safety and effectiveness of a therapeutic or preventive intervention.<sup>[1]</sup> RCTs are difficult to design, implement and translate into clinical practice or public health policy and combine four fundamental elements. i) Volunteers are randomly assigned to study groups; ii) An intervention or control treatment is administered to all individuals in the respective groups; iii) It is prospective; iv) The

success of the test intervention versus the control is judged based on an outcome that is specified before the trial begins. Small and underpowered clinical trials common in oral health research are very different from large sample, multicenter clinical trials that have the necessary power and generalizability to change standards of clinical practice, inform public health policy or gain marketing approval from Government regulatory agencies.<sup>[10]</sup> Trials can be conducted at one location with a single group of investigators, but those requiring hundreds or thousands of participants are usually conducted at multiple clinical centers. The benefits of multi-center trials include access to a larger number of participants from different geographical, socio economic and ethnic groups. Multi-center trials may also increase generalizability of results by comparing results among centers. They also facilitate opportunities for investigators with similar interests to work together on a common problem.<sup>[11]</sup>

#### **Steps in conducting RCTs includes<sup>[12]</sup>**

1. Drawing up a protocol
2. Selecting reference and experimental populations
3. Randomization
4. Manipulation or intervention
5. Follow up
6. Assessment of outcome

### **ETHICAL CONSIDERATIONS IN CLINICAL TRIALS:<sup>[13-15]</sup>**

Many ethical issues arise in the context of clinical trials

- Is randomization ethical in clinical trials?
- Is it ethical to use placebo?

*How can we knowingly withhold a drug from patients, particularly those with serious and life threatening disease?*

- Randomization is ethical only when we do not know whether drug A is better than drug B.
- Using a Placebo is ethically justifiable when it does not expose subjects to undue risk and when best available therapy alternatives are not available.
- Best available therapy is appropriate when evaluating whether new interventions are superior to current practice

#### **Is it ethical not to randomize?**

- When we are considering drugs, preventive measures or systems of health care delivery that apply to large numbers of people, it is mandatory to carry out a randomized trial to

the questions of benefit and harm.

#### **Whether truly informed consent can be obtained from patients?**

- Many protocols for multicentered clinical trials require that patients should be entered into the study immediately after diagnosis.
- After diagnosis, the patient may be incapable of giving consent and the family may be shocked by the diagnosis and its implications that they have great difficulty in dealing with randomization
- For example if the child has acute leukemia, multicentered protocols require enrollment of the child immediately after the diagnosis, at such times the parents are so distressed that one may question whether they are capable of giving truly informed consent.
- But only through such rigorous trials the progress has been made that has saved the lives of so many children with acute leukemia.

#### **Under what circumstances a trial should be stopped earlier than originally planned?**

- This question arises when harmful effects or beneficial effects of the treatment become apparent early, before the full sample has been enrolled or before subjects have been studied for the full follow up period.
- In such situations, an outside data monitoring board monitors the data as they are received and the board makes the decision.

#### **LIMITATIONS OF RANDOMIZED CONTROLLED TRIALS<sup>[16,17]</sup>**

1. The extent to which RCTs' results are applicable outside varies; that is, RCTs' external validity may be limited.
2. The conduction of a RCT takes several years until being published, thus data is restricted from the community for long years and may be of less relevance at time of publication.
3. It is difficult to study rare events
4. It is difficult to study outcomes in distant future
5. Randomized clinical trials are usually only inspect one variable or very few variables, rarely reflecting the full picture of a complicated medical situation;
6. Although subjects almost always provide informed consent for their participation in an RCT, many RCT subjects believe that they are certain to receive treatment that is best for them personally; that is, they do not understand the difference between research and treatment.

7. RCTs are subject to both type I (false positive) and type II (false negative) statistical errors. Regarding Type I errors, a typical RCT will use 0.05 (i.e., 1 in 20) as the probability that the RCT will falsely find two equally effective treatments significantly different. Regarding Type II errors, the sample sizes of many RCTs were too small to make definitive conclusions about the negative results.

#### **CONCLUSION**

RCTs are the ideal study design to answer questions related to the effects of health care interventions like preventive strategies, screening programmes, diagnostic tests etc. Although Randomized clinical trials are powerful tools, their use is limited by ethical and practical concerns. Exposing patients to an intervention believed to be inferior to current treatment is often thought unethical. There are many situations in which they are not feasible, necessary, appropriate or even sufficient to solve important problems. RCTs may not be appropriate even to study some interventions. It may be unfeasible because of financial constraints, low compliance rates, or high drop out rates to design an RCT, to evaluate the effects of interventions with very rare outcomes or with effects that take long periods of time to develop. In these cases, other study designs such as case-control studies or cohort studies are more appropriate. Apart from these constraints, it remains an ideal that all new healthcare interventions should be evaluated through Randomized controlled trials. RCTs are generally considered the gold standard of study designs. When hierarchies of study design are created to assess the strength of the available evidence supporting clinical and public health policy, randomized trials are virtually always at the top of the list when study designs are ranked in order of descending quality.

#### **REFERENCES**

1. Pihlstrom BL, Barnett ML. Design, Operation and Interpretation of Clinical Trials. *J Dent Res* 2010;89:759-71.
2. Gordis L. *Epidemiology*, Third edition. Philadelphia: Elsevier Saunders; 2004.
3. Smith RD. Avicenna and the Canon of Medicine: A millennial tribute. *West J Med* 1980;133:367-70.
4. Lalkhen AG, McCluskey A. Introduction to clinical trials and systematic reviews. *Continuing Education in Anaesthesia, Critical Care & Pain* 2008;8(4):143-6.

5. Stolberg HO, Norman G, Trop I. Fundamentals of Clinical Research for Radiologists. *AJR* 2004;183:1539-44.
6. Au DH, Castro M, Krishnan JA. Selection of Controls in Clinical Trials. *Proc Am Thorac Soc* 2007;4:567-9.
7. Bhatt A. Evolution of Clinical Research: A History before and beyond James Lind. *PICR* 2010;1(1):6-10.
8. The Evolution of the Clinical Trials Process-A Brief History Lesson, [online], available from: [http://www. PsoriasisCouncil.org/](http://www.PsoriasisCouncil.org/) [Accessed on 14th January 2012].
9. Drucker CB. Ambroise Pare and the Birth of the Gentle Art of Surgery. *Journal of Biology and Medicine* 2008;81:199-202.
10. Jekel JF, Elmore JG, Katz DL. Common Research Designs used in Epidemiology. Chapter 5. In: *Epidemiology, Biostatistics and Preventive Medicine*. First edition. Philadelphia: Saunders company, 1996:70-1.
11. Kothari CR. Research Methodology: An Introduction. Chapter 1. In: *Research Methodology Methods & Techniques*. Second edition. New Delhi: New age International Publishers, 2005:1.
12. Park. Principles of Epidemiology and Epidemiological methods. Chapter 3. In: *Preventive and Social medicine*. 21st edition. Jabalpur: Bhanot publications, 2011:77-80.
13. Randomization in Clinical Trial studies,[online], available from:<http://www.lexjansen.com/>[Accessed on 2nd February 2012].
14. Bebeau MJ, Davis EL. Survey of Ethical Issues in Dental Research. *J Dent Res* 1996;75(2):845-855.
15. Elnimeiri. Nuremberg Code: A Landmark document on medical research ethics. *Sudanese Journal of Public Health* 2008;3(2):94-6.
16. Borrelli B. The assessment, monitoring and enhancement of treatment fidelity in public health clinical trials. *Journal of Public Health Dentistry* 2011;71:52-63.
17. Ferreira CA, Loureiro CAS, Saconato H, Atallah AN. Assessing the risk of bias in randomized controlled trials in the field of dentistry indexed in the Lilacs. *Sao Paulo Med J* 2011;129(2):85-93.