Review Article

ABC of Clinical Trials

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Abstract

Clinical trials are necessary for development of a new drug or intervention. A busy clinician needs to be acquainted with the fundamentals of clinical trials. This article outlines the need for clinical trials, the place of clinical trials in the hierarchy of research designs and details the various aspects of the design and conduct of clinical trials.

Introduction

The last three decades have witnessed a dramatic increase in conduct of randomized controlled clinical trials, which have become the gold standard scientific method for evaluation of pharmaceuticals, drugs, interventions, or procedures. This research strategy has been successfully used in both therapeutic and disease prevention trials in number of disease specialties including cardiology, ophthalmology, cancer and AIDS.

Clinical Trial (RCT) is the key to develop modern drugs for treatment of diseases and to the discovery of latest diagnostic methods. Effective, safe and affordable drugs are necessary to cure and treat diseases.

The evolution of clinical trial dates from the eighteenth century. James Lind in 1747 evaluated six treatment options for scurvy in 12 patients (two patients in each treatment arm). One of the two who were given oranges and lemons recovered dramatically, proving that scurvy should be treated with vitamin C rich oranges and lemons. The British Medical Research Council Trial of Streptomycin in tuberculosis in 1948 was the first to use random allocation to experimental and control group.

One should differentiate Laboratory Research from Clinical Research in humans. Extraordinary discoveries have been made in labs to help us understand causes of diseases at cellular level. In laboratories, research is usually done on animals, where everything can be controlled and is, therefore, considered as "real or hard" Science. However, research in Humans involves Ethical issues, and in real world, everything cannot be controlled since humans are free to do what they want. Research questions concerning human health have to be answered by research on humans only and research on rats done in laboratories cannot be extrapolated to humans since humans are not rats.

A large, simple, randomized double blind, placebo-controlled multicentre trials is considered as a methodological standard of excellence, which is designed to eliminate bias and produces Gold Standard of evidence of the highest grade. It is key to evidenced based practice and is necessary to avoid medico-legal problems.

In the hierarchy of research designs, the results of randomized, controlled trials are considered to be evidence of the highest grade.

However, it is important to realize that choosing the research design depends entirely on the research question which you want to answer. If you wish to determine the prevalence of a particular disease in the population, a cross-sectional study design is necessary. If the research question involves estimating incidence or prognosis of the disease, then a cohort study design is chosen, if it involves assessing risk factors of a disease then case-control or a cohort study design is needed and for assessing whether a particular treatment or intervention works or not then a randomized clinical trial is warranted.

In a clinical trial, groups of subjects are allocated at random to receive or not to receive an intervention or drug, which is to be tested. The control group may receive a placebo or usual routine treatment /drugs. **Double blinding or masking** means that neither the subject or the treating physician or the investigator knows whether the subject is receiving active drug or a placebo. This helps to minimize measurement bias. Blinding attempts to make the various participants in a study unaware of which treatment patients have been offered (i.e. active or placebo). "Masking" is a more appropriate term; however, 'Blinding' is a time-honored term. A clinical trial should, ideally, have a double blind design to avoid potential bias during data collection and assessment. Randomization is

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Research Strategies	
Experimental	**Observational**
Clinical trials (patients are subjects **Field Trials (healthy subjects)** **Community Intervention Trials (Groups of healthy subjects)** **Vaccine trials (groups or populations)**	**Case Series** **Cross sectional,, Ecological** **Case-Control** **Cohort**

Relative Strengths of study designs in generating: evidence

STRENGTH	DESIGN
Strong	Randomized Clinical Trials
	Cohort
	Case-Control
	Cross-sectional
	Case-Series
Weak	Case reports

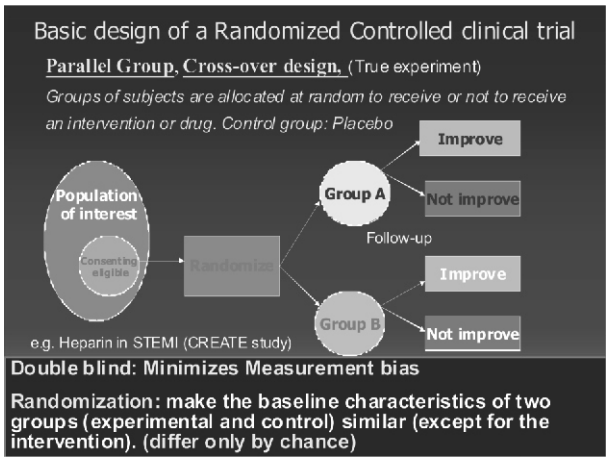
a process by which each participant has the same chance of being assigned to either intervention or control group. It produces comparable study groups and removes investigator bias in allocation of participants. Subjects are allocated to treatment or placebo group by chance. Randomisation is conceptually like tossing a coin and makes the baseline characteristics of two groups (experimental and control) similar (except for the intervention), with respect to known and unknown risk factors.

Relevant baseline data should be measured in all study participants before start of the intervention, and if your randomization has worked, the baseline characteristics in the intervention and control groups will be similar.

The goal of a randomized trial is to establish a new intervention or a drug and change clinical practice for the specific medical or health condition since it generates strongest evidence. The results of clinical trials alone (and not observational studies) changes prescribing habits of physicians and have enormous public health implications. It has the potential to improve quality of health care and control costs through careful comparison of alternative treatments.

Why is it necessary to do Clinical Trials?

Our clinical practice is many times based on 'clinical experience'. While this is an excellent way to introduce some form of therapy, however, without the evidence from a clinical trial, it may do more harm than good and we may not be offering the best advice to our patients. Hence, it is necessary to move beyond clinical experience and physiological principles, since what appears to be rationale and physiologically obvious has been proven to be wrong, many times, when tested by clinical trials. There have been a number of clinical trials which have produced surprising result. For example, Coronary Arrhythmia Suppression Trial (CAST) showed that routine use anti-



arrhythmic drugs after myocardial infarction actually increased mortality, despite the fact that arrhythmias after myocardial infarction predicted increased mortality, suppressing them was surprisingly found in the study to be harmful. Prior to 2002, based on observational studies, it was routine for physicians to prescribe hormone replacement therapy for post-menopausal women to prevent myocardial infarction. In 2002 and 2004, however, published RCTs from the Women's Health Initiative claimed that women taking hormone

replacement therapy with estrogen plus progestin had a higher rate of myocardial infarctions than women on a placebo, and that estrogen-only hormone replacement therapy caused no reduction in the incidence of coronary heart disease. Possible explanations for the discrepancy between the observational studies and the RCTs involved differences in methodology, in the hormone regimens used, and in the populations studied. The use of hormone replacement therapy decreased after publication of the RCTs. Similarly, increased levels of homocysytein are a risk factor for cardiovascular disease and supplementation with vitamin B12 and folic acid reduce homocysteine and it seems logical that it would prevent CVD also. However, a number of large randomized trials have conclusively shown that Vitamin B12 and Folic acid do not prevent CVD and hence should not be used for reducing heart attacks and strokes. Similarly, clinical trials have shown that though bypass surgery in coronary heart disease is useful, however, in stroke patients, bypass surgery (anatomizing a branch of external carotid artery with a branch of internal carotid artery) is harmful and actually increased mortality. Hence, it is essential that we move away from clinical experience or physiological rationale and base our clinical practice on the evidence generated from a well conducted clinical trial.

Limitations of Clinical trials:

All RCTs have ethical issues since it involves experimentation in humans. Many Research Questions, especially those involving risk factors, cannot be answered by RCT due to ethical reasons. For example, it is not possible to randomize subjects into a smoking and non-smoking group and wait for their death certificates to determine whether smoking is injurious to health. RCTs are also difficult to conduct and are expensive. They are conducted in an artificial environment where everything is controlled and drugs are given free of cost, investigations done free, special attention given to patients, whereas in the real world everyone is free to do what he wants. The participants of a clinical trial are not randomly selected but consist of volunteers, who fulfill the eligibility criteria. Clinical trials are also expensive, time consuming and are difficult to conduct as compared with observational studies.

Random assignment in clinical trials rather than random sampling

Observational study designs involve taking a random sample. Clinical trials, due to ethical reasons from intervening on humans, are a convenience, non-probability sample of volunteers. Inferences are possible only if we randomly assign the volunteers to the study interventions

Co-Intervention:

After randomization, patient may receive other interventions other than the ones studied. If these occur unequally in the two groups and affect outcomes, they can introduce a bias.

Good Clinical Practices

(GCP) is an ethical and scientific quality standard for designing, conducting and recording trials that involve the participation of human subjects. Good Clinical Practice (GCP) is defined as a 'standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected'. GCP ensures a combination of good, quality data and ethical issues in clinical trial and are generally accepted, international best practices for conducting clinical trials. It aims to ensure that the studies are scientifically and ethically sound

Strict FDA Monitoring, Quality Assurance minimizes the possibility of fraud in a clinical trial. It is mandatory for all clinical trials to be registered. Protocol violations are not allowed and are viewed very seriously. All end points are adjudicated by an independent “adjudication committee”. Strict 'stopping rules' are pre-decided and mentioned in the protocol. An independent “data safety and monitoring committee”, checks the data at regular intervals, does the interim analysis regularly and decides whether the trial should be stopped or not if the drug is doing more harm than good. The “steering committee” is involved in designing the protocol and monitors the conduct of the trial. There are regular monitoring visits by FDA. Case Record Forms entries cross checked with source data. GCP-ICH (Good Clinical practice and Internal Conference of Harmonization) guidelines should be followed strictly, in which all investigators have to be mandatorily trained. GCP-ICH compliance is legally and ethically mandatory for the conduct of clinical trials. All clinical trials have a standard method in which they have to be reported. Consolidated Standards of Reporting Trials (CONSORT) Statements is an evidence-based, minimum set of recommendations for reporting RCTs.

Phases of Clinical trials:

All drugs or interventions have to tested in clinical trials before they are approved to be marketed. The average cost of bringing a new drug to market in the USA is estimated at $802 million. It takes about 12 years to develop a drug from concept to market, out of which about 6-7 years are spent in various phases of clinical trials. Hence, this process is not only expensive but also time consuming.

There are various phases of clinical trials (Phase 1 to 4), through which all drugs have to be tested. Initial safety of the new drug is established in phase 1 of clinical trial, while the later phases establish the efficacy and safety. The next phase can be initiated only if the drug clears the earlier phase. Preclinical testing is done in the laboratory using cell cultures, biochemical assays and animal models before initiating clinical trials in humans.

The clinical trials are conducted in 4 phases.

— Phase 1 trials are for determining initial safety, dosing, documenting how a drug is metabolized and identifying side effects.

— Phase 2 trials gather further safety data and evidence of the drug's efficacy.

— Phase 3 further tests the product's effectiveness on a greater number of participants, and monitors side effects.

— Phase 4 trials can be conducted after a product is already approved and on the market to find out more about the treatment's long-term risks (post-marketing surveillance studies for further safety data)

It is estimated that only 5 in 5,000 compounds that enter preclinical testing make it to human testing, and only 1 of those 5 may be safe and effective enough to reach pharmacy shelves.

"Trials of N=1":

is done with individual patients. A patient is given one or the other treatment (active or placebo) in random order; each for a brief period of time, such as for a week or two. This is an improvement in a more informal process of 'trial and error".

"Factorial design" 2 x2 :

where two hypothesis/treatments/interventions are tested simultaneously, in a single experiment, in the same patients with one treatment group serving as a control group for the second treatment group and vice-versa.

"Cross-Over Designs":

Allows each participant to serve as his own control. Each participant will randomly receive either intervention or control in the first period and the (after an appropriate wash out period), alternative in the succeeding period.

Large, simple Multicentre Trials have increased dramatically in last 2 to 3 decades, in order to increase sample size and to assure a more representative sample of target population. All participating centers should agree to follow a common study protocol.

Efficacy Trials vs. Effectiveness Trials:

The Efficacy trial answers the question "Does receiving treatment work under 'ideal' conditions?". The effectiveness trial answers the question "Does offering the treatment work in ordinary settings or 'real world' circumstances?". The efficacy trials have high 'internal validity'. These trials usually have many inclusion and exclusion criteria and are restricted to those patients who will cooperate fully with medical advice. Hence, usually efficacy trials have poor 'external validity' or 'generalisability' i.e. the results of these trials are not applicable to broad range of patients found in clinical practice, who have been excluded from the study and to those patients who are not compliant with treatment.. The effectiveness trial, on the other hand, has higher 'external validity' or 'generalisability' but lower 'internal validity'.

Management and Explanatory trials:

The results of a clinical trial can be analyzed and presented in two ways:

1) According to the treatment the patients were randomized to. This is called 'intention to treat' analysis. Once randomized, the patient is analyzed in that group – whether or not the patient actually takes the treatment or not. Trials presented in this manner are called management trials and answers the question "Which treatment policy is best, at the time the decision must be made?' – whether or not some patients receive the treatment they were supposed to receive.

2) According to the treatment the patients actually received regardless of the treatment they were randomized to. Trials presented in this manner are called explanatory trials and answers the question "Is the experimental treatment, if actually received, better?", because they emphasize the mechanism by which the effects are exerted.

Analysis in Clinical Trials:

Using simple contingency table

	Outcome	
	Present	Absent
Exposed Intervention	a	b
Not Exposed	c	d

Relative Risk = (a/a+b) / (c/c+d); Excess risk

Disease rate (Incidence) in exposed divided by

Disease rate (Incidence) in not-exposed

95% Confidence Intervals around RR (if it includes 1, then the association is not significant)

Attributable Risk:

Disease rate in exposed - Disease rate in not-exposed

Population Attributable risk: AR X Prevalence

Altruism, and curiosity should be the forces motivating scientists to do clinical trials. Only then the clinical trials will be bias free. However, many scientists do clinical trial for the wrong reasons - in order to make money or to gain fame.

On should differentiate an Industry (pharma driven) initiated vs investigator initiated trial. In an industry initiated trial, the pharmaceutical company writes the protocol and dictated terms. The investigator has Little or no input into trial design. There is no access to raw data, no participation in data interpretation and no control over data analysis. The academic credit to the investigator is limited. The onvestigators become mere data gatherers. The rsults of the trial are buried if they are unfavorable to the pharma company. On the other hand, in an Investigator initiate trial, the investigator designs his own trial and owns the data, which is analyzed, interpreted and published by the investigator. This also gives considerable academic credit to the investigator.

1. Write a good protocol -Weigh risks vs. benefits. Protocol is a road map for the clinical trial
2. Obtain IRB/IEC approvals
3. Protect the subjects – Obtain Informed Consent, Ensure safety, rights & confidentiality
4. Use qualified study team
5. Handle investigational products appropriately
6. Implement quality systems
7. Record and analyze information appropriately
8. Follow the protocol and trial SOP's!!!! Protocol violations are viewed very seriously
9. Obtain Clinical trial insurance / Non-negligent harm cover
10. Publish the results of the trial (even when it is negative).

Conclusion: The randomized controlled clinical trial is the gold standard scientific method for the evaluation

Phases of Clinical Trials

Phase	Participants		Research questions
	Number	Characteristics	
I	20-80	Usually young, healthy, male volunteers	Tolerability Pharmacokinetics Pharmacodynamics
II	100-300	Patients rather than volunteers	Effectiveness Dosage, Safety
III	1,000 -3,000	Approximate real-life patient population	Effects of compound on targets, side-effects, comparison with standard drug /placebo
IV	Several thousands	Post-marketing	Additional information on risks, benefits and optimal use

pharmaceuticals, biologics, devices, procedures, interventions and diagnostic tests. There is persistent unmet need to develop newer drugs and therapies by conducting clinical trials. Newer, affordable, more effective and safer drugs are constantly in demand for treating diseases. Getting an answer from a clinical trial could influence the way patients are managed or make a new drug/vaccine available. It is possible to improve health outcomes of thousands, rather than one patient in front of you, through clinical trials. Clinical trials have the potential to improve quality of health care.

Further Reading:

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