IJBCS
ISSN: 2147-1428

Review Article
International Journal of Basic and Clinical Studies (IJBCS)
2016; 5(2): 1-11 Celik Y.

Logic, Power and Randomisation in Clinical Trials

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Abstract

The study design is the most appropriate to answer the specific question being investigated. The efficacy and safety of medicinal products should be demonstrated by clinical trials. Clinical trial phases are include Phases 0, I, II, III, IV, and V clinical studies. **Phase 0 trials: c**urrently, pre-clinical trials using animal models, cell culture methods and bio-informatics takes up to 18 months and the typical development for investigational new drugs takes between ten to fifteen years and associated with high cost and low rate of approval. **Phase I** starts with the initial administration of an investigational new drug into humans. Although human pharmacology studies are typically identified with Phase I. **Phase II** is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients. **Phase III** usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate, or confirm therapeutic benefit. **Phase IV** begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug's safety, efficacy and dose definition. **The power** of a statistical test is the probability that the test will reject the null hypothesis when the null hypothesis is false **Sample size** calculation for continuous and binary variables in controlled trials does not differ from sample size calculation in other fields. The sample size needed to meet clinical objectives of both phase 2 and phase 3 clinical trials is generally estimated using statistical methods based on the power of the trial. Ultimately, the statistician's role planning process should be to help the decision making process, and the expected power based analysis will give a more appropriate result for decision making. **A Randomised Controlled Trial** is a type of experimental study considered as gold standard in a clinical trial. Only 1/6 (17%) randomized control trials showed significant results in support of the therapy. Randomized controlled trials represent the "ideal" and, perhaps, simplest method to evaluate the effectiveness and safety of medicinal products, as they help protect against bias.

Key worlds: A Randomised Controlled Trial, RCT, Phase 0 trials, Phase I, Phase II, Phase III, Phase IV

Introduction

The most important phase of any research is the planning and design phase. Statistical errors and pitfalls related to the planning and design of a study. Statistical errors and deficiencies related to the design of a study. However, as multiple testing often occurs as a result of poor study design (1).

Clinical trials aim to find the best ways for scientists and other healthcare professionals to diagnose and treat disease in people. Many clinical trials are designed primarily to support a decision about whether drug A should

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be licensed, or a research study that tests a new medical treatment or a new way of using an existing treatment. Clinical trials are conducted to test new medicinal products and medical procedures in humans. The objective of clinical trials is to evaluate the efficacy and safety of medicinal products or medical procedures in humans so new medical treatments can be identified for medical practice. Two potential mistakes or errors are as follows: (I) we concluded there was a difference between two treatment groups when there was, in fact, no difference (false positive result), or (II) we concluded there was no difference between two treatment groups when there was, in fact, a difference (false negative result). Biostatistics is an important science of clinical trials, since it provides an estimate of probability for making any of those two false conclusions. Biostatistics also forms an important part of clinical trial design and statistical analyses of clinical trial data (2, 3).

Clinical Trial Phases

Clinical trial phases are steps in the research to determine if an intervention would be beneficial or detrimental to humans and include Phases 0, I, II, III, IV, and V clinical studies. Understanding the basis of clinical trial phases will help researchers plan and implement clinical study protocols and, by doing so, improve the number of therapies coming to market for patients (4).

Phase 0 trials

Currently, pre-clinical trials using animal models, cell culture methods and bio-informatics takes up to 18 months and the typical development for investigational new drugs takes between ten to fifteen years and associated with high cost and low rate of approval. Unlike traditional phase I trials, these studies have no therapeutic or diagnostic intent but instead aim to provide only pharmacokinetic and/or pharmacodynamic data to inform the next step in developing an agent (5, 6). Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body) (2).

Within the realm of clinical research, clinical trials are classified into four phases (7-9):

Phase I (Most typical kind of study: Human Pharmacology):

Phase I starts with the initial administration of an investigational new drug into humans. Although human pharmacology studies are typically identified with Phase I. To explore possible toxic effects of drugs and determine a tolerated dose for further experimentation. Also during Phase I experimentation the pharmacology of the drug may be explored. Subject population is healthy

normal subjects or end-stage patients. Men and women can included. Sample size like as tens. Studies in this phase can be open, baseline controlled or may use randomisation and blinding, to improve the validity of observations. Typical study design is Cohort dose escalation or multiple dose administration, Single center (prolonged observation). Usual study duration is according to one year.

Phase II (Most typical kind of study: Therapeutic Exploratory):

Phase II is usually considered to start with the initiation of studies in which the primary objective is to explore therapeutic efficacy in patients. Screening and feasibility by initial assessment for therapeutic effects; further assessment of toxicities. The evaluation is Efficacy, Target population, Safety, Dose range. Utilizes the regimen determined in phase I. Subject population is Potential target population of patients. May be heterogeneous indication Phase II (cont.). Sample size is approximately is between 50 - 200 patients. Studies in Phase II are typically conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population and are closely monitored. Doses used in Phase II are usually but not always less than the highest doses used in Phase I. The typical study design is Controlled (placebo or comparator), Open label or blinded/randomized, 2 - 4 study sites, Often surrogate endpoints. Usual study durations is according to 1 - 2 years.

Phase III (Most typical kind of study: Therapeutic Confirmatory):

Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate, or confirm therapeutic benefit. Comparison of new intervention (drug or therapy) to the current standard of treatment; both with respect to efficacy and toxicity. Also called "Pivotal trial", primary evidence for FDA submission. These studies are intended to provide an adequate basis for marketing approval. Final manufacturing facillities. The evaluation is as follows: Effectiveness, Validity of endpoints, Long term safety. Subject population: – Target population of patients – Single specific indication/study. Sample size is hundreds – thousands. Typical study design: Controlled to standard treatment (placebo if no standard), Randomized, Double blinded, Multicenter, Validated endpoints. Usual study durationis according to usually >2 years.

Phase IV (Variety of Studies: - Therapeutic Use):

Phase IV begins after drug approval. Therapeutic use studies go beyond the prior demonstration of the drug's safety, efficacy and dose definition. They are studies that were not considered necessary for approval but are often important for optimising

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the drug's use. They may be of any type but should have valid scientific objectives. It is post marketing study. Observational study of morbidity/adverse effects. After approval of the drug/device (post-marketing). Maybe required as contingency of approval. The evaluation is differential effects in segments of the population: like as: age, gender , race. Low incidence toxicities/longterm safety. New uses/indications. New combinations with other drugs. New dosages/regimens. The evaluation is marketing issues: Comparison with competitor, market priming/testing, market expansion/exposure. It needs also:dDrug utilization, cost effectiveness, quality of life, compliance. May be designed like Phases I-III. May require an IND if poses an increased risk.

Sample Size and Power in Clinical Trials must be Designed in the First Step of the Study:

A common question posed to a biostatistician from a medical researcher is *"**How many subjects do I need to obtain a significant result for my study?**"*

Sample size calculation for continuous and binary variables in controlled trials does not differ from sample size calculation in other fields. Time-to-event analysis, on the other hand, poses problems peculiar to controlled trials. The number of participants in a randomized controlled trial can vary over several orders of magnitude. Rather than choose an arbitrary sample size, an investigator should allow both the variability of response to therapy and the assumed degree of effectiveness of therapy to drive the number of people to be studied in order to answer a scientific question. Calculation of sample size requires precise specification of the primary hypothesis of the study and the method of analysis (10).

The power of a statistical test is the probability that the test will reject the null hypothesis when the null hypothesis is false i.e. it will not make a Type II error, or a false negative decision. As the power increases, the chances of making a Type II error decrease. The probability of a Type II error is referred to as the false negative (β). Therefore power is equal to 1-β, which is also known as the sensitivity (11).

The probability of *not* committing a Type II error is called the power of a hypothesis test. Making the wrong decisions can have serious results and risks. Sample
size is closely tied to statistical power, which is the ability of a study to enable detection of a statistically significant difference when there truly is one. A trade-off exists between a feasible sample size and adequate statistical power. Sample size is important primarily because of its effect on statistical *power*. To increase power of the

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study depends to the main factors as follows; Increase alpha, conduct a one-tailed test, increase the effect size, decrease random error, increase sample size. Underestimation of sample size may result in drug turning out to be statistically non-significant even though clinical significance exists (12).

Most phase 1 clinical trials involve a small number of healthy subjects (n < 20). A small cohort is treated at each drug dose and is closely observed for adverse effects. The sample size needed to meet clinical objectives of both phase 2 and phase 3 clinical trials is generally estimated using statistical methods based on the power of the trial. Ultimately, the statistician's role planning process should be to help the decision making process, and the expected power based analysis will give a more appropriate result for decision making (13-15).

In practice there are, of course, many different formulae for sample size determination. If the trial is not a simple parallel-group trial, if there are more than two treatments, if the outcomes are not continuous (for example, binary outcomes, or length of survival or frequency of events), if prognostic information will be used in analysis, or if the object is to prove equivalence, different formulae will be needed (16).

Randomization Process:

Only 1/6 (17%) randomized control trials showed significant results in support of the therapy. Selection bias in the nonrandomized trials being similar to the presumed true effect, could have yielded positive answers even if the treatment had no benefit. Randomization is a process that assigns research patients by chance, rather than by choice, to either the treatment group or the control group. The role of randomization is to remove bias in patient allocation to treatments. To produce more comparable groups (w.r.t. risk factors). To allow statistical tests to have valid significance levels (17).

Common Phase III Trial Designs are as follows (17):

Randomized Control
Trials (parallel design)
Uncontrolled Trials
(single-treatment)
Historical Controls
Non-Randomized
Concurrent Trials
Crossover Designs
Factorial Designs
Group Sequential Design
...

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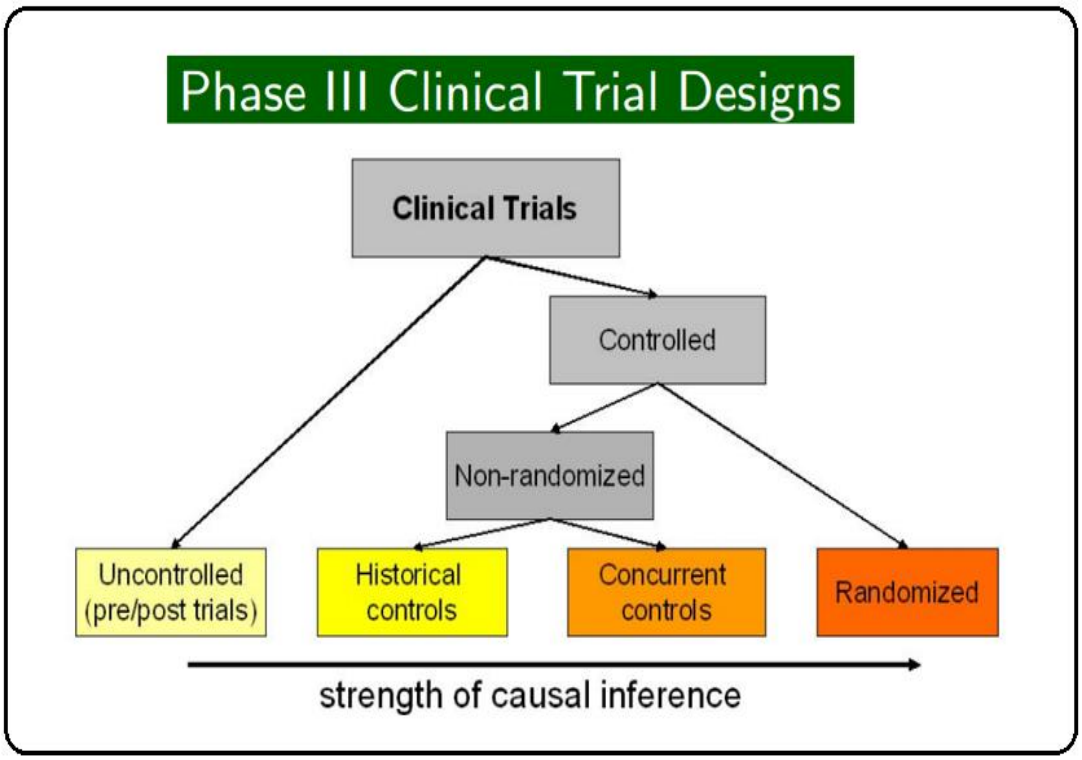

Figure 1. Randomized Controlled Trials (Parallel Designs) (17)

Randomized Controlled Trials (Parallel Designs):

Each patient receives one and only one treatment in a random fashion for Randomized Controlled Trials-Parallel Designs (Figure 1). It is simple and easy to implement; applicable to acute conditions. The interpretation of the results is straightforward. Good if the interpatient variability relatively small compared to the intrapatient variability (17).

A Randomised Controlled Trial is a type of experimental study considered as gold standard in a clinical trial (Figure 2) . Individuals who meet specific clinical trial inclusion and exclusion criteria, are randomly allocated to receive either the experimental treatment, or the control treatment. These individuals are followed for a specific length of time (e.g. until a certain event occurs or for a precise number of months/years) and then the outcomes of the two groups analysed and compared (18).

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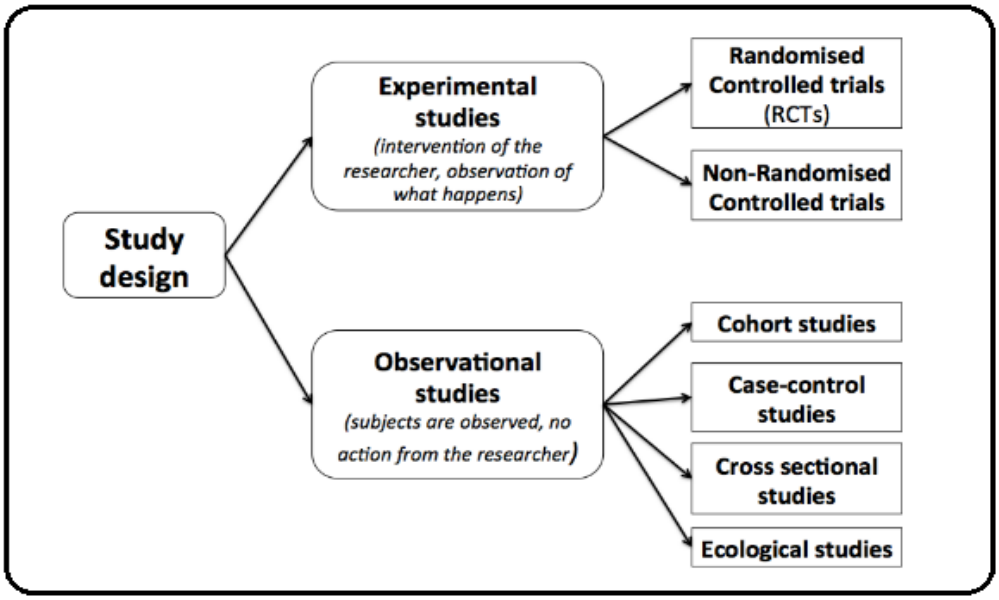

Figure 2. A Randomised Controlled Trial is a type of experimental study (18)

Each person in reference population must have equal chance of being included in study or control group (Figure 3) (19)

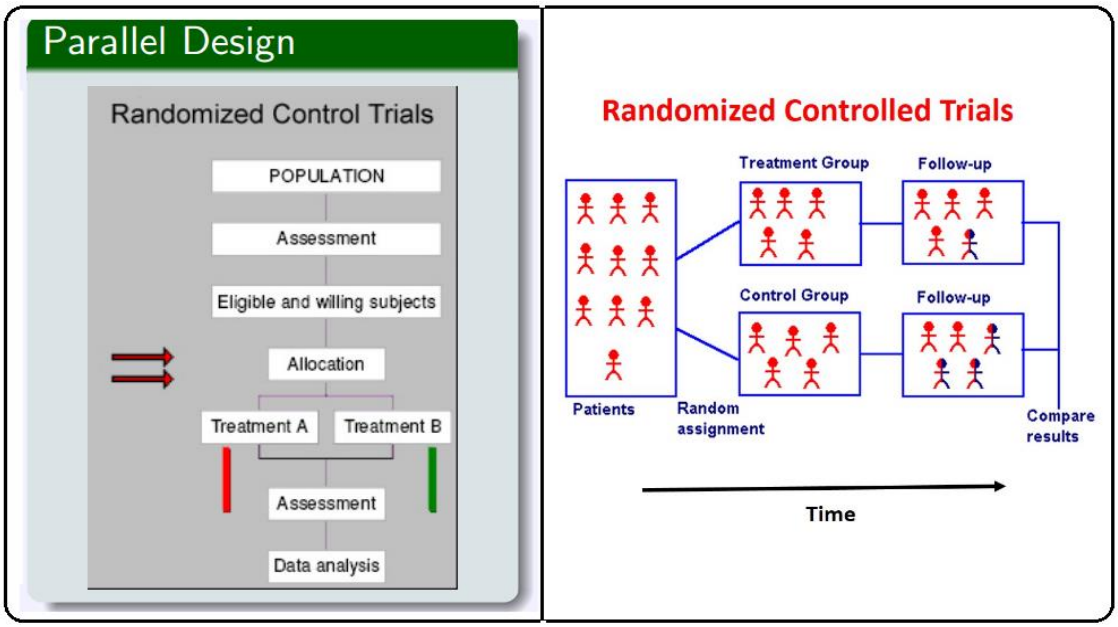

Figure 3. Randomised Controlled Trial (17, 19)

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Randomized controlled trials represent the "ideal" and, perhaps, simplest method to evaluate the effectiveness and safety of medicinal products, as they help protect against bias. To minimize bias, possible methods such as centralized randomization, double-blind follow-up and outcome evaluation should be applied to trial designs (20-22).

Simple randomization method is as follows (23):

Generate a random digit from the table of random numbers (Figure 4).

A table of random numbers

0	5	2	7	8	4	3	7	4	1	6	8	3	8	5	1	5	6	9	6	8	1	8	0	4	7	8	8	7	4
5	9	7	2	4	0	2	3	6	3	1	8	5	0	2	6	0	9	9	6	9	2	1	8	8	5	0	3	7	9
2	5	9	8	4	3	8	9	5	2	8	4	6	4	4	2	7	5	4	4	9	2	8	1	8	6	9	3	2	2
3	0	3	6	6	5	1	3	1	8	7	7	6	0	0	9	4	3	6	8	0	5	9	5	1	7	5	2	4	2
6	8	1	5	6	7	7	5	7	5	3	4	8	8	0	8	8	8	6	5	2	1	2	8	1	2	8	9	5	5
7	3	6	5	8	3	7	8	1	0	7	9	7	5	5	9	9	9	7	3	8	9	3	8	4	2	5	8	3	2
7	0	1	0	0	7	5	4	1	3	0	1	9	6	6	9	9	5	5	7	5	5	0	8	4	6	1	6	5	6
2	8	1	5	3	3	1	2	8	3	9	0	2	0	2	5	1	5	4	0	0	0	4	5	4	7	4	7	4	4
1	5	6	6	7	2	9	3	0	9	2	4	6	1	7	7	9	1	0	5	3	4	5	0	1	5	0	5	3	3
0	0	2	1	8	2	3	2	0	0	6	8	3	6	5	9	7	3	4	5	6	3	3	4	2	1	0	4	9	6
9	9	6	7	3	8	3	2	5	4	8	3	2	5	3	3	9	5	3	5	5	3	5	2	9	1	4	9	5	0
3	6	8	0	5	3	3	8	1	5	2	1	2	1	4	8	3	0	5	3	7	8	9	1	3	4	7	7	2	7
2	9	1	9	2	9	1	8	8	4	0	9	9	0	8	7	0	4	9	3	7	9	0	4	9	0	4	1	7	9
5	4	6	3	6	0	3	1	6	5	3	5	9	5	4	5	1	4	0	8	0	8	6	8	0	4	9	9	9	9
0	2	2	7	2	4	6	0	5	7	0	5	1	6	4	7	5	0	2	2	0	1	2	6	4	9	5	4	9	3
7	3	2	5	6	8	3	2	4	4	6	1	2	5	9	7	9	6	2	2	9	9	9	1	1	2	5	0	4	3
9	0	2	8	6	7	2	6	9	7	6	3	0	4	2	7	5	6	2	4	8	0	1	1	0	1	6	3	3	4
6	1	3	3	9	3	6	2	4	0	6	0	6	8	9	9	1	9	2	2	4	2	3	2	8	7	1	6	3	4
7	0	7	7	1	1	5	7	2	1	3	4	4	6	1	1	2	4	7	2	4	2	4	4	8	2	7	5	6	9
8	3	6	4	0	7	2	2	9	3	3	2	4	5	5	1	5	3	6	3	7	8	0	4	7	1	2	7	1	2
7	3	3	2	5	8	8	6	2	5	0	4	6	6	0	0	5	8	3	9	0	1	5	8	9	3	0	1	9	6
7	6	6	3	0	0	8	8	7	4	2	3	9	5	8	1	2	6	7	1	4	8	5	8	6	9	7	1	9	9
4	3	2	8	9	0	4	5	7	9	0	5	2	3	8	6	7	9	1	6	1	6	4	2	6	2	9	6	9	4
0	5	6	6	0	1	5	1	7	2	8	7	3	5	1	6	8	9	9	6	2	4	0	2	9	3	2	5	6	6
0	6	1	4	3	7	7	4	1	2	8	9	1	6	2	7	7	5	2	0	4	0	3	9	5	9	3	9	2	7
6	9	7	7	8	5	1	4	9	6	1	8	4	0	6	3	8	7	4	3	5	2	3	3	5	8	5	7	6	8
2	1	4	8	6	3	9	7	7	9	2	0	3	1	2	1	1	6	5	6	0	3	9	9	2	3	8	4	6	2
4	7	6	9	6	5	1	7	5	8	6	8	2	9	2	5	4	3	9	5	3	1	0	5	5	0	6	9	5	9
2	5	5	7	7	5	8	3	3	1	9	1	4	3	7	9	1	3	6	5	0	3	8	8	7	4	6	0	2	0
5	6	5	2	8	8	7	4	5	1	6	3	4	8	0	1	9	5	2	9	3	3	8	3	6	4	7	3	1	1
4	8	3	6	7	3	7	5	3	9	5	9	8	4	5	2	6	8	5	8	9	7	2	4	8	5	9	7	5	5

Figure 4. Table of random numbers.

If it is even or "0 to 4" is assigned to intervention, If it is odd or "5 to 9" is assigned to control like as follows:

- Even # → intervention, odd # → control
  or
- 0 to 4 → intervention, 5 to 9→ control

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* Two treatments
  0 to 4 → A
  5 to 9 → B

Random digits:	7	2	4	0	2	3	6	3	1
Treatment assigned:	B	A	A	A	A	A	B	A	A

Number assigned to each group: 7A, 3B

* Three treatments
  1 to 3 → A
  4 to 6 → B
  7 to 9 → C
  (0 → ignore)

Random digits:	7	2	4	0	2	3	6	3	1
Treatment assigned:	C	A	B	-	A	A	B	A	A

(5A, 2B, 1C)

Conclusion

The study design is the most appropriate to answer the specific question being investigated. The efficacy and safety of medicinal products should be demonstrated by clinical trials. Randomized controlled trial is a type of clinical trial, in which people subjected under clinical trials are randomly selected for the treatment or intervention. it's important to remember that when choosing evaluation design it's about what methods are appropriate to the evaluation questions and the intervention being studied.

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