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Designing, Conducting and Reporting Randomised Controlled Trials: A Few Key Points

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1. Introduction

Randomized Controlled Trials (RCTs) are the most valuable study which play an important role in the field of medicine. Other study types including descriptive studies (e.g. case reports, case series, cross-sectional studies) and certain analytical studies (e.g. case control studies, cohort studies) are also important pieces of evidence but RCTs which are designed for evaluation of the interventions in clinical practice are probably the highest level of evidence in the pyramid of Evidence Based Medicine. It is simple, yet the most powerful tool in modern clinical research.

2. RCTs: Top of the evidence-pyramid

RCTs are considered the most powerful evidence that exists. This is most probably due to the fact that 'randomizing' people into two different groups probably takes care of all the confounding factors and equals out all the causes which may affect the final result of the study.

This is mostly because of their accurate design. This reduces any possibility of bias in the result. Every year, the numbers of RCTs that are published in Medical Journals are increasing and thus, they have a great effect on changing the way medical science is practiced all over the world. Evidence-Based Medicine is highly dependent on the RCTs.

Therefore designing, conducting and reporting RCTs is an important aspect of medical science and all medical professionals should learn these skills. Critical appraisal of RCTs is probably as important as conducting them. All medical professionals need to understand and evaluate RCTs for the possibility of bias or any shortcomings. RCT results translate

directly into changing clinical practice. Hence, it is important that they are free of bias and are strong in their design and execution.

3. RCTs: The other side of the coin

However, RCTs are not far from their fair share of disadvantages. They may be the most powerful tool in the world of research but many ethical and practical concerns limit their use.

3.1. Not all randomized trials are unethical. However, a RCT may be ethical but infeasible. This may be due to difficulties in randomization or recruitment. For example, interventions like cancer screening at an early age might have an extremely long follow up with not many positive outcomes.

3.2. Once a convention is set in the community or a particular intervention gains popularity, it is tough convincing the subjects to “experiment” with their alternative options. A recent attempt to conduct a trial of counselling in general practice failed when practitioners declined to recruit patients to be allocated at random.

3.3. Certain populations of people may have certain strong ideologies and preferences. This may also limit recruitment and result in biased outcomes if not accounted for and accommodated within the study design.

3.4. Randomised trials are not always practical for evaluation of rare diseases or rare outcomes or even outcomes which take a long time to develop.

3.5. A successful and valid RCT requires a large sample size because the outcomes generally have smaller effects and a large measurable difference is required when comparing two groups of interventions. So, the larger the sample size, the better the randomized trial but the larger the financial constraints as well as the time required for the trial to be completed.

3.6. They also have fairly large drop-out rates and a huge population of the sample size is often lost to follow up making it even harder to assess the final results.

3.7. Even with the people who do follow up, not all religiously adhere to the regimen prescribed to them and some may even be totally non-compliant.

3.8. Since they require a lot of time and manpower, they are fairly expensive to conduct. Financial constraints are probably the most common reason for a trial to be shelved.

3.9. Randomized trials have a huge ethical dilemma. If an intervention is considered inferior to the current treatment modality, exposing some patients to it and not others (or exposing one group to placebo and the other to the treatment) is often thought unethical. For example, a non-random study suggested that multivitamin supplementation during pregnancy could prevent neural tube defects in children. Even though the study was seriously flawed, ethics committees were unwilling to deprive patients of this potentially useful treatment, making it difficult to carry out the trial which later showed that folic acid was the effective part of the multivitamin cocktail.

Thus, these randomized trials should only be undertaken if there is an important question which needs to be answered by the physician and other small scale observational or analytical studies justify its conduction.

4. Justification of your trial: Ask two keys questions

A simple way of knowing if you should go through the trouble of conducting the randomized trial is to ask yourself these two simple questions:

4.1. Is the intervention well enough developed to permit evaluation?

This can be especially difficult to decide when new interventions are heavily dependent on clinicians' skills (surgical procedures⁷ or "talk" therapies).

4.2. Is there preliminary evidence that the intervention is likely to be beneficial (from observational studies), including some appreciation of the size of the likely treatment effect?

Such information is needed to estimate sample sizes and justify the expense of a trial.

However, there is another side of the story. Failure to perform these important trials which should have been conducted may sometimes result in harmful treatments being used continuously without validation and evaluation. For example, neonates were widely treated with high concentrations of oxygen until randomized trials identified oxygen as a risk factor for retinopathy of prematurity.

Other study designs, including non-randomised controlled trials, can detect associations between an intervention and an outcome. But they cannot rule out the possibility that the association was caused by a third factor linked to both intervention and outcome. Double blinding ensures that the preconceived views of subjects and clinicians cannot systematically bias the assessment of outcomes.

5. History of randomised controlled trials

Daniel Judah has been thought to have conducted the first and earliest recorded clinical trial which dates back to approximately 600 B.C. He compared the health effects of the vegetarian diet with those of a royal Babylonian diet over a 10-day period. The trial was obviously not even close to the current modern standards set for trials and was majorly flawed with allocation bias, ascertainment bias, and confounding by divine intervention, but the report has influenced medical decision for now over two millennia.

The 19th century saw a steep development curve in the history of clinical trials. In 1836, the editor of the *American Journal of Medical Sciences* wrote an introduction to an article that he considered "one of the most important medical works of the present century, marking the start of a new era of science," and stated that the article was "the first formal exposition of the results of the only true method of investigation in regard to the therapeutic value of remedial agents." This article was the French study on bloodletting in treatment of pneumonia by P. C. A. Louis. Sir Austin Bradford Hill takes all the credit for the modern concepts of randomization trials. The Medical Research Council trials on streptomycin for pulmonary tuberculosis are rightly regarded as a landmark that ushered in a new era of medicine. Since Hill's pioneering achievement, the methodology of the randomized controlled trial has been increasingly accepted and the number of randomized controlled trials reported has grown exponentially. The Cochrane Library already lists more than 150,000 such trials, and they have become the underlying basis for what is currently called "evidence-based medicine"

6. Evidence supporting randomised trials

Enough evidence exists that a successful RCT is one which is well-designed. These RCTs are superior to other study designs in estimating an intervention's true effect. Meta-analysis of controlled trials shows that failure to conceal random allocation and the absence of double blinding yield exaggerated estimates of treatment effects.

It is also well known that well-matched comparison-group designs may be a good alternative when an RCT is not feasible.

7. Issues in designing and conducting RCTs

As, mentioned before RCTs are conducted to evaluate the importance of an intervention of any sorts. They can be used to understand the effectiveness of a screening test or the effect of any surgical or medical intervention by comparing the outcomes like mortality or disease recurrence.

Let's discuss several important issues in designing and conducting of RCTs.

7.1 Inclusion and exclusion criteria

In all study types the researchers need to define their target population and the criteria for inclusion and exclusion of every individual in the study. This forms an important aspect of the trial which needs to be decided before starting the trial.

Accurate definition of the study population in RCTs is extremely important and some key pointers are:

7.1.1. In RCTs, the researcher needs to make an intervention on the study population and it is required that these candidates in the study are eligible for receiving the intervention according to the current guidelines.

7.1.2. If the intervention is contraindicated in a population, then that population meets the exclusion criteria of the study target.

7.1.3. Sometimes it is difficult to assess the effect of an intervention in a large population because that needs a large sample size. So the researcher intervenes on a specific portion of the population (for example a specific sex or age group).

7.1.4. Case selection bias is one of the most important bias in RCTs which can be prevented by using appropriate inclusion and exclusion criteria.

Sometimes, the same criteria can be used as either for inclusion or exclusion from the study. For example, a specific drug reaction can serve as both depending on what the researcher wants to study. It can be an inclusion criterion if the study is about a particular drug and the associated adverse reaction. It can also be an exclusion criterion in case the investigator wants to analyze the efficacy of the drug.

The researchers need to report the exact number of the individuals assessed intending to meet the inclusion criteria, the exact number of individuals included in the study after fulfilling all inclusion and exclusion criteria, the exact number of individuals excluded from

the study at the end along with the reasons for the same. It is useful to note that unwillingness of an individual to receive the intervention is an exclusion criterion.

7.2 Study designs

All randomized trials usually have similar study design. However, still some differences exist. If classified according to the patient exposure and the response to the intervention, the following styles exist:

7.2.1 Parallel design

This is the most popular design and is based on the comparison of the effects of the intervention in the case group with the control group or another intervention group. The two groups receive a maximum of one intervention. Normally two parallel groups with equal sample size will be selected through a randomized selection. However, at times the number of the two groups isn't equal. It is important that the researcher reports this as well as the ratio of the individuals in the two groups at the time of reporting the trial.

Randomized trials can also be done by involving more than two groups. It is then known as a multi-arm parallel RCT.

7.2.2 Cross-over design

Each participant receives all the interventions involved in the trial. The sequential order in which they receive them is decided randomly. This study design however should be limited to stable chronic conditions where the disease profile doesn't fluctuate over time as well as short interventions. Also a key concern in these trials is the adequate washout period between the two therapies in order to avoid the carry-on effect.

7.2.3 Factorial design

This is a complex design where more answers can be found in a single trial. The two or more interventions are compared between themselves as well as a control group. Since RCTs are expensive to conduct, it's better that we get more answers in a single trial.

Due to such differences, it is important that the study design is described in detail at the time of reporting the trial. This helps the reader a much better understanding of the research conducted. All the study designs must be considered and the best one chosen at the time of designing one's RCT.

Usually the study design is fixed once the protocol is submitted and the researchers don't change it till end of the study. However, sometimes there is need to modify the study due to various reasons. It is important that researchers explain the cause of the same and also the outline the changes in the RCT design in detail.

7.3 Intervention

One of the most important issues in RCTs is the intervention. Researchers need to answer several questions about this aspect before even starting their trial.

An intervention can be a drug or device. It can be used for prevention or treatment. For drugs it is important to carefully determine the dosage, timing, duration and administration route. All information about the drug needs to be provided to the reader at the time of reporting. Even the manufacturer of the drug or device can be mentioned for the sake of complete reporting and easy reproducibility of the trial if required.

Even very small differences either in the type, dosage, duration or the route of administration may lead to a significant difference in the outcomes. The intervention should be obvious in order to give the possibility of comparison to other study to the researchers as well as a chance to reproduce the results if required.

7.4 Outcome/ Results

Probably the most important think we are looking for in a randomized trial article are the outcomes or the results. These can be divided into primary and secondary outcomes. They should have been determined before even starting the study.

Primary outcome is the main intervention outcome. Other study outcomes aer put in the category of secondary outcomes. For example the drug side effects are usually put in that category.

Another important issue in the outcomes is the 'measures' used to measure these outcomes. The outcomes may be laboratory test results. For these outcomes, it is important to list the methodology for the measurement, kits used for the same as well as the manufacturer where they are produced.

Other type of outcome is the clinical outcome. For this, it is important to mention the guidelines used by the researcher for the determination of the variable as well as the name of that person (e.g. General physician, specialists or medical students).

It is recommended that before selection of the primary and secondary outcomes the researchers reviews the literature thoroughly and chooses the similar outcomes in similar studies. This is important for comparing the results of the evidence already out there with their study.

An advantage of designing a trial with clearly pre-determined inclusion criteria/exclusion criteria, intervention and outcomes which are similar to other studies, is the possibility of collecting these data to form a meta-analysis which gives us even more clarity and consolidates all the evidence to give a final conclusion.

7.5 Sample size

A small sample size is unable to show all differences between case and control group. As we mentioned before, the effects are usually small and thus, we need to demonstrate large results to show sizable difference and this is why we need a large sample size. However, large sample sizes need more time and budget. There are also issues with recruitment and reaching out to large populations. Sample size should be determined after a thorough literature review and full access to previous studies in populations similar to the current study and also after determination of the power of the study. The sample size is the answer to the power of the study and simply answers the question: how many

participants are needed in order to show the difference in a particular outcome in a certain statistical significance?

Sample size should be determined using sample size calculator software or the standard formula. It is recommended to consult a statistician for calculation of the study sample size.

7.6 Randomization

Randomization is what gives the RCTs its strength. In RCTs patients are randomly assigned into the two or more study groups and each individual has an equal chance to be assigned to any group. The clinician, the investigators or the patient have no choice in the allocation. This prevents the selection bias. Random allocation ensures no systematic differences between intervention groups in factors, known and unknown, that may affect outcome. No other study design allows this kind of a balance. It is crucial that the investigators pre define the allocation guidelines and stick by it till the end of the trial. It is extremely important that the guidelines are not modified at any point in the trial. Randomization can be done in several different methods.

The easiest method to do randomization of the sample is 'simple randomization'. In this method, individuals are assigned equally to the groups using a random process, for example, a computer generated list of random numbers. Other methods like blocked randomization and stratified randomization are more complex, less common and are usually used for very specific trials. Blocked randomization aims to numerical balance between groups and stratified randomization aims to balance characteristics between the groups.

7.7 Blinding

Blinding means that the person is not aware of what group he/she is in and what treatment or placebo he/she is receiving. According to the various levels of blinding like blinding the participants, researchers, outcome assessors and statisticians, RCTs are divided into four types: open label, single blinded, double blinded and triple blinded RCTs. Due to confusions and discrepancies about who exactly was blinded in the single and double and triple blinded studies, The 2010 CONSORT guidelines specify that authors should not use these terms. It is required to report the details of the blinding like "If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how."

Blinding obviously helps to prevent personal bias in the study which is a huge concern in conducting a RCT. Every effort should be made to reduce any bias as much as possible. In case the study population is neonates, researchers may decide not to use blinding because of the differences in interventions like oral or IV feeds. The most prevalent type of blinding is the double blinded design where the investigator and the patient are both unaware of the details of who is in which group.

7.8 Statistical analysis

The most common statistical tests used for all type of papers are descriptive. These tests include mean and standard deviation for quantitative variables and frequency and

percentage for qualitative variables. They also use Chi-square test or Exact fisher test for comparison and the T tests are also commonly used. Other descriptive statistical tests are less commonly used. However, researchers may need other statistical tests for subgroup analysis and adjusted analysis.

Two main ways to analyze RCTs are per protocol analysis and intent to treat analysis. In per protocol analysis, analysis will be done based on the groups which the patients are assigned into, but in intent to treat analysis the analysis is based on receiving treatment or not.

Some RCTs need large sample sizes and may continue for a long time. The researchers may decide to cease the study if significant difference was observed in important study outcomes. For example if a specific drug be associated with significant increase in a side effect, then the study should be stopped. Also if a significant improvement be observed during the study, the researchers can stop the study. To reach this aim interim analysis can be done. But the number of interim analysis, the time, the individuals who will do it and the conditions in which the study will stop should be clear.

8. Clinical trial registry

All RCTs need to be registered in international clinical trial registry databases before starting enrolment of study participants. Once the researchers register their clinical trial in a clinical trial registry database they will receive a unique trial registry number.

Almost all medical journals request their authors mention their trial registry number in the abstract of their paper. The editors of these journals avoid publication of RCTs without trial registry number even if they have high quality in study design and writing.

According to the registry database where the researchers register their clinical trial, detailed information about the trial is needed by them.

This information includes: Title, purpose, condition which the study is studying in detail, type, name and dosage and all other information about the intervention, study type, allocation, endpoints and outcomes, intervention model, masking (Blinding), the number of patient enrolled in the study, study start and completion dates, inclusion and exclusion criteria etc.

RCT registration has several benefits. They are a good source of previous trials and it is possible to search and reach the content of the registered RCTs easily.

During the registration the researchers needs to review all important issues in the study design and methodology of the research. This helps them to reduce bias in their design and consider all aspect of the RCT design.

All RCTs need to obtain the ethics approval of the committee of the institute or the hospital where they want to conduct the trial. This practice will guarantee that all the RCTs published in the top-notch high impact medical journals are validated and ethically correct.

The International Clinical Trial Registry Platform (ICTRP) has introduced ten primary registries in its registry network which can register the clinical trial with their profile and the link to their website

- Australasian New Zealand Clinical Trial Registry
- Brazilian Clinical Trial Registry
- Chinese Clinical Trial Registry
- Clinical Research Information Service (CRIS) , Republic of Korea
- Clinical Trial Registry – India
- Cuban Public Registry of Clinical Trials
- EU Clinical Trial Registry
- German Clinical Trial Registry
- Iranian Registry of Clinical Trials
- Japan Primary Registries Network

9. Summary

Randomised controlled trials are the most rigorous way of determining whether a cause-effect relation exists between treatment and outcome and for assessing the cost effectiveness of a treatment. Some key pointers at a glance are:

9.1. Random allocation to intervention groups

9.2. Patients and trialists should remain unaware of which treatment was given until the study is completed-although such double blind studies are not always feasible or appropriate

9.3. All intervention groups are treated identically except for the experimental treatment

9.4. Patients are normally analysed within the group to which they were allocated, irrespective of whether they experienced the intended intervention (intention to treat analysis)

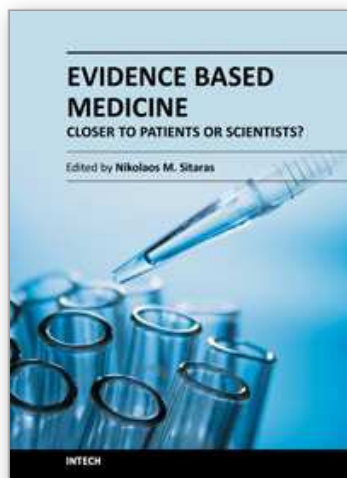
9.5. The analysis is focused on estimating the size of the difference in predefined outcomes between intervention groups.

Given that poor design may lead to biased outcomes, investigators should strive for methodological rigour and report their work in enough detail for others to assess its quality.

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