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FEATURES SECTION

How to … do a randomized controlled trial

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In this section of the series on orthodontic research we intend to give a brief outline of how to carry out a randomized controlled trial (RCT). The RCT is one of the most simple and powerful research tools in which people are allocated at random to receive one of several clinical interventions. We hope that this will not only provide information to anyone who is aiming to carry out research of this type, but also help in the interpretation of RCTs that have been published.

Before we consider the mechanics of how to carry out an RCT we should consider the advantages of this type of research over other study methods. These are:

- The RCT is prospective. As a result, the subjects and the data are under some control by the investigator.
- The treatment or intervention is randomly allocated. Therefore, the perceptions of the investigator on the value of a particular treatment should not influence treatment allocation that could bias the results.
- The study is planned before the data is collected. This is the important distinction between the RCT and the retrospective investigation, and this results in a minimization of bias that is inherent in the retrospective study.

We hope that this simple guide will stimulate efforts to carry out randomized trials of some of our treatment methods. As with most of the 'How to do' papers in this series, the ideas and concepts are a simple interpretation of the work of other authors.

We have decided to use the CONSORT guidelines (http://www.consort-statement.org/) as a framework for this chapter.[1] These are a set of guidelines that have been formulated to aid the reporting of RCTs. They also help with study design. We will use these guidelines to plan a theoretical investigation into different methods of orthodontic space closure, based on the study by Dixon *et al.*,[1] as an example of the type of study that can be carried out.[2]

Objectives

The first stage in planning a trial is the generation of a question. In this example, our question is concerned with whether nickel-titanium coils springs are more effective than power chain in space closure. The null hypothesis is 'There is no difference in the rate of space closure with Ni-Ti springs when compared to power modules'.

Outcomes

It is important to know before you start how you are going to measure the effect of each intervention. In our study, this will be the rate of closure of extraction spaces. It is also necessary to determine what size of difference will indicate a clinical difference between interventions.

The study population and site of the study

We now need to consider our study population. This is an important step because it is important that this population is relevant to both the question that we hope to answer and to the provision of orthodontic treatment. It is fairly obvious that the study population for this example is easily defined and may be confined to children under 16 who are wearing the same type of appliance with extraction spaces that require closure. This is not as simple as it sounds. We have to make it clear that we are only going to include patients who have had first premolars extracted. It is tempting to include all patients who have had an extraction, but this complicates the study by introducing the additional variable of 'tooth extracted' and this would need to be included in the analysis. As a result we would need to recruit a larger sample. Furthermore, we should ensure that all patients are being treated with the same appliance type and prescription. Finally, it is best to produce a list of inclusion and exclusion criteria for the study. For our study the inclusion criteria are:

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- Children under 16 years old at the start of treatment.
- Appliances will be MBT brackets.
- Teeth extracted will be first premolars.
- Space closure will start one month after the placement of 019 × 025 stainless steel archwires.

There are also exclusion criteria:

- The patient has had Phase I treatment with a functional appliance.
- The patient has a craniofacial syndrome.
- Teeth other than first premolars have been extracted.

While we need to consider the study population, we must not forget to pay some attention to the operators in the study. It is important that the findings of the study have generality and the results are relevant to current orthodontic practice in the setting of care where most treatment is provided. This, however, is not always possible, especially when the RCT is investigating a new method of treatment. As a result, most orthodontic RCTs have been carried out in Dental Schools. This has the advantage of being able to keep close control of the operators and patients in the study. However, the trade-off for this control is the potential lack of generality. In our planned study, we would like to make the study results applicable to current practice and the operators will be selected from local specialist orthodontic practitioners.

Sample size

To be able to state with sufficient probability that any difference found between groups is likely to be due to the intervention, rather than to the particular samples you have, it is necessary to have a large enough sample. Tatiana Macfarlane has written an excellent introduction to this topic in the June 2003 edition of the *Journal*.[3]

The intervention

This is the treatment of interest in the study and it is vital for the success of the study that the interventions are clearly stated. It is essential that the existing literature does not already strongly suggest that one intervention is 'better' or more effective than another. Furthermore, the operators in the study should not have a preference for any of the interventions that are being tested. This is termed equipoise. Importantly, if there is no equipoise it cannot be ethical to randomize people to different interventions (or to intervention *v.* control) because we already 'know' the answer to the question we are trying to investigate. This is a difficult situation, but in orthodontics it can be approached by considering the level of the evidence that the perceptions of any operator are based upon. If this is based on 'evidence' from retrospective studies or more commonly expert opinion, this may also be considered to be unethical and, perhaps, equipoise is the best place to be. Furthermore, if the operator has a preference this may influence the way that they enter patients into the study and could lead to bias. In our hypothetical study the interventions may be clearly stated as:

- Nickel-Titanium coil springs; or
- Power chain.

An RCT may have a treatment compared with a 'no treatment' or control group. Ethically, it may not always be possible to randomize to a control group and not provide treatment to some patients. Therefore, most RCTs in orthodontics will compare two or more treatments or interventions.

Patient registration

Once ethical committee approval has been obtained, the next stage is patient recruitment. This may be considered in several stages.

Patient requires treatment and is eligible

It is important to ensure that patients entered into a trial are representative of the population. This is achieved by the operator considering that all patients who s/he sees with the entry criteria are eligible for the study. The clinician should not be selective.

Agreement to randomize

The clinician should be in equipoise for a patient who is eligible for the trial and s/he should be willing to accept the randomization.

Patient consent

The patient should be informed of the theoretical risks and benefits of the interventions under test, both verbally and in writing. This allows the patient to give fully informed written consent before being registered and randomized. Ideally, patients should be given the trial information and then given at least 24 hours to consider whether they would like to participate.

Formal entry

Details of the patient are then entered onto a log sheet of the trial or, more commonly, onto a computer database. The information that is collected is frequently the patient's name, their hospital number, date of birth and institution (if the trial is multi-centred) and date of entry. The reason for this step is that the trial organizers need know about every patient entered. This enables them to obtain information on trial drop-outs and patients who are not entered, and guards against the deviant investigators who do not give the randomized treatment.

The method of registration depends upon the setting of the trial. In a multi-centre trial this is usually carried out by the clinician making contact with a central registration office by telephone. In a single centre study, this should be carried out by a person who is not a participating clinician. However, if the trial only has one investigator, then patient registration may need to be left to the investigating clinician, although this is not ideal. In this case, it is important that care is taken that no bias is introduced, for example, through the investigating clinician having access to the randomization, which may influence whether they approach particular patients.[4]

Random assignment

The assignment of an intervention must only be made after the patient has agreed to take part in the trial. It is important that the clinician does not know in advance what the allocation will be.

Randomization

This stage is central to the mechanics of the trial, because by allocating participants randomly, patient characteristics are likely to be similar across the groups at the start. By keeping the groups balanced at baseline, the outcomes can be attributed to the intervention with minimal effects from other factors that may influence the treatments.

The method of randomization should be decided before the trial starts. There are many methods of randomization and we will not go into detail but interested readers should refer to two excellent texts that cover this in detail.[5,6] In brief, the object of randomization is to allocate one or more interventions (or control), in a manner that ensures that the samples that you are going to compare, are similar in every respect apart from the intervention. In most trials, a randomization list has been prepared in advance using random numbers.

Allocation

The next stage is the method by which the operator finds out which treatment the patient has been assigned to. It is essential that the operator does not know what the assignment will be in advance and there are several methods of concealing this. One popular method is to transfer the randomization list to a series of sealed envelopes each containing the allocation on a card. The clinician then opens the next envelope in the series when the patient formally enters the trial. This method is particularly relevant when the clinician registers his/her own patients. However, care needs to be taken to ensure that the clinician does not reseal the envelope having discovered that the allocation was not what he/she was hoping![4]

The best method of allocation is to make use of a central registration office. In this method the treatment assignment is read from a prepared list and given to the investigator while still on the phone, following the registration of the patient. While this method is more expensive and requires more preparation than using envelopes it does provide an almost foolproof method of allocation.

Blinding for orthodontic studies?

One important concept of medical studies is blinding. This is important because we should consider that if a patient or operator knows the identity of the treatment the results of the study could be distorted. The effect of this is minimized by concealing the identity of the treatments and by the use of placebos. Blinding may occur in many ways, for example, blinding the patient, the operator, the investigator who measures the outcomes and the statisticians. However, when we consider the nature of orthodontic treatment it is impossible to blind treatment allocation to both the operator and patient. As a result, the only type of blinding that we can practice is blinding of the person who records and analyses the data. This is important because if, for example, the evaluator knows that a group of patients have had a new treatment then they may record outcome data in a favourable manner. Blinding can be done by concealing the identity of the patient and the treatment allocation using numbers, or by having the data recorded by a different person from the one who is going to analyse the data. If handled carefully, in our space closure RCT the patient, the evaluator, the data recorder and the analyst can all be unaware of the treatment method allocated.

Monitoring progress

So now you have set up your trial, and you think that you can just sit back and the trial will run, and all you have to do is to collect and analyse the data. Unfortunately, this is not the case! It is essential that the progress of the trial is closely monitored. Several areas should be evaluated as part of this process. The first of these is protocol compliance. You need to check that the study protocols are being followed by the operator(s) in the study. The easiest way of doing this for an orthodontic study is to periodically look at the records of the patients in the study and check for protocol deviations that are recorded. You should also check for adverse effects. While these are unlikely for an orthodontic study you could find, for example, that a new type of archwire is constantly fracturing, and patients are beginning to complain about this and are withdrawing from the trial.

Another error is to allow the patient records to pile up so that there is no organized check on trial progress. It is far better to record the data as the trial progresses. This allows you to identify any problems with your outcome measures or even your method of data collection.

Finally, a careful record of all study withdrawals or drop-outs should be made, and as much baseline data as possible recorded. This will ensure that a statistical check can be made to discover whether the drop-outs were similar to those people who remained in the trial.

Interim data analysis

An area of controversy is the analysis of the interim results of the trial. It is very tempting, particularly in a lengthy study, to run an interim analysis and 'have a look to see how things are doing'. This is a common occurrence if the trial is attracting a degree of attention and you need some data to present at a conference, etc. The problem with this is that the patients that are analysed first may not be representative of the trial population and any conclusions that are released are incorrect.

However, the counterargument to this is that it is necessary to run an interim analysis to check that the treatments are not causing harm, which is important for the ethics of the trial. While this may be essential in some medical trials, this may not be necessary for orthodontics. Importantly, if an interim analysis is done for this reason then the results should not be published.

Treatment intervention and stopping rules

It is important that only the treatment interventions of interest are carried out during the trial. In our study, the operator wishing to use inter-arch elastics may complicate the treatment effect of the different space closing mechanics. In this example, inter-arch elastics should not be used for the trial duration as this operator decision could bias any results

Stopping rules are defined at the start of the trial to ensure that there is a 'safety valve'. If, for example, it becomes obvious during a trial that one or more treatments is significantly worse or better than another, then the trial should be stopped.

Data analysis

Methods of data analysis for RCTs do not markedly differ from other orthodontic studies and these shall not be discussed in this paper. However, it is important to consider the difficult question of how to handle data from patients who dropped out of the investigation.

When this occurs we are left with several choices. The first is to report the number of patients who withdrew from the investigation and emphasize that the two interventions under investigation had certain success and failure rates. Or the data analysis should include the results of the treatments on all the patients who entered the study, regardless of successful compliance or completion of the treatment. This is termed an intention to treat analysis (ITT analysis). This type of approach results in a measure of the true effectiveness of the treatment and should be attempted wherever possible. One possible drawback of this approach with orthodontic treatment is that we may not have collected data on the patients who dropped out of the investigation, as they may not have returned to the clinic. One solution to this is to statistically impute data to compensate for the lost data. Several statistical packages have the ability to be programmed to carry out this type of analysis.

Writing up

The final stage in carrying out an RCT is to write up the project. It goes without saying that the dissemination of the results of a study, even if the results are negative is a vital step. There is little point in carrying out a project and keeping the results a secret! When an RCT is written up, many journals are now requesting that RCTs are

presented using the CONSORT guidelines as a framework (http://www.consort-statement.org/).[1] On first reading, these may seem to be rather complex and difficult to follow; however, we find that, when the guidelines are followed, then writing a paper is made easier as the framework provides headings for the prospective author to follow.

Conclusions

In this review we have attempted to provide a brief outline of how to carry out a randomized controlled trial. You will see that carrying out this type of research is relatively difficult and time consuming, but prospective investigators should not be put off from carrying out this type of research. The effort is worth it, because a well prepared and run RCT will provide highest levels of evidence base for the treatment that we provide.

References

1. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001; **134:** 663–94.
2. Dixon V, Read MJ, O'Brien KD, Worthington HV, Mandall NA. A randomized clinical trial to compare three methods of orthodontic space closure. *J Orthod* 2002; **29:** 31–6.
3. Macfarlane T. Sample size determination for research projects (Editorial). *J Orthod* 2003; **30(2):** 99–100.
4. Schulz KF. Subverting randomization in controlled trials. *JAMA* 1995; **274:** 1456–8.
5. Jadad A. *Randomized Controlled Trials: a users guide*. London, BMJ books, 1998.
6. Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials*. New York, Springer-Verlag, 1998.