Clinical Orthodontic Research

5

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5.1 Introduction

One of the great buzz phrases over the last few years is evidenced-based care. However, while this is easy to promote as a concept, we have to carry out the research that is going to provide us with the evidence that will either reinforce or make us change the care that we provide. At this point it is relevant for us to consider the type of investigation or research that is going to give the highest level of evidence, and this is always the randomized controlled trial or systematic review. All other types of study, such as case report, retrospective study, or comparison of case series, may not give us adequate information. As a result, I will confine this chapter to a description of how to carry out a randomized controlled trial.

If you are considering carrying out a trial, it is very important to be systematic in your planning, and the first stage of this is to prepare a protocol, and I will outline the steps that are necessary in preparing this important document. It is not my intention to be prescriptive in the outline; I am simply providing guidelines for the potential researcher who hopes to carry out a research project. None of these ideas are my own; they are a condensation of those derived from several readily available sources. Throughout this chapter I will provide examples from a hypothetical project that aims to investigate the influence of functional appliances upon facial growth.

5.2 The Research Protocol and Its Sections

A protocol is a document that explicitly states the reasoning behind and structure of a research project. The preparation of a protocol is the most important stage in the research process and is carried out for the following reasons:

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1. It encourages you to plan the project in detail, before you start.
2. It allows you to see the total process of your project.
3. It acts as a guide for all personnel involved in the project
4. It acts as a "reminder" to you and your supervisor (or coworkers) of the initial structure and aims of the project.
5. It enables you to monitor the progress of the project.
6. It is necessary if you need to apply for funding or ethical approval.

All protocols are divided into two main sections: (1) the problem to be investigated and (2) the method of investigation. These sections may be further subdivided as follows:

5.2.1 The Problem to Be Investigated

- Project title
- The research problem
- Background (including the literature review)
- The aims
- The hypothesis

5.2.2 Method of Investigation

- Plan of the investigation (including sample size calculation and statistical methods)
- Project milestones
- Dissemination of the results
- Resources required

5.2.3 The Problem to Be Investigated

5.2.3.1 The Project Title

The project title is one of the most important features of the protocol because it attracts the attention of the potential reader. It is, therefore, necessary to make it as short and to the point as possible. Let us consider two possible examples:

(a) An investigation to evaluate the effectiveness of functional appliances for the treatment of Class II skeletal growth anomalies.

This title is overlong and states the obvious in a rather "wordy" way. It goes without saying that because it is the title of a research protocol, it is an investigation that will evaluate something. A preferable approach may be:

(b) Do functional appliances modify facial growth?

The second title comes straight to the point without stating the obvious. It not only attracts the attention of a reader but it immediately tunes them into the subject matter.

5.2.3.2 The Research Problem

Before you start to develop a research project of your own, you must first identify a research problem. This is a difficult step particularly if you are an inexperienced researcher. Research problems are explanatory devices; they are carefully designed sentences about what you intend to find out.

It is difficult to design a problem statement and you should give it a great deal of careful thought. When you write the problem statement, your words must show an understanding of the research phenomena and should explicitly reveal your purpose.

You should go directly to the problem in the first sentence of page 1. Resist the temptation to give background or set the stage for the problem. When the protocol is ready, the readers will want to know the purpose of the study immediately. They will not want to search through several pages of text to discover what the protocol is about. To be effective your opening words should be clear and demand attention, for example:

(a) In this study I intend to find evidence that facial growth can be modified by functional appliances. If I can show that this occurs, this will be an important finding for orthodontic care.

(b) This will be an investigation to evaluate the effect of functional appliances upon facial growth.

If we examine the two statements above, statement (a) is easier to read because it is in the first person. This should be your preferred writing style as opposed to the use of passive voice (example b). You should, however, be careful that the first person is not overused and that your protocol does not read like a "letter to mum."

Avoid the look-around approach to a research problem. It is very important to avoid the "let's start a project and see what happens" approach. This will inevitably lead to a poorly coordinated and cumbersome project that drifts and may not have a well-defined ending. As a result, the statement of the problem should be explicit.

5.2.3.3 Background (Including the Literature Review)

The most important feature of the background to the project is that it should be brief and direct to the point. For a research protocol the background should be no longer than two single-spaced pages of A4 paper. In this section you should concisely review the literature that is relevant to the problem that you are trying to solve and is current. While it may be tempting to include all the literature, particularly classic papers, you should carefully consider whether to include research that is published more than 5 years before your project. In this respect it is probably good practice to limit the number of papers quoted to less than 20.

When you write the review, you should draw attention to the good points and the deficiencies of the studies quoted. You should also remember that it does not always mean that if a study has been published in a journal, it is flawless in its methodology and conclusion. Nevertheless, you should not be too critical of previous investigators because research technology and understanding of data analysis is a fast-moving field. Remember, if your study is published and it is considered state of the art today, it could be torn to shreds by neophyte researchers in 10 years' time!

In terms of writing style it is good practice to make your writing flow. There is a tendency to introduce concepts and previous studies by simply going through a shopping list of papers; for example,

> McNamara has shown that the Frankel appliance produces an increase in mandibular length of 3 mm. Pancherz (1979) used Herbst appliances and showed an effect of 3 mm increase in mandibular length; this is in agreement with a study by Hansen (1984). However, Tulloch et al. (1990) have suggested that it is not possible to come to any conclusions concerning the effect of functional appliances.

It is better to take the following approach:

> There have been many retrospective investigations that have concluded that either fixed or removable functional appliance have a growth-modifying influence on the mandible (McNamara 1984; Pancherz 1986; Hansen 1991). However, Tulloch et al. (1990) in a review of this literature have been critical of past research, and concluded that most studies are characterized by weak designs. As a result, it is not possible to come to any conclusions concerning the effect of functional appliances.

The literature review should logically lead to the statement of the aims of the proposed project.

5.2.3.4 The Aims

The aims of the project should be explicitly stated. These should be confined to the intention of the project, and they should arise from the literature review which is likely to show where more research is needed.

5.2.3.5 The Hypothesis

A hypothesis that you are trying to prove should be stated in the simplest form possible. It is considered good practice that hypotheses are stated in the null form, because they have their basis in inferential statistics. That is, you assume that there is no relation between variables and statistics are then used to calculate the probability that this relationship does exist. As a result, for our theoretical growth modification project, the null hypothesis will be: *Functional appliances do not have an influence upon the growth of the mandible*.

5.2.4 Method of Investigation

5.2.4.1 Plan of the Investigation

This is a description of the tactics of the research and is probably the easiest part of a research protocol to prepare. If you want to make the method easy to read, it is better to use the active voice, instead of the passive; for example,

> We will randomly allocate the subjects to the functional appliance and no-treatment groups, stratifying on age and sex. This is easier to read than: The subjects will be randomly allocated to the functional appliance and no-treatment groups, stratified on age and sex.

In a study protocol the method should be stated in the future tense. The method should be structured using the following subheadings: (1) subjects, (2) design, (3) experimental procedure, (4) materials, measurements and apparatus used, (5) sample size calculation, and finally (6) the statistical methods that you are going to use.

5.2.4.1.1 The Subjects

Many studies analyze information derived from patients that have been or are going to be treated. It is very easy for us to lapse into clinical language and state that the population under investigation is the "patients." This is patently not so when we have an untreated control group. It is therefore better practice to refer to the study population as subjects. When you describe the subjects of a study, you should report the following information:

1. The population the subjects will be drawn from.
2. The total number and the number in any subgroups within the investigation.
3. All aspects of subject selection that will provide information on the removal or minimization of bias.
4. The inclusion and exclusion criteria for the subjects

5.2.4.1.2 The Design

At this stage of the protocol, your readers should be beginning to understand the general design of your project. In this part of the method, they will learn exactly how you are going to do the study. The best way to approach this is to describe exactly how the total subject pool is to be divided into comparison groups.

> Subjects will be eligible for inclusion in the study if they satisfy the following criteria: (i) they have an overjet of greater than 6 mm (ii) they are still growing. Subjects with congenital clefts, or who have suspected or identifiable syndromes, will be excluded from enrollment. All subjects who are eligible for inclusion will be interviewed, and the purpose of the trial will be outlined. If informed consent is obtained, the operator will contact the central trial coordinator and provide details of the subject. The subject will then be randomly allocated, stratifying for operator and sex, to the experimental (treatment) or control (no-treatment) groups.

5.2.4.1.3 The Procedure

This will describe exactly what you are going to do with the subjects. This includes details of (1) the treatment to be provided to the experimental group and (2) the method to be used to collect data. For example,

> We will provide treatment to the subjects in the experimental group using the Twin Block appliance. Our treatment protocols will be those usually used in the department (more detail may be given here). After the subjects have received treatment for 12 months any changes will be evaluated. The control group will be observed only and evaluated 12 months after enrollment.

5.2.4.1.4 Measurement Used

Describe the materials and the method of measurement to be used in the study. For example, "In order to evaluate the effect of the treatment we will use the Pancherz

cephalometric analysis. This divides any reduction in overjet into dental and skeletal components. We will take cephalometric radiographs at the end of 12 months for both groups. The radiographs will be traced by one operator, and a sample of 30 will be retraced to calculate error."

5.2.4.1.5 Sample Size Calculation

I do not intend to describe the various methods for calculating the sample sizes to be used in an investigation. This is adequately covered in most statistical textbooks. Nevertheless, I should emphasize that this is an essential part of all protocols. If the sample size is too small, there is a considerable risk that the study may not be sufficiently powerful to detect a difference between the groups, if a true difference exists. The study would, therefore, be worthless, and a great deal of effort will be wasted.

5.2.4.1.6 Statistical Methods to Be Used

It is also essential that the statistical methods to be used in the investigation are outlined in detail. It is not sufficient to merely state the names of the tests to be used; you should describe the rationale for your choice of statistical tests. For example,

> The research question is concerned with the comparison of two groups (functional vs. control). The dependent variable will be the proportion of overjet reduction that is due to skeletal change. The independent variables will be study group, sex, age, compliance, and initial skeletal discrepancy. Because the influence of several, possibly interrelated independent variables, will be evaluated, we will use multiple linear regression analysis.

5.2.4.2 Project Milestones

This section is not essential. Nevertheless, it does provide a guide (and reminder!) for you and your supervisor to inform if you are ahead or behind schedule with your project.

5.2.4.3 Method of Dissemination of Findings

Again, this is not always essential, but it does let the reader know what you intend to do with the results of the study. It is occasionally possible to list the potential titles and publication strategy of the investigators. However, this can sometimes be considered an overly optimistic approach.

5.2.4.4 Resources Required

Finally, you should make a list of all the resources that you are likely to require to successfully complete your investigation. If these resources have cost implications, you should also note the potential cost of the investigation.

Preparing and presenting a protocol is one of the most difficult parts of carrying out a research project. It can also be the most interesting and satisfying. The result of this process should be a short (no more that 2,500 words) document that clearly outlines your research project. If the protocol is poorly prepared and not adhered to, it is unlikely that the project will yield the information that you hope for. At the worst the project may become unwieldy as you aimlessly drift through the research process, discovering little except disenchantment. On the other hand, if the protocol

is correctly structured and tight, your research will be an exciting experience that you and others will enjoy, and you will, hopefully, add to knowledge.

This has been a fairly generic description of the first part of carrying out a research project. Now I would like to consider the planning of a randomized controlled trial, which is an investigation that will provide us with the highest level of scientific evidence.

5.3 Planning a Randomized Controlled Trial

The randomized controlled trial (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. 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:

1. The RCT is prospective. As a result, the subjects and the data are under the direct control of the investigator.
2. 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.
3. The experiment is planned before the data are collected. This is the important distinction between the RCT and the retrospective investigation and results in a minimization of bias that is inherent in the retrospective study.

While these advantages are clearly important and make the case for carrying out RCTs compelling, the orthodontic scientific community has shown remarkable reticence in adopting this method of research. The reasons for this are not important, and we hope that this simple guide will stimulate efforts to carry out randomized trials of some of our treatment methods.

When we considered a framework for this chapter, we decided to use the CONSORT guidelines (www.consort-statement.org). These are a set of guidelines that have been formulated to aid the reporting of RCTs, but they also help with study design. We will also use this paper to plan a theoretical investigation into the different methods of orthodontic space closure, as an example of the type of study that can be carried out. This study is an example of an effectiveness or "real world" trial evaluating the effects of an intervention under everyday clinical conditions.

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

5.3.1 The Study Population and Site of the Study

We now need to consider our study population. This is an important step because 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. But this is not as simple as it sounds, as we have to make it clear that we are only going to include patients who have had first premolars extracted, as there may be a difference between space closure depending upon the tooth extracted. It is tempting to include all patients who have had an extraction, but this complicates, or "confounds," the study by introducing the additional variable of "tooth extracted." Furthermore, we should ensure that all patients are being treated with the same appliance type and prescription, as this is another confounder. Generally, it is best to produce a list of inclusion and exclusion criteria for the study. For our study the inclusion criteria are:

- 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 1 month after placement of 019 × 025 stainless steel archwires.

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 that 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.

5.3.2 The Intervention

This is the treatment of interest in the study, and it is vital for the success of the study that this is clearly stated. Furthermore, it is essential that the existing literature does not already strongly suggest that one intervention is "better" or more effective than another. Finally, 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 vs. control) because we already "know" the answer to the question that you 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 operators have 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
- Berman ligatures

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

5.3.3 Patient Registration

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

5.3.3.1 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 he or she sees with the entry criteria are eligible for the study. The clinician should not be selective.

5.3.3.2 Agreement to Randomize

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

5.3.3.3 Patient Consent

The patient should give written consent to take part in the study and agree to accept the randomization of any treatment. Importantly, the patient should be informed of the theoretical risks and benefits of the interventions under test. This allows fully informed consent that should be obtained in writing before the patient is registered and randomized. Ideally, patients should first be given the trial information and then given at least 24 h to consider whether they would like to participate.

5.3.3.4 Formal Entry

Details of the patient are then entered onto a logsheet of the trial or more commonly onto a computer database. The information that is collected is frequently the patient's name, hospital number, date of birth, and institution (if the trial is multicenter). The reason for this step is that the trial organizers need know about every patient entered. This enables them to obtain information on trial dropouts 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 multicenter trial this is usually carried out by the clinician making contact with a central registration office by telephone. In a single-center study, this may be carried out by a person who is not a participating clinician. However, if the trial only has one

investigator, then patient registration can be left to the investigating clinician. In this case it is important that care is taken that no bias is introduced, such as, for example, through the investigating clinician having access to the randomization, which may influence whether they approach particular patients.

5.3.3.5 Random Assignment

It is only after these steps have been carried out does the operator learn to which treatment the patient has been assigned.

5.3.4 Randomization

This stage is central to the findings of the trial, because by allocating participants randomly, the 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 the two excellent texts listed at the end of the chapter that consider this in detail. In brief, the object of randomization is to allocate one or more interventions (or control) in a manner that ensures 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. 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 with 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 to when the clinician registers his/her own patients. However, care needs to be taken to ensure that the clinician does not reseal the envelope after having discovered that the allocation was not what he/she was hoping!

The best method of randomization 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 he or she is 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.

5.3.5 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 analyzes the data. This is important because, for example, if the evaluator knows that a group of patients have had a new treatment, then he or she may record this data in a favorable manner. This can be done by concealing the identity of the patient and the treatment allocation by using numbers or having the data recorded by a different person from those who are going to analyze the data. If handled carefully, the space closure RCT in our example could be a single-blind study where the patient does not know the treatment method allocated.

5.3.6 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 analyze 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, and 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 dropouts 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 dropouts were similar to those people who remained in the trial.

5.3.7 Interim Data Analysis

An area of controversy is the analysis of the interim results of the trial. It is very tempting, particularly, in a study that is lengthy, 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 who are analyzed 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, and this is important for the ethics of the trial. While this may be essential in some medical trials, again for orthodontics this should not be necessary. Importantly, if an interim analysis is done for this reason, then the results should not be published.

5.3.8 Treatment Intervention and Stopping Rules

It is important that only the treatment intervention of interest is carried out during the trial. In our study the treatment effect of the different space closing mechanics may be complicated by the operator wishing to use inter-arch elastics. In this example, inter-arch elastics should not be used for the trial duration or their use must be accounted for in the statistical analysis.

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 are significantly worse or better than another, then the trial should be stopped.

5.3.9 Data Analysis

Methods of data analysis for RCTs do not markedly differ from other orthodontic studies, and these shall not be discussed in this chapter. 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. Alternatively, 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. 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 input data to compensate for the lost data. Several statistical packages have the ability to be programmed to carry out this type of analysis.

References

These two books provide excellent and detailed overviews of randomized controlled trials:

1. Jadad A (1998) Randomised controlled trials: a users guide. BMJ Books, London
2. Friedman LM, Furberg CD, DeMets DL (1998) Fundamentals of clinical trials. Springer, New York