Article:
Atwal, A. and Benson, P.E. orcid.org/0000-0003-0865-962X (2019) How to design and set up a clinical trial part 1 : the research question. Orthodontic Update, 12 (3). pp. 111-116. ISSN 1756-6401

10.12968/ortu.2019.12.3.111

How to design and set up a clinical trial: Part 1 the research question

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Abstract

Data from clinical trials involving human participants are essential in establishing an evidence base about the safety and effectiveness of our treatments. This article describes the steps involved in designing and setting up a clinical trial, from establishing the research question(s), searching the literature, writing a protocol and gaining the necessary approvals. Acquiring some knowledge about how to set up a clinical trial will allow the conscientious clinician to use the most relevant information to provide the highest possible standards of clinical care for their patients.

Clinical relevance statement

Even if a clinician is not, has never been, nor is ever planning to be involved in research, they should understand and be able to interpret the data from clinical trials.

Objectives statement

The reader should understand the importance of the research question(s) and have some knowledge about what should be included in a protocol for a clinical trial.

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Introduction

Clinical trials involve observations or interventions undertaken with human participants (usually patients) to provide information concerning specific questionsabout the safety or effectiveness of treatment. Laboratory and animal studies might provide some initial indications in these areas, however they almost always lack clinical validity and can rarely replace clinical data obtained in a scientific manner.[1] The evidence derived from clinical trials may be used together with clinical judgement and patient's valuesas part of an evidence-based approach to care (Figure 1).

There are various designs of study and the most appropriate design depends upon the research question to be answered. Current conventional wisdom is that a randomised controlled trial (RCT), which attempts to reduce the potential influences of both the patient and researcher, is the best design for interventional studies in both medicine and dentistry. There may however be practical, ethical or cost considerations that prevent the use of this design. The study of human motivations and behaviour may require a qualitative approach but, for the purposes of this article, we will mainly focus on the design and setting up of a clinical trial using a quantitative approach.

A number of organisations can provide guidance on designing, conducting, analysing and publishing clinical trials. The first organisation to contact is the local Clinical Research Network (CRN), which works closely with both the National Health Service (NHS) and Higher Education Institutional Research and Development offices (R & D). The CRNs are funded by the National Institute for Health Research (NIHR), a UK organisation that supports research in the NHS. Applications for money to pay for a clinical trial can be developed with the help of the local Clinical Trials Units (CTUs), which have expertise in all areas of trial design and management.

The NIHR has devised an online clinical trial toolkit routemap designed to help researchers set up and manage a clinical trial of an investigational medicinal product (CTIMP)[2]. At first glance they may seem quite complicated, as the regulations involving CTIMPs are more stringent than those regulating most orthodontic trials. The routemap however does provide good guidance about the many requirements that must be satisfied when setting up and running a clinical trial.

Designing the research question for the clinical trial

Step 1: Identify a knowledge gap

The first step for any research project is to decide what question the study is attempting to answer. When the question(s) has or have been identified, then it is useful to determine if anyone has attempted to answer the question(s) before. If the answer is 'yes', then ask 'how good was this attempt'?

The NIHR recommends that the development of a clinical trial starts with a systematic review of the existing literature.[3] A systematic review will provide reliable information to justify your research and should help develop your study design.[3] Do not worry if the research has been carried out before and therefore is not considered innovative. Systematic reviews rarely find that there is enough high-quality evidence to answer a research question. Almost every area of clinical interest, certainly in dentistry, requires confirmation that the original results are reproducible and applicable in a variety of settings, with a large number of the target population (generalisable).

Step 2: Formulate the research question

The FINER criteria can be used to help formulate a good research question (see Table 1).[4]

Step 3: Focus the research question

Focusing the question for the clinical trial can be undertaken using the acronym PICO:

P = Patient, population or problem

I = Intervention being investigated (e.g. medical, surgical, preventative)

C = Comparator or control (best proven intervention(s), no intervention, placebo)

O = Outcome(s) attributable to a specific disease, condition or injury

Step 4: Decide on the study design

Clinical trials can have several designs (Figure 2):

- Observational studies (e.g. cross sectional, cohort, case control);
- Interventional studies or clinical trials (e.g. randomised controlled trials (RCTs)).

Observational studies are generally non-interventional, because the researcher is not able to influence the treatment or environment in which the study takes place, usually for practical or ethical reasons. If an observational study is deemed the most appropriate or the only feasible approach, the researcher then needs to decide if data will be collected for a group of individuals:

- At one point in time (e.g. cross-sectional);
- Over the course of time (e.g. longitudinal);
- Without an outcome of interest, being divided into subgroups based upon their exposure to a potential cause (e.g. cohort study);
- With an outcome of interest being compared to a suitable control group to determine the occurrence/timing of exposure to a potential cause (e.g. case-control).[5]

Once this has been decided, the researcher then needs to decide if data will be collected retrospectively or prospectively. Prospective data collection generally provides stronger evidence, because changes within individuals can be assessed and any loss of data or participants from the study can be accounted for.

A prospective, longitudinal study, with registration and follow-up of all consecutive patients who start treatment, is often the best way of collecting information about a new technique, particularly when it might not be possible to undertake a randomised controlled trial (RCT).

Interventional studies involve comparing the outcomes in a group of individuals who have received a treatment (usually novel or new) with a group who have not received the treatment or an alternative (usually the conventional) treatment. The decision about who receives the new treatment is either allocated randomly (i.e. by chance) or by a quasi-random technique, such as alternates (not ideal). This aims to ensure the groups are comparable at the start of the trial, with any differences that might influence the outcome (e.g. confounders) evenly distributed between the groups. This will depend on the correct use of an unpredictable, random allocation order and hiding that sequence until assignment, to remove any possible biases of the treating clinician or the patient on assignment (i.e. blinding).[5]

The theoretical strengths of evidence provided by each type of study design are shown in Figures 2 and 3. Ideally, once selected, the study design should be included in the research question, so that it can be easily indexed and identified from electronic databases.[6]

Step 5: Eliminate bias

A bias is a systematic error, or deviation, which could affect the interpretation of the results, leading to an over or underestimation of the intervention effect.[7] There are several sources of potential bias within a clinical trial (Table 2) and these should be addressed during the design of the trial.[7]

Step 6: Refine the specific objectives and hypotheses of the trial

Objectives: Questions the trial is designed to answer;

Hypothesis: Specific question being tested to help meet the objectives of the trial and amenable to statistical testing.

Step 7: Patient and public involvement

Patient and public involvement (PPI) is an important consideration to confirm that the research question is important and relevant to the people it directly affects. The trial should also be practical and feasible.

Clinical trials protocols

Writing a formal protocol is helpful for a number of reasons:

- Provides a step-by-step guide which can account for any problems and concerns (e.g. bias and confounding);
- Essential for obtaining funding and sponsorship, as well as the necessary regulatory approvals (e.g. ethical and NHS research and development (R&D) approvals);
- Should limit the possibility of undeclared changes once the trial has begun and/or selective outcome reporting.

Summary

This first article has described the steps involved in designing and setting up a clinical trial from establishing the research question(s) to searching the literature. A forthcoming second article will describe how to write a protocol and gain the necessary approvals for a clinical trial

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Figure captions

Figure 1: What is evidenced based medicine?

Figure 2: Flow chart of clinical trial study designs
Strength of evidence is colour coded: High = Green, moderate =orange, low = red

Figure 3: Levels of evidence pyramid
Strength of evidence is colour coded: High = Green, moderate =yellow/orange, low = red

Tables

Table 1: The FINER criteria

Table 2: Sources of bias within a clinical trial

Figures

Figure 1: What is evidenced based medicine?

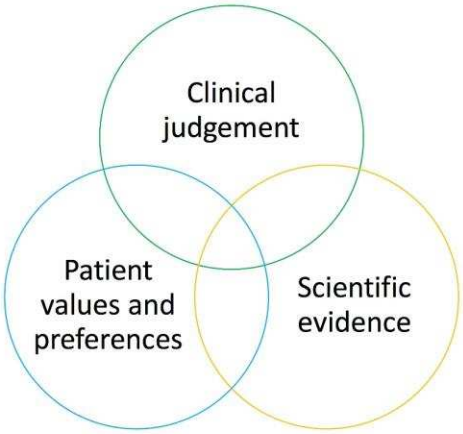


Figure 2: Flow chart of clinical trial study designs

Strength of evidence is colour coded: High = Green, moderate =orange, low = red

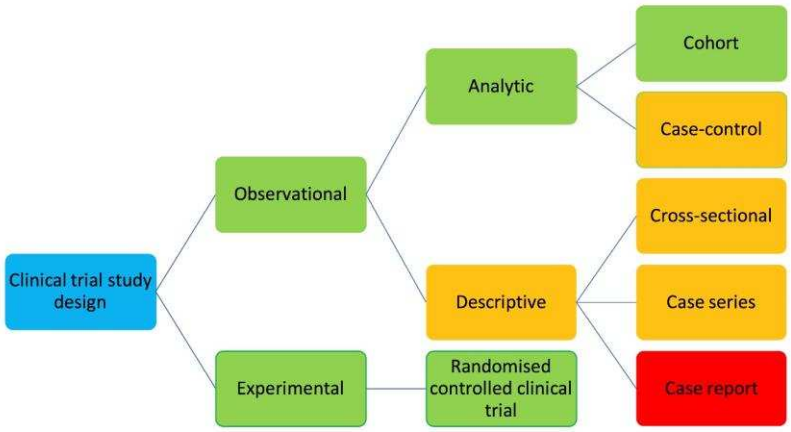
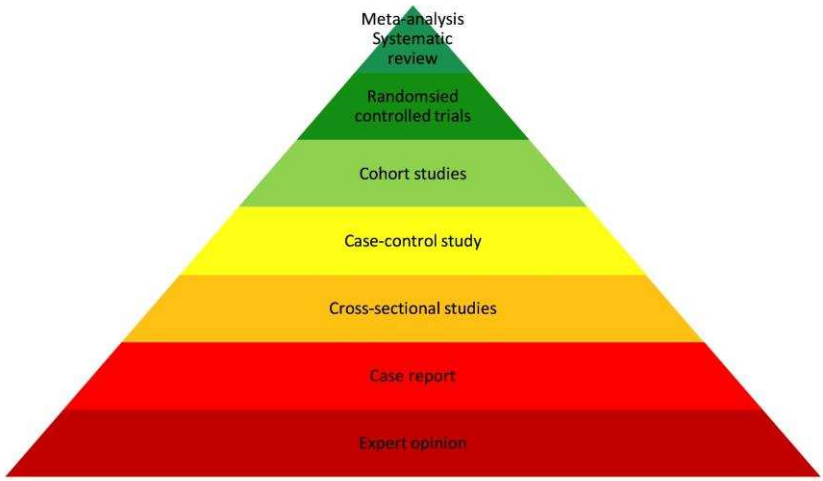


Figure 3: Levels of evidence pyramid

Strength of evidence is colour coded: High = Green, moderate =yellow/orange, low = red



Tables

Table 1: The FINER criteria

FINER	CRITERIA	EXPLANATION
F	Feasible	• Evidence of previous work (e.g. pilot, feasibility studies, scientific literature) • Manageable in scope (e.g. subjects, clinical expertise, time and money)
I	Interesting	• Getting the answer intrigues investigators, peers and community
N	Novel	• Investigators are in equipoise regarding the question • Research findings are anticipated to resolve clinical uncertainty
E	Ethical	• A study that an institutional review board would approve
R	Relevant	• To scientific knowledge • To clinical and health policy • To future research

Table 2: Sources of bias within a clinical trial

Type of bias	Description	Factors to consider in clinical trial design to avoid bias
Selection bias	Significant differences in the baseline characteristics of the groups due to bias in the selection of participants	Clear inclusion and exclusion criteria
Allocation bias	Significant differences in the baseline characteristics of the groups due to bias in the allocation of participants	Sequence generation Allocation concealment
Performance bias	Bias due to participants and investigators knowing which intervention was received	Blinding of participants and investigators to intervention.
Detection bias	Bias due to assessors knowing which intervention was received	Blinding of outcome assessment
Attrition bias	Bias due to significant differences between the groups in terms of withdrawals	Incomplete outcome data
Reporting bias	Bias due to selective reporting of outcomes	Selective outcome reporting
Publication bias	Selective publication of reports, usually in favour of statistically significance results	Trial registration