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Title of article: How to design and set up a clinical trial: Part 2: protocol and approvals

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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 second article describes the steps involved in designing and setting up a clinical trial, from writing a protocol to 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.

Introduction

This article will describe the steps involved in designing and setting up a clinical trial, from writing a protocol to gaining the necessary approvals.

How to write a protocol

Study setting and location

The number (single or multi-centre), location (country), types of settings and care providers involved (e.g. primary, secondary, tertiary or community) must be determined. These will influence the generalisability and relevance of the trial to other settings and therefore the ability to guide clinical practice and policy.[1]

Eligibility criteria

The main research question will aid researchers to determine the type of participants required (Figure 1). Clear inclusion and exclusion criteria are required to recruit suitable participants and simplify implementation of the trial. The eligibility criteria will allow others to interpret in which patients the results of the trial will apply. Baseline participant characteristics should be collected during the clinical trial for the same purpose.[1]

Sample size calculation

All clinical trials involve selecting a group of individuals (i.e. the sample), from a population, usually with a particular condition. The sample group is investigated and the results are used to infer that a similar outcome would occur in all individuals with that condition, because it is not practical to include all individuals with that condition in a study.

Before starting the trial, it is necessary to try to estimate how many participants should be included in the study. The reasons for this are both ethical and practical. It would be unethical to start a study unless there were sufficient participants to have a reasonable chance of answering the research question posed. Also, individuals are putting themselves at risk (however small) when volunteering to participate in a study with an unknown outcome, and ethically you would not want to put more individuals at risk than is absolutely necessary. Practically, only a certain amount of funding and time will be available to run the trial and therefore it would not be possible to include an endless number of participants.

There are a number of excellent articles about how to undertake a sample size calculation.[2] It is common to recruit a few participants more than the sample size calculation initially suggests, to account for an inevitable number being lost to follow-up, either through withdrawal or dropout.

Recruitment

It is important to describe how participants will be identified and recruited. The recruitment process (e.g. referral, self-selection through advertisement, financial incentives) must be described in the protocol. Recruitment can be time consuming and a realistic amount of time should be allowed for this. The dates of recruitment should be defined, as this will affect the generalisability of the trial (e.g. accepted medical and surgical practices continually change and this could affect the routine/control treatment given to patients).[1]

Interventions

All interventions should be thoroughly described, including any control interventions, to allow other clinicians to reproduce the methods.[1] Interventions should only be administered once the participant has been enrolled in the trial, according to the chosen method of assignment.

Blinding

The protocol should describe who will be blinded (i.e. unaware of participant assignment) to the intervention group(s), including the trial participants, treating clinicians, and outcome assessors.

Outcomes

Prior to undertaking the trial, the primary and secondary outcomes must be predefined.[1] It is important to have one primary outcome (or at most two). This is the outcome that is judged to be of single most

importance to all stakeholders and which could be used to answer the main question/focus of the study.[1] The time point(s) when the primary outcome data is to be assessed should also be decided. This is used to estimate how many participants should be recruited to the trial.

Multiplicity of primary outcomes, as well as statistical testing, should be avoided, as this reduces clarity and increases the risk of spurious findings (e.g. finding a statistically significant difference by chance).[1] There can be several secondary outcomes (e.g. including harms), but the same needs to be borne in mind.

The Core Outcome Measures in Effectiveness Trials Initiative (COMET) is an organisation which supports the development of 'core outcome sets' (COS).[3] These are agreed, standardised sets of outcomes, which represent the minimum that should always be measured and reported in clinical trials of a specific condition. COS allow the results of different studies to be compared and combined, as appropriate.

Once the primary and secondary outcomes have been defined, it is necessary to determine valid outcome measurement tools. It is usually best to use an existing tool that has a proven track record and has been tested for validity and reproducibility. This will enhance quality and allow comparisons with other studies.[1] Other important considerations include, who will make the assessments, if there will be any masking of allocation during measurement (blinding) and if there will be any means of determining the consistency of measurements by the same rater (intra-rater repeatability) and/or between raters (inter-rater reproducibility).

Follow-up and end-points

The time-points of assessment (frequency) and the endpoint of assessment (duration of follow-up) should be explicit and clinically appropriate to answering the primary research question.

Informed consent

An assessment of capacity must be performed on all potential participants within a trial and written informed consent obtained.[1,4,5] Information should usually be given verbally, through discussion and in another form (e.g. written, audio-visual etc.) which should be outlined in the protocol. This should include the trial aims, methods, potential benefits/risks, post-study arrangements and any other relevant aspects (e.g. sources of funding, possible conflicts of interest, researcher affiliations etc.).[6] Participants must have the opportunity to ask questions, told that they do not have to take part and can withdraw consent at any time, without it affecting their treatment.

Flow of patients through the trial

The Consolidated Standards of Reporting Trials (CONSORT) group recommend explicitly describing the flow of participants through the study when reporting randomised trials, including the reasons for exclusions and loss to follow-up. A CONSORT flow diagram (Figure 2) must be planned in the protocol and completed within the trial.[7] This will allow others to judge how much the estimated effect of the intervention might be over or under-exaggerated in comparison with ideal circumstances.[1]

Interim analysis and stopping guidelines

This is usually at pre-determined time-points and involves analysing the interim results, with or without maintaining the blinding present.[1] If an intervention is showing larger than expected benefits or harms, or no important difference, the data monitoring (and ethics) committee can recommend that the trial continues, is modified or stopped earlier than planned.[5]

Statistical methods

Statistical methods can be used to compare the groups in the trial for both the primary and secondary outcomes.[1] Additional analyses, such as subgroup analyses and adjusted analyses can be undertaken, but care should be exercised to avoid increasing the risk of finding spurious results.

An intention-to-treat analysis is often recommended for RCTs, as any missing participant data in the analyses (i.e. due to exclusion, loss to follow-up and/or deviations from the protocol) will compromise the randomisation and may lead to bias.[1] An intention-to-treat analysis involves analysing all participants that were enrolled and randomised, in the exact groups to which they were randomised to.

This can be quite difficult if there is missing data.[1] Solutions might include imputing the final outcomes or less favourably, carrying the last known observation forward.[1]

Post-trial provisions

Before the trial starts, access to treatments found beneficial, after the trial has finished, should be considered and this information disclosed during the consenting process.[5]

Obtaining funding and support grants

The cost of the trial should be considered at the protocol stage. Money can be obtained from industry (e.g. new medicinal product, device or technology), a research funding body (e.g. NIHR or Medical Research Council) or from a charity (e.g. the British Orthodontic Society Foundation).

Three types of research costs are defined by the Department of Health (DH):[8]

- Research costs – these are related to activities carried out to answer the research question (e.g. data collection and analysis, and are usually met by the funders of the trial);
- Treatment costs – these are related to patient care, and are usually met through the normal NHS commissioning process;
- NHS service support costs – these are related to additional activities, which are part of the research process, rather than the treatment, (e.g. consenting patients for the study, and are usually administered through the local Clinical Research Networks (CRNs)).

For a commercial research trial (e.g. pharmaceutical company) the NHS is required to recover all costs, over and above the standard NHS treatment, from industry.

Sponsorship

A sponsor is required for any research involving patients, their tissues or NHS resources.[6, 9] The sponsor can be defined as an individual, company (e.g. pharmaceutical company), institution (e.g. university hosting the research), or organisation (e.g. NHS organisation), which assumes overall responsibility for starting and managing the trial, and is not necessarily the main funder. These responsibilities may be shared by joint- or co-sponsors. A risk assessment is usually undertaken using the study protocol and a decision made about whether to grant sponsorship or not. If successful, a letter of sponsorship is issued. Sponsorship is required prior to any other approvals.[10]

Peer review

Finally, the protocol should be scientifically peer reviewed by a number of independent clinicians and preferably patients as well. It may be necessary to make changes to the protocol during the trial, in response to changing circumstances, but such changes should be transparent and acknowledged during reporting, to allow a reasonable interpretation of the results.[1]

Approvals required to commence a trial within the UK

After the protocol, funding and sponsorship have been agreed, the necessary legal permissions and approvals must be sought.[10]

Ethical and regulatory considerations

Clinical trials require ethical[11] and research governance[6] approval. Other approvals that may be required, including the Medicine and Healthcare Products Regulatory Agency (MHRA).[12] The process for approval has been simplified, with an online system called the Integrated Research Application System (IRAS).[13] This is a single, stream-lined system to apply for permissions for health and social care research in the UK. With this system, the information for the trial can be entered onto one form and IRAS will automatically update the information onto all of the relevant approval forms.

IRAS captures the relevant approvals from the following review bodies:

- Administration of Radioactive Substances Advisory Committee (ARSAC)
- Confidentiality Advisory Group (CAG)
- Gene Therapy Advisory Committee (GTAC)
- Health Research Authority (HRA) for projects seeking HRA Approval
- Medicines and Healthcare Products Regulatory Agency (MHRA)

- NHS / HSC Research and development offices (R&D)
- NHS / HSC Research Ethics Committees (REC)
- Social Care Research Ethics Committee (REC)

Once completed, the forms are transferred electronically to the appropriate organisations, along with any supporting documentation (e.g. participant information sheets and consent forms). Depending on what is involved in the study, compliance with other regulatory bodies may be required including ionising radiation (IRMER), Medicines for Human Use (Clinical Trials) Regulations (2004) etc.

Data protection, patient confidentiality and Caldicott guardians

Privacy and confidentiality for research participants and their personal information are essential.[5] Caldicott guardians are individuals within an organisation, who should be notified of all research and related activities, to ensure that any patient identifiable information (PII) used complies with the Caldicott principles[14] and Data Protection Act.[15]

Indemnity insurance

All trials should be covered by some form of indemnity insurance, either through the hospital trust or university.

Trial registration

All clinical trials must be registered on a publically accessible database.[1, 5] Trial registration and publication helps prevent duplication, non-publication and selective reporting of outcomes. There are several trial registration sites to choose from, and once registered, a unique trial registration number is given.

Common trial reference numbers

IRAS number: Generated by IRAS and will be the primary reference number for the trial used by REC, HRA and if applicable MHRA.

EudraCT number: It is now compulsory that all clinical trials of investigational medicinal products (CTIMPs) are registered on the EudraCT database.[16]

Clinical trials register number: Acceptable registers include EU Clinical Trials Register,[17] International Standard Randomised Controlled Trials Number (ISRCTN) Register[18] and ClinicalTrials.gov.[19]

Sponsors number: Generated by the sponsor

Funders number: Generated by the funder

Roles and responsibilities of trial team and committees

Trial team

Chief Investigator: The named Chief Investigator (CI) is responsible for the conduct of the research (e.g. design, management, reporting) in the UK and, if at more than one site, the co-ordination of the Principal Investigators.

Principal Investigator: The Principal Investigator (PI) is responsible for their own research site.

In a single-site study, the CI and PI will usually be the same person. Other members of the trial team might include a trial co-ordinator/manager, research nurse, data manager, programmer, site monitor, statistician, health economist, data entry/clerical support etc.

Trial committees

Trial Management Committee: Meets regularly to ensure all practical details of the trial are progressing and everyone understands the processes.

Trial steering committee: Meets regularly to ensure that the trial is running well and sends reports to the sponsor. The majority of its members must be independent of the trial (including the chair), and it is desirable to include experienced trial researchers and patient representatives.[20]

Data monitoring (and ethics) committee: Scrutinizes the study progression and its members must be independent of the trial.[20]

Training requirements for researchers and Good Clinical Practice (GCP)

The international ethical, scientific and practical standard for conducting clinical research is called Good Clinical Practice (GCP).[21, 22] All individuals conducting a trial should be suitably educated, trained and experienced to perform their tasks.[21] GCP compliance reassures the public that the rights, safety and wellbeing of research participants are protected and the research data is reliable.[23] Depending upon each individual's role within the trial, there may be a requirement to undertake GCP training.[23]

Typical trial time line

A typical clinical trial time line is:

- Set-up (9 months)
- Recruitment (2 years)
- Follow-up (1-3 years)
- Analysis (6 months)

Dissemination

Once participants have been recruited, data collected and analysed, a report must be prepared and disseminated, so the results can be used in clinical practice. If this is not done, then the contributions of the researchers and participants will have been wasted. There are many ways of publicising the results, usually through a conference presentation and publication in a suitable academic journal (preferably open access). There are a number of statements that outline what should be included in the report of a clinical trial to ensure quality and transparency of reporting. The appropriate statement to use depends upon the design of the study (Table 1) and most can be found on the Equator Network.[24]

Summary

This second article has described the steps involved in designing and setting up a clinical trial from writing a protocol to gaining the necessary approvals. Clinicians should be aware of how research is undertaken. Without a reasonable knowledge about how data, related to the safety and effectiveness of treatments is obtained, it would be challenging to undertake appropriate evidence-based clinical practice.

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Figure captions

Figure 1: Deciding on the study sample for the trial

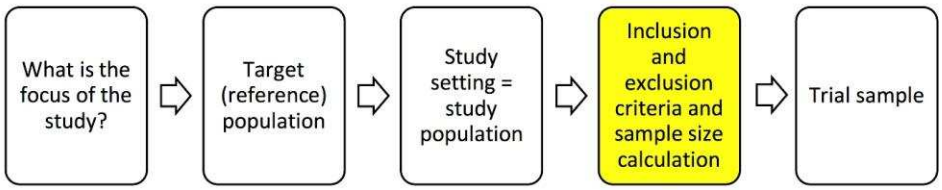
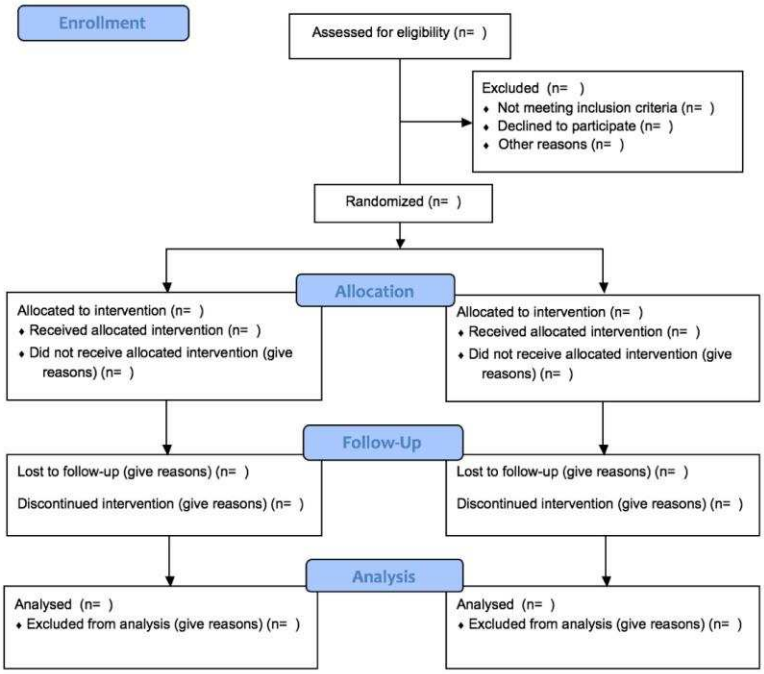


Figure 2: CONSORT flow diagram (Available from http://www.consort-statement.org)



Tables

Table 1: Reporting statements for different trial designs (Available from: http://www.equator-network.org)

Trial design	Reporting statement
RCT	CONSORT
Diagnostic accuracy studies	STARD
Observational studies	STROBE
Systematic reviews of trials	PRISMA
Meta-analyses of observational studies	MOOSE