

A Guide for Writing a Protocol for a Clinical Trial

Awad Mohamed Ahmed, MD

Professor of Medicine, University of Bahr Elghazal, Khartoum, Sudan

For correspondence

Professor Awad Mohamed Ahmed

E-mail: awad.sd@gmail.com

Tel.: +249 912344936

ABSTRACT

Randomized controlled trial or randomized clinical trial (RCT) is an epidemiological experiment to study a new preventive or therapeutic regimen. It is most commonly used in assessing the effectiveness of health care services or health technologies such as pharmaceutical products (e.g. drugs or vaccines), medical devices or new surgical procedures. A simple description of a trial design is: patients' recruitment and allocation into study and control groups, intervention, follow up and analysis and drawing of conclusions.

A protocol for a clinical trial is a study plan, designed to describe objectives, background, methodology, organization, the participants, interventional procedures and assessments tools of the trial. In this paper we will describe the different steps of preparing a sound and efficient trial protocol.

INTRODUCTION

Research is defined as a systematic methodologic scientific approach for basic facts in order to find solutions based on these facts. Research investigations may be carried out in one of two ways: interventional studies (experiments), or non-interventional surveys of naturally occurring phenomena (descriptive and analytic studies).

The experiment differs from survey in that it involves a planned change (extraneous factor) in naturally occurring events. The overall aim is to seek a possible explanation (hypothesis) for an answered question (the research problem).⁽¹⁾ A classical example is use of a certain drug (D) to control blood glucose level on a diabetic patient. The research problem, here, is 'control of blood glucose within a desired level'. The hypothesis is 'if the drug D can lower blood glucose to that level'. The research is then designed to test the relationship between these two variables. The types of research experiments include animal and laboratory experiments and randomized clinical trials.

The clinical trial is a type of scientific experiments most commonly used in assessing the effectiveness of health care services or health technologies such as pharmaceutical products (e.g. drugs or vaccines), medical devices or new surgical procedures. Thus

clinical trials can include diagnostic, therapeutic or prophylactic agents. Clinical trials can be preclinical studies to investigate effects and safety of a product (phase I and II), or full evaluation of the new product.² Clinical trials can vary in size from a single centre in one country to multicentre trials in multiple countries. Common purposes of clinical trials include testing effectiveness and safety of new medications and devices, or to compare their effectiveness with already known (standard) medications and devices. Also trials are performed to test already known medications in a different dose or for a new indication. Clinical trials may be required before the national regulatory authority approves marketing a new drug, or a new dose for a standard drug, or a new device for use on patients. The US National Institute of Health (NIH) organized clinical trials into five categories: prevention trials (vaccines, medications, lifestyle changes), screening trials to test the best ways to detect diseases, diagnostic trails (to find best tests or procedures to diagnose certain disease), treatment trials and quality of life trials (to explore ways to improve comfort and the quality of life for individuals with a chronic illness).

The clinical trial includes three main items: an intervention, comparability through controlling and randomization and blinding. An intervention is done

through application of the new technology (e.g. a new drug). The controlling aims at influencing factors that may affect the outcomes of the study; without a control we can not be sure that any response is solely due to the new treatment. Randomization and blinding reduce the chance of occurrence of bias as awareness of trial's assessors of treatment allocations of participants may influence their recording of signs of improvement and adverse events. Most of the clinical trials are parallel trials in which each participant receives one of the two treatments that are being compared. ⁽²⁾ A fewer trials adopt a crossover design, where each patient is considered as his own control, with a period to separate the use of the second drug (washout period) to dissipate any residual effect (carryover) of the previous drug. ^(3,4)

A protocol for a clinical trial is a study plan, designed to describe objectives, background, methodology, organization, the participants, interventional procedures and assessment tools of the trial. The protocol is the 'operating manual' for the clinical trial, and ensures that researchers (especially in multicentre trials) all perform the trial in the same way on patients with the same characteristics. The purpose of this paper is to help researchers to prepare a sound protocol of a clinical trial. Throughout this guide, for the purpose of simplicity, we assume that the product of the trial is a new therapy.

CONTENTS OF THE PROTOCOL

Title Page (Page i)

* Title

The full title should include summary of the study design, medicinal product(s), nature of the treatment, comparators and/or any placebo, indication, patient population and setting. The short title is a summary of this.

* Purpose

To state the purpose of performing the study (e.g. student project, commercial / non commercial trial, licensing).

* Names (titles), roles and contact details (addresses, telephone numbers) of:

- Sponsor Investigator(s) who is (are) responsible for conducting the trial.
- Physicians and other experts who are responsible for trial site related medical decisions (if other than investigator)

- Trial site(s), clinical laboratory(s), technical departments and other institutions involved in the study.

* Protocol details

- Version number and date
- Final / draft

Signature page (Page ii)

- Signatures of all healthcare professionals involved in the trial
- Who have had significant input into the design of the protocol and clinical trial

Content Page (Page iii)

List of Abbreviations and Definitions (Page iv)

A Study Summary (Page v)

- * Title
- * Short title
- * Phase
- * Design
- * Study centre(s)
- * Duration of the study.
- * General objective
- * No of subjects
- * Diagnosis and main inclusion criteria
- * Study product, dose, route, and regimen
- * Duration of administration
- * Statistical methodology

Items of the Protocol (Start numbering from Page 1)

1. Introduction (background)

The detail given in this section should be backed up by a full literature review and should make reference to relevant papers, previous clinical experience and pilot work.

This section should include:

- 1.1. A clear explanation of the main research question i.e. the hypothesis to be tested.
- 1.2. Detailed justification for the trial including:
 - Explanation of why the study is appropriate, potential benefits to patients/ health service, relevance to current policies and priorities.
 - Description of the indication, its diagnosis, incidence, current treatments and their limitations.
 - Description of the treatment under investigation

including reference to any previous evidence of its usefulness, in addition to (mechanism of action, production, formulation, pre-clinical data, dose rationale, potential risks and benefits, risk-benefit ratio).

- A statement of what would be a worthwhile improvement in the study outcomes and what evidence there is that the treatment under investigation may achieve this.

2. Objectives: General and specific.

3. Design

3.1. Clear description and justification of the study design/type (e.g. double-blind, placebo controlled)

3.2. Statement of the primary and secondary endpoints / outcomes (including at what point in the trial these will be measured)

- Primary endpoints: mean the outcomes most accurately measure the benefit of the new therapy.
- Secondary endpoint (if any): these are related to toxicity and undesired effects of the new therapy.

3.2. Phase of the trial (e.g. phase I / II / III / IV)

- Phase I tests initial studies to determine the metabolism and pharmacological actions of drugs (to define dose and to evaluate toxicity) in a small group on healthy participants and/or patients (usually 15-20)
- Phase II: controlled studies to study the effectiveness and short term side effects of a drug in patients with the disease under study. The sample size is larger than in Phase I.
- Phase III: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug.
- Phase IV takes place after the drug or treatment has been licensed and marketed, to delineate additional information including the drug's risks, benefits, and optimal use.

3.3. Summary of treatments being compared with reasons for choice of comparison group (e.g. active control / placebo).

- Active (positive) control: usually the standard treatment of the disease.
- Placebo (negative control): looks like trial drug in shape and taste but with no active compounds.

3.4. The expected length of time for which each subject will participate in the study for and the sequence and duration of all study periods.

3.5. Description of all procedures (sequentially) to be performed, identifying what is standard and non-standard care where possible.

3.6. The criteria for discontinuation of parts of the study or the entire study.

4. Patients selection and withdrawal

4.1. Inclusion criteria.

4.2. Exclusion criteria.

4.3. Where will the potential subjects be approached (e.g., outpatients)

4.4. Expected number of eligible participants available per year and proportion of these expected to agree to the trial.

4.5 Number of centres involved

4.6. Who will make initial approach to potential subjects?

4.7. How will the subjects be recruited (e.g. advertisements, notices)

4.8. Details of procedures, tests, and screenings carried out to assess trial suitability

4.9. Enrollment: The act of signing up participants into a study, involves evaluating a participant with respect to the eligibility criteria of the study and going through the consent process.

4.10. When and how to withdraw subjects: describe under what circumstances and how subjects will be withdrawn from the trial.

4.11. Data collection and follow up of withdrawn subjects.

4.12. Whether and how subjects would be replaced.

5. Study drug (trial intervention)

5.1. General information

Description: if approved by the concerned authorities, chemical name, trade name, pharmacological class and action, recommended dose range, form of administration, known or possible interaction with the non-trial drugs, known and potential benefits and side effects or adverse reactions.

5.2. Use in the trial

- Description and justification for the proposed route of administration, dosage, and treatment period
- Method for assigning subjects to treatment groups
- Detail of who will be administering the product

(e.g. patient, nurse, doctor)

- Description of dosage form, packaging and labeling of products
- Subject compliance monitoring (e.g. watching subject swallow pills).
- Prior and concomitant therapy
- Blinding of study drug (patients, clinicians, assessors).
- Details of who will supply the products
- Receiving of drug supplies: a drug receipt log filled out and signed by the person accepting the shipment
- Storage
- Description of dispensing records, accountability and disposal procedures during the trial
- Arrangements for continuation of treatment for study patients after the end of the trial

6. Measures to avoid bias

6.1. Randomization

Randomization is the process where participants are allocated into study and control groups to receive or not to receive an experimental or therapeutic procedure or intervention. Randomization aims to make the groups comparable. Randomization eliminates the selection bias by that the investigator has no control over the allocation of participants into either study or control group (i.e. each individual has equal chance of being allocated to each group). Randomization is best done by using statistical random table.

6.2. Blinding

The awareness of treatment allocations may influence the recording of signs of improvement or adverse events.

- Single blind trial: Here the participant is not aware whether he belongs to the study or control group.
- Double blind trial: Here one researcher allocates a series of numbers to 'new treatment' or 'old treatment'. The second researcher is told the numbers, but not what they have been allocated to.
- Triple-blind trial: Here the participant, the investigator and the person analyzing the data are all blind. This is the ideal but double-blinding is the most commonly used.

NB. In cross-over trials each participant receives all/ both treatments in random order with a washout period in between.

7. Study procedures (follow up)

This includes examination of the study and control groups' subjects at defined intervals of time in a standard manner under the same conditions in the same time frame till the final assessment.

Visit 1

Visit 2

Etc

How many visits/admissions of participants will this project involve?

Give also an estimate of total time involved for participants at each visit.

8. Assessment of efficacy

8.1. Efficacy parameters:

The final assessment of the trial is carried in terms of:

Positive results: include benefits of the experimental study such as reduced incidence of the disease or severity of the disease, cost of health services or other appropriate outcome.

Negative results: These include the severity & frequency of side-effects and complications.

8.2. Method and Timing

Insert methods and timing for assessing, recording and analysing efficacy parameters

9. Statistical plan

9.1. Sample size determination

- Detail the methods used for determination of the sample size and a reference to tables or statistical software used to carry out the calculation.
- Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

9.2. Statistical analysis

- The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluate-able subjects).
- Detail of the variables to be used to assess baseline comparability of the randomized groups and how these will be reported (e.g. means, standard deviations, medians, proportions).
- Detailed plans for statistical analyses of primary and secondary outcomes.

9.3. Plans for handling missing data, non compliers and withdrawals in analysis.

9.4. Statement of who will carry out analyses and at what point.

10. Safety and adverse events

10.1. Definitions

Safety and adverse events are defined as any symptom or illness that develops or worsens in severity during a course of a study (including intercurrent illnesses or injuries). Adverse events can be classified as serious or non-serious. Serious events can be fatal, life-threatening, require prolonged hospital stay, result in a significant disability or incapacity or important medical event.

10.2. Adverse events reporting period

The study period during which adverse events must be reported is defined as the period from the initiation of the study procedures to the end of the study treatment follow up (this follow up period is usually defined as 30 days following the last administration of study treatment).

10.3. Recording adverse events

At each contact with the subjects the investigator must seek information on adverse events by specific questioning and examination. Information on all adverse events should be recorded immediately. On occasion of adverse events the following information should be provided:

- Study centre
- Who identified the event
- Subject name
- Description of the event
- Date and time of onset
- Current status
- Whether study treatment was discontinued
- The reason(s) why the event was classified as serious
- Investigator assessment of the association between the event and study
- The type and duration of follow up for subjects after adverse events.

10.4. What facilities, procedures and personnel to deal with emergencies (who have what responsibility).

10.5. Unblinding procedures: In the event that subject are prematurely discontinued from the trial,

10.6. Stopping rules and criteria for terminating the study.

10.7. Medical monitoring

It is the responsibility of the principal investigator to oversee safety of the study at his site.

This monitoring should include careful assessment and appropriate reporting of the adverse events as mentioned above, as well as construction and implementation of a site data and safety monitoring plan

- **Data and safety monitoring board (DSMB):** consist of community representatives and clinical research experts. Its mission is to ensure that participants are not exposed to undue risks. It has the right to terminate a trial if there are safety concerns or if its objectives have been achieved.
- **Study monitoring plan:** The Investigator should allocate adequate time for monitoring activities. He should also ensure that the monitoring board (or quality assurance reviewer) is given access to all of the study documents and study-related facilities (e.g. laboratory, pharmacy) and have adequate space to conduct the monitoring visit.

11. Data

11.1. Data to collect

- Source of the data (e.g. patient questionnaires, patient notes, electronic data, procedures).
- Time point for collection (baseline, during treatment, at follow up point)
- Who will collect the data?
- Why the data is being collected (e.g. baseline comparison data, main outcome, important prognostic / explanatory variable)
- Describe methods used to maximize completeness of data (e.g. telephoning patients who have not returned postal questionnaires)
- Include data collection forms (case report forms) as appendices

11.2. Data handling and record keeping

- Describe procedures for data collection and recording (software to be used, location of the data etc)
- Detail methods implemented to ensure validity and quality of data (e.g. double entry, cross validation etc)
- Confidentiality: who will have access to information and why
- Who will use that information?
- How long and where will the data from the study be kept and who will be responsible for its safe keeping

- What will be done with the raw data when the study is finished (e.g. whether it will be used in further studies)

12. Ethical considerations

12.1. Approvals from concerned authorities.

12.2. Informed consent: this document should contain rights of the study participants (including the right to withdraw at any stage of the trial), main facts about the study drug, (test, procedure), purpose, duration, required procedures, expected risks and benefits (and the likelihood or probability of their occurrence). There should be allowances for special groups (e.g. non Arabic speakers, children, mentally ill)

12.3. Patient withdrawal / discontinuation (above)

12.4. Trial monitoring (above)

13. Study finances

13.1. Funding source

13.2. Conflict of interest

13.3. Subjects' payment

13.4. Cover for managing adverse events

14. Publication plan:

(e.g. following the study, will there be access to raw data and right to publication freely by all investigators in the study? What publications / conference presentations will be planned?)

15. References:

A numbered list of recent references matching those cited in the text is needed The Vancouver style is preferred in biomedical research.

16. Appendices

- Including (where relevant):
- Patient information sheet
- Patient consent form
- Data collection forms (case report form- CRF).
- Summary of product (test, procedure characteristics)

References

1. Lumley J, Benjamin W. (1994). Research: some ground rules. Oxford University Press, p 7
2. Petriere A, Sabin C. Medical Statistics at a Glance.2000. Blackwell Scientific, UK, PP 30-37.
3. Senn S. Crossover trials in clinical research, Wiley, Chichester
4. Kerry, S.M, Bland, J.M. Sample size in cluster randomization. *British Medical Journal* 1998; 316: 549-555.