Writing the introduction and methods of a controlled trial

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A controlled trial is an experimental study in which participants are assigned to receive one or more interventions (or no intervention), and the subsequent biomedical or health-related outcomes are compared in participants.[1] The term "controlled" refers to the standard practice or placebo (substance with no active ingredient) to which the new intervention is compared within the trial. Randomized controlled trials (RCT) in which the participants are randomly assigned to treatment, i.e., intervention or control, are considered as gold standard by most because of the significant reduction in bias.[2] RCTs' methods can vary in a number of ways e.g., problem under study (disease or behavior), population (individuals, groups etc.), types of interventions (e.g., drugs, procedures, therapies etc.), design (e.g., parallel, crossover, cluster etc.), expected outcome (superiority, non-inferiority etc.), allocation concealment, blinding, analytical approach etc., the details of which are available elsewhere.[3,4] This is perhaps the reason why inconsistencies in trials' reporting were increasingly noticed by research community during the last three decades.[1,2] These observations led to the development of reporting standards famously known as the CONSORT statement (Consolidated Standards of Reporting Trials) in 1996.[4] The CONSORT statement has been revised twice, in 2001 and in 2010 to further clarify the reporting needs.[4] Other agencies involved in trial scrutiny for registration,[1] quality assurance[3] or funding[5] also have their own guidelines regarding what information they need for trial appraisal.

This objective of this commentary is to briefly explain what is expected when writing the introduction and methods of an RCT in a manuscript. We will use a fictive example from previous commentaries to elaborate the reporting requirements of a controlled trial.[6,7] This example assumes that the standard treatment for a chronic disease "D" is drug "A." Now researchers hypothesize that a drug "B" has a better clinical efficacy than drug "A" in patients of disease D. They propose an RCT to compare the clinical efficacy as well as safety of drug "B" with drug "A" in patients of disease "D." In the following we describe what might be expected by readers in description of an RCT like this one.

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Writing the Title and Abstract

The CONSORT statement and agencies involved in trial scrutiny recommend that the RCT and important features of its design should be identifiable from title and abstract of the report.[4,6] The fictive example can be entitled as "Clinical efficacy of Drug B in disease D patients: A randomized controlled trial." The CONSORT statement indicates what information of an RCT should be reported in an abstract as it is often available to a larger public than the full report — Moher et al.[4] have described the information that should be reported in an abstract of an RCT.

Writing the Introduction

The most important questions, the responses to which are actively searched in the introduction of an RCT are: problem(s) addressed, research question(s), rationale, literature review, and potential beneficiaries.

Every RCT starts by a general introduction about the health problem dealt in the trial. This introduction leads to a clear problem statement. For instance, in the above example, the introduction can start by a brief introduction of disease "D" including the clinical definition and epidemiology e.g., prevalence, incidence, associated risk factors etc. Then in few lines the problem statement is presented e.g., the standard treatment of disease "D" i.e., drug "A" has a clinical efficacy of only 30% in patients, and there is a need to find a better treatment. A new drug "B" is hypothesized to have better treatment outcomes than drug "A" in disease "D." This description leads to phrasing of the research question i.e., "Has drug "B" (intervention) a better clinical efficacy (outcome) than the drug "A" (control) in patients of disease "D" (population)?" (Please refer to previous commentary[7] for formulating a research question).

The next subsections in introduction should convince

readers about the rationale i.e., why this RCT is needed. The relevant information can include pre-trial data or information about underlying biological and physiological mechanisms. E.g., data from animal studies or experience with patients with disease "D" for drugs "A" and "B" can be presented along with their strengths and weaknesses as well as a discussion about underlying mechanisms of actions. This can take form of a literature review and present a broader perspective of what has been done previously in disease D treatment, findings about the drug "A", and then findings about the drug "B", and thereby a scientific argument in favour of an RCT for drug B. Review should also cover safety concerns, if any, related to disease as well as intervention e.g., drug "B". Literature review should be up to date, brief and to the point. Reviewers also expect that potential beneficiaries of the RCT who are supporting or will be using the findings. For instance, in this example the direct beneficiaries are the patients of disease D. Similarly, all potential knowledge users and mechanisms of knowledge use should be clearly described. For example, how the physicians will be informed of the RCT results, and how they will use the results in case they favour a change in practice. Lastly, a summary at the end of introduction can help readers to recapitulate the essence of what is the trial about and why it should be conducted. The ending phrases of introduction should lead to a brief section of hypotheses and objectives. They should be reported in direct and clear phrases e.g., the objective of the fictive RCT is to compare the clinical efficacy and safety of drug "B" with the drug "A" in patients of disease "D."

Writing the Methods

The phrasing of this section is usually structured as RCT design, participants, intervention and control, outcomes, sample size, treatment allocation and randomization, blinding (if planned or performed), follow-up, compliance/adherence to interventions and statistical analyses.[5,6] Writing methods following above structuration and using subheadings improves readability and completeness of reporting.

The first statement of methods usually presents important features of the RCT's design (parallel, factorial and assessment such as superiority or non-inferiority). In our example, the trial can be written as: "This is a single center, parallel-group, controlled, participant-physician blinded study, with balanced randomization, conducted in Karachi, Pakistan." "Parallel group" means that there are two intervention arms i.e., patients are either allocated to drug "B" or drug "A". RCTs comparing multiple therapies should state all therapies compared in the RCT. "Participant-physician blinding" means that both the research staff and patients are blinded to the drugs that they are receiving. It is important to highlight here the changes made in the original design as the trial progressed e.g., whether some patients in the drug "B" group were given drug "A" because of no improvement in symptoms etc.[3]

The subsection on participants includes the explanation of eligibility criteria e.g., age, sex, disease/health characteristics and how participants were selected. This is fundamental to understand to whom the trial findings apply and the generalizability of findings. The inclusion and exclusion criteria should be very clearly reported.

It is also imperative to report the settings of the trial including details about the department and/or institution where the trial is based e.g., the fictive trial takes place in outpatient setting. This provides a backdrop for implementation of trial results where trial setting may differ from implementation setting.

The next subsection should clarify the reader about intervention and control i.e., what is compared with what. This can include names of intervention (e.g., drug "B"), control (e.g., drug "A"), doses, modes of administration, conditions in which the intervention and/or control is withheld, and other information necessary for comprehension and replication of the RCT. The control group even if it is placebo should be described.

Following subsection should clarify readers about the outcomes assessed in an RCT, especially their definitions and measurement processes. In the fictive example, we would have to clarify what clinical efficacy means, and when and how it would be assessed to determine outcomes in both groups. In RCT, there can be several outcome measures - the most important of which are defined as principal or primary outcome or endpoint measure and the others are called as secondary outcome measures. In the fictive example, clinical efficacy is the primary outcome measure whereas the safety concerns e.g., adverse effects can be considered as the secondary yet important outcome measure.

Randomization and blinding (masking) have become the integral part of RCT especially when the efficacy and safety of drugs is under consideration.[3-8] Information required about randomization includes process of assignment such as sequence generation (e.g., manually by random tables or automatically by using a software), types of randomization (coin toss, stratified, block etc.), concealment of allocation until intervention assignment, and implementation of randomization process (who and how) and ratio of assignment to groups.[3] Process of

blinding who and how, if implemented, is also required to be explained in detail.

RCTs' methods section is incomplete without the description of sample size and statistical analyses. The research question, hypothesis and pre-trial data dictate sample size. For instance, if a large effect of intervention is hypothesized then a small sample is required, and vice versa. All relevant calculations and references should therefore be presented for sample size justification. For instance, in the fictive example, previously observed efficacy (effect) of drug "A" and hypothesized efficacy (effect) of drug "B" could be referenced in sample size estimations. Sometimes, the sample size is revised based on results from interim analysis, such information should also be reported. Similarly, the plan of statistical analyses such as univariate, multivariate and subgroup analyses is required in methods section.

Additional Information

Other information needed is the ethics approval reference which indicates that the trial has been reviewed and approved by an institutional (ethics) review board. Most journals now require that a clinical trial be registered with an independent body e.g., www.ClinicalTrials.gov,[1] and the registration number be reported in the methods section. This prevents authors from withholding results about outcomes planned in the start of an RCT. Funding organization(s) and conflicts of interests, if any, are also systematically reported in the trial manuscript.

Conclusion

Writing a clinical trial varies with respect to the audience it is intended. For the manuscript submission after the trial has been completed, the focus is more on a clear explanation of methods and results, and what they would mean for practice. In case of funding agency, the focus is more on the clarifying research questions and procedures to judge feasibility and impact of investment.[6] Funding agencies often require information about RCT management i.e., who is involved in different processes such as recruitment, randomization/blinding, coordination, analyses etc. This information is also required when reporting to institutional review boards. We have intentionally limited the scope of this commentary to RCT manuscripts. The CONSORT statement is widely accepted by healthcare journals, and should be considered when reporting the findings to the Journal of Pakistan Medical Association.[6] We invite future trialists to read previously published protocols and guidelines carefully before starting to write, and work with a mentor who has been successful with funding and publications.

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