Writing the methods section of a clinical trial report

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Aims:

- To introduce the best practices for reporting the Methods section of a clinical trial.

Objectives

- To enumerate the CONSORT guidelines pertaining to the Methods section
- To provide the key elements of the Methods section
- To describe the proper reporting of participant eligibility criteria, the interventions, and the trial setting in sufficient detail to enable readers to assess external validity of the trial results
- To clearly define the primary and secondary outcome measures for a trial
- To summarize essential aspects about the randomization of an intervention that must be included in the Methods section
- To explain why specific features of the sample size calculation and statistical analysis plan are required in a trial report

Most of the material we need to include in the Methods sections of a clinical trial report is written before trial commencement in the trial protocol. In the final report, we will need to summarize what was written in the protocol, and succinctly convey to the reader the key points on how the trial was carried out. In a previous JPDSarticle on the *ABCs of Dermatology Research*, we discussed how to use the CONSORT guidelines to formulate the Results section. We will use the same guidelines to check that we have included all the essential elements of our trial's Methodology in our final report.

The items listed in the CONSORT checklist pertaining to the Methods section show us the possible main subheadings we can use to create the Methods section of our final paper. The subheadings that we could use are as follows:

- **Trial design**
- **Participants**
- **Interventions**
- **Outcomes**
- **Sample size**
- **Randomization – sequence generation, allocation concealment, and implementation**
- **Blinding**
- **Statistical methods**

We will discuss each subheading in this article.

I. Writing About the Trial design

Description of trial design:

The Methods section should begin with a clear description of the type of trial to be conducted. It could be a parallel group, (a clinical study where two groups, A and B, receive two different types of treatment—one goes to group A only, while the other to group B only), cluster-randomized, crossover, factorial, etc. The trial design description must also include the conceptual framework (superiority, equivalence, or non-inferiority), the unit of randomization (patient, center/institution, geographical location, etc.), and allocation ratio (1:1 in equal randomization).

Important changes to methods after trial commencement (such as eligibility criteria), with reasons:

Most trials will have a protocol that specifies how the clinical trial will be conducted. Further, many journals include as a publication requirement the enrolment of the trial protocol in a registry. Trial registration creates a public record of clinical trials with emphasis on its methodology. Registering clinical trials makes the research process more transparent and encourages researchers to publish all research that is carried out, even if the outcome was non-significant, which in turn will help prevent publication bias. It also prevents outcome selection bias where researchers change the outcomes of their study or just report some of the results.

Some clinical trials may have changes to the methods after trial commencement, and these need to be clearly

stated (e.g., changing sample size due to a low recruitment rate and adding or removing outcome measures due to external information becoming available from other studies). These changes, with reasons, must be explicitly stated in the final trial report. Enrolment in a trial registry allows the reader/editor to confirm if the original methodology as stated in the protocol was adhered to.

II. Writing About the Participants

The two issues we need to consider when reporting details of study participants in a trial report are the eligibility criteria and the setting and location of the trial.

Eligibility criteria

The trial protocol must clearly state the eligibility criteria used to select the trial participants. This entails defining the study population and providing complete details of exclusion and inclusion criteria such as the disease being studied, exclusion of participants believed to be vulnerable to harm from the study intervention (e.g. pregnant women, patients with comorbidities) or less likely to benefit from the intervention (e.g. severe disease states, refractory illness). These criteria enable to reader to assess the generalizability (applicability) of the trial results.

The manner of recruitment should also be stated such as self-referral (e.g. coming to the outpatient department voluntarily or responding to an advertisement about the trial) or referral by others (e.g., physician or dermatologist).

Setting and location

The setting and the geographical location of a trial can likewise affect its external validity. For example, the results of a trial carried out in a tertiary hospital in Metro Manila may not be applicable to individuals who receive the same intervention in a local health center in a provincial setting. Similarly, results of trials conducted in developed countries may not be applicable to the developing world. Patients in the latter setting may have a different baseline risk of the disease being studied and the health personnel may have different resources available and different levels of training in administering the intervention. It is then imperative when reporting a trial to provide information on both the setting and the location of the trial (when and where the trial took place) to allow readers to assess the applicability of the results of the trial to their own settings.

III. Writing About the Interventions

The details of the intervention(s) given to each arm of the trial that must be stated in a clinical trial report include:

- Formulation, dosage, timing, and duration of interventions
- Characteristics of placebo given, including the way it was disguised
- Usual or standard care given to control group, particularly in studies with a "no intervention" control group
- Non-pharmacologic and behavioral interventions (e.g. sunscreens, skincare products, avoidance of sun exposure, etc.)
- Who administered the intervention including their experience and any previous training in giving the intervention, if any

IV. Writing About Outcomes

Primary and secondary outcome measures

It is important to clearly define the outcomes of interest and how these were measured. This helps the reader assess if the trial results are valid, and to whom the findings may be generalized.

Most trials often have more than one outcome measure. These measures are subdivided into:

- **Primary outcomes:** these are the pre-specified outcomes that are considered the **most important** to measure treatment success. Statistical analyses and sample size calculations will focus on these outcomes.
    - For example, in a trial investigating the efficacy and safety of drug X in venous ulcers, the primary outcome measure is the percentage/proportion of patients with complete ulcer healing or ulcer closure.
- **Secondary outcomes:** these are other outcomes of interest which may contribute to the establishment of treatment success. Statistical analysis may or may **not** be done for these outcomes as trials are not usually powered to detect differences in secondary outcome measures.
    - For example, in the abovementioned trial, secondary outcome measures may include mean surface area healed, mean dermatology quality of life indices, mean time to ulcer healing, and adverse events associated with the intervention.

A report of each outcome measure should include the following where possible:

- Definitions for each outcome, including details of any diagnostic guidelines followed or validated measures used
- Methods used to maximize the quality of measurements (e.g., training, repeated measurements then averaging the result, etc.)
- Frequency and timing of outcome measurements

- Who assessed the outcome
- Machine/s used for assessment (with information on manufacturer and country), if any

Any changes to trial outcomes

Any changes to trial outcomes after trial commencement must be reported along with reasons. Sometimes unforeseen circumstances occur, i.e., recent evidence from other trials or systematic reviews/meta-analysis suggesting that an outcome measure might not be appropriate, or recruitment or event (outcome) rate in the trial may be lower than expected with the current sample size. These may require researchers to modify current outcome measures. Comparing the outcomes reported in the paper against those in the trial protocol (usually by way of trial registry) can provide evidence of outcome reporting bias if some of the original outcomes are missing without good reasons.

V. Writing About Sample Size

If a trial reports no significant difference between treatments in terms of the primary outcome measure, the reader needs to be able to assess whether this is because there is **no true effect** in the population from which the study population was taken, **or** because the study **sample size was too small to detect an effect**.

In another JPDS *ABCs of Dermatology Research* article, we discussed the intricacies of sample size calculation. The article explained that the existence of sampling error means that whenever a hypothesis is tested (for example, the **null hypothesis of a superiority trial** that there is no significant difference between treatments hence no effect of an intervention), there is a possibility of either rejecting the null hypothesis when it is true (type 1 or α error) or accepting it when it is false (type 2 or β error). The probability of a type 1 (α) error is known as the **significance level** of a test, while one minus the probability of a type 2 error (1- β) is known as the **power** of a test.

One of the most important elements in planning a trial is to calculate a sample size that will be enough to detect a clinically important effect with a specified level of significance and power. Therefore, a well-written clinical trial report should provide information about how the sample size was determined. Details such as the primary outcome measure that was chosen for power calculation, the values used (proportions/means/minimum size of effect/standard deviation), and the target sample size per study group must be enumerated. Other elements of the sample size calculation include: (i) the estimated outcomes in each group; (ii) the α (type I) error level; (iii) the statistical power (or the β (type II) error level); and (iv), for continuous outcomes, the standard deviation of the measurements. Any adjustments to sample size (e.g., increase in the sample size to allow for loss to follow-up during the study) must also be explained. Reference studies used in the calculation should be cited. The sample size calculation must be described with enough detail to enable readers to reproduce the calculation if they wish.

Interim analyses and stopping guidelines

Although this is not a common practice in small, short-term RCTs with relatively innocuous interventions, some large-scale clinical trials monitor interim results (results that accumulate throughout the study prior to completion) often overseen by an independent Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB). Monitoring trial results allows decisions to be made as to whether the trial should be stopped or modified in some way. For example, if results of interim analyses show evidence that an intervention is showing a particularly beneficial effect or a harmful effect, the DMC or DSMB might consider it unethical to continue to randomize patients to the intervention.

The problem with carrying out repeated analyses of the data over time is that we increase the probability of a type-1 error – of obtaining a p-value of 0.05 (a significant difference) for one of these analyses, even if there is no true effect of the intervention (a false positive). This phenomenon is called multiplicity, and can be due to too many outcome measures, repeated testing of outcome measures, or multiple treatment arms. All these situations increase the number of statistical tests done and increase the false positive rate. This can be adjusted statistically by adjusting the p-values at each analysis. For example, doing 14 statistical tests already increases the false positive rate by 50%! One way to adjust the p-values is through the **Bonferroni correction,** where one divides the original p-value by the number of tests done. Going back to our example, this will be 0.05 (original p-value) divided by 14, giving us a new cutoff of 0.004 for each statistical test.

Ideally, trials must also have **stopping rules,** rules or set of guidelines to aid decisions about whether or not to recommend the early stopping of a trial. These rules may be clinical (e.g., stopping the trial if a patient experiences a flare of disease, worsening of symptoms, severe adverse effects, etc.) or statistical (not in the scope of this discussion). These should be described in detail in the trial report.

VI. Writing About Randomization

A valid comparison of treatments is enhanced by random assignment. Random allocation is the best method to remove selection bias. Randomization, if done correctly, results in groups that will, on average, be the same before the trial starts for both measured and unmeasured characteristics that might be associated with the outcome of interest (e.g., age, gender, and disease severity at baseline).

The three aspects to consider when describing randomization in the Methods section of a trial report are:

- How the random allocation sequence was generated
- Concealment of the allocation
- Implementation of the allocation sequence

Generation of the random allocation sequence

Here are some questions one must be able to answer in describing the generation of the sequence:

1. What was the exact method of generating the random allocation sequence (e.g., random-number table or computerized random-number generator)?
2. Were steps taken to ensure that there were similar numbers in each treatment group throughout the trial (e.g., block randomization)?
3. Were steps taken to ensure that patients in each treatment group were similar in terms of key risk factors for the outcome (e.g., stratification or minimization)?

Concealment

Reports must also discuss how the allocation was concealed from study investigators and potential participants. Allocation concealment is different from blinding as the former aims to conceal the allocation sequence from those assigning participants to intervention groups until the moment of assignment (**before randomization**), while the latter ensures that the patient and/or the person[s] administering the treatment and/or the trial evaluators don't know (i.e., are 'blind to') which treatment is allocated to whom (**after randomization**).

Implementation of the allocation sequence

Here are some questions one must be able to answer when describing the implementation of the sequence:

- Who generated the allocation sequence – preparing the random sequence and the system of allocation?
- Who enrolled participants into the trial – assessing whether they were eligible, explaining the trial, obtaining informed consent, and then enrolling the participants?
- Who assigned participants to each group – finding out the next treatment assignment and then administering the intervention?

It is important that individuals who generate the allocation sequence are different from those enrolling participants and assigning them to each group because knowledge of the allocation sequence might affect the researcher's decision whether to enroll a participant or to which group the participant is assigned, resulting in selection bias. However, it is acceptable that a researcher be involved in both generation of the allocation sequence and enrolment/assignment as long as they do not have access to a copy of the allocation sequence and cannot predict the sequence when allocating patients.

VII. Writing about Blinding

After the intervention has been randomly allocated, it is highly recommended (if possible) to blind study participants, study investigators, and outcome assessors to minimize the likelihood of influencing the results through differences in patient care and measurement or reporting of outcomes. Unlike allocation concealment, blinding all parties in a trial may not always be possible.

Here are some important details about blinding to include in the Methods section:

- Which parties in the trial were blinded
- The method used to ensure blinding (e.g., use of placebo)
- How similar the treatments were (e.g., similar color, smell, and consistency of interventions)
- Whether the success of blinding was evaluated and how it was done (e.g., asking participants to guess which intervention group they thought they were in)

VIII. Writing About Statistical Methods

Trial data can be analyzed in many different ways and each analysis may provide different results. For transparency, it is important to specify in advance what outcome measures are going to be reported to avoid the temptation of selecting and reporting only the most interesting results in the final paper, or reporting only what is most favorable to the researcher. Again, this is why a trial registration is highly recommended as this increases accountability.

Investigators need to provide information on all the statistical methods that were used in the analysis. We previously discussed in another JPDS *ABCs of Dermatology Research* article how to write the Results section in a

clinical trial report. To reiterate, the main results from a trial are best presented in terms of:

- Treatment effect – absolute difference (e.g., a risk difference, difference in means, or difference in proportions), a relative difference (e.g., a relative risk), or a relative risk reduction
- Measure of uncertainty around the treatment effect estimate – e.g., confidence interval and (usually) a p-value.

Subgroup analyses

Sometimes, additional analyses that were not specified in the original trial protocol are carried out; e.g., to investigate the effect of the intervention in different age groups or different disease severities. The problem with such analyses is that we could carry out a very large number of possible comparisons (until we find a positive association), and then focus in our report on the result that seems interesting **after** we have looked at the data, leading to significant bias. As previously discussed, a large number of tests can lead to false positive results, leading to unreliable associations.

IX. What else needs to go in the Methods?

Two important details not covered by the CONSORT guidelines but is essential in any clinical trial report are details of:

- Ethical approval obtained for the trial
- Informed patient consent

In summary, this article focused on the CONSORT guidelines for reporting the Methods section of trials. The three important questions one must consider in appraising a clinical trial are: (1) Was the trial **design** valid? (2) Was the **conduct** of the trial valid? and (3) Was the **analysis** of the trial findings valid? Investigators should be able to answer these questions in their final reports, and most of the answers to these questions will be found in the Methods section. It is then imperative that investigators report their trial methods thoroughly and accurately to allow readers to conclude that the results of the trial are likely to be valid.