Reporting the results of a controlled trial

Naveed Zafar Janjua,[1] Junaid Ahmad Bhatti,[2] Faiza Rizwan[3]

Randomized controlled trials (RCTs) are considered the gold standard for evaluation of healthcare interventions. Biases introduced by inadequate methods, however, affect rigor of evidence from RCTs. Thus, a complete and transparent reporting of methods and results is needed to help readers to evaluate the quality of evidence from RCTs. Results section is the most important part of the manuscript reporting findings from an RCT where the effect of an intervention on outcomes is presented along with necessary information needed for interpretation of results. CONSORT (Consolidated Standards of Reporting Trials)statement provides a framework of essential elements for reporting of RCT.[1] Recent reviews assessing quality of reporting of RCTs have suggested that although CONSORT statement has improved reporting consistency, not all published papers adhere to reporting standards and completeness of reporting is suboptimal.[2-6]

In this second commentary of our two part series,[7] we provide a summary of essential elements of an RCT results that should be reported in the manuscript. We have drawn on CONSORT statement for this commentary.[1,8] We have also included the fictive example from our previous commentary which refers to a comparison of clinical efficacy of drug "B" with drug "A" using randomized controlled design.[7] The essential subsections of RCT results described here are participants' flow, baseline characteristics, primary analyses, additional analyses, adherence, and harmful effects.

Participant flow through the study

The RCT manuscript should describe participant flow starting with numbers screened for eligibility to those included in the primary analysis, presenting all exclusions and losses and reasons for losses throughout the study. This information is important for interpretation of results to assess validity of findings and potential for selection bias related to withdrawal from the study after

....

[1]British Columbia Centre for Disease Control, University of British Columbia, School of Population and Public Health, Vancouver, Canada, [2]McGill University, Douglas Hospital Research Centre, Montreal, Canada, Department of Emergency Medicine, The Aga Khan University, Karachi, Pakistan, [3]Department of Family Medicine, McGill University, Montreal, Canada.
Correspondence: Naveed Zafar Janjua. Email: naveed.janjua@bccdc.ca

randomization/treatment allocation, loss to follow-up across study arms, and exclusion from main analysis, all impacting results of the study. The CONSORT statement recommends a figure presenting the flow of participants.[1,8] In this figure, authors should provide number of participants screened for eligibility and provide number for major conditions for ineligibility. Then in the diagram, authors should describe that of eligible participants how many were randomized intervention or comparator, and briefly describe the reasons of non-randomization. Then, the diagram should include the numbers of those who had received intervention or comparator, and the numbers of those who completed study treatments (intervention or control). A description of those completing planned follow-up or not by treatment arm (intervention or control), and those included in the final analyses should be available in the diagram and text. Periods of enrollment and follow-up provide historical context for interpretation and relevance of findings, and therefore must be included in methods or results section. Please see Figure-1 adapted from CONSORT guidelines based on our fictive example of comparison of drugs "A" and "B." The diagram is divided into four sections which are enrollment, allocation, follow up and analyses to describe exclusions and losses and the reasons for losses during each step of the study.

Baseline characteristics of participants

Table providing comparison of characteristics of treatment groups at baseline is an important part of the RCT results' section. It summarizes for a reader information necessary to assess relevance/generalizability of findings to their population of interest. Baseline characteristics table is also used to assess balance of prognostic factors across treatment groups (intervention or control) providing an indication on adequacy of randomization process.[9] Usually important variables such as age, gender, and important clinical variables are presented in the baseline characteristics tables. Please see Table-1 based on our example. The qualitative variable i.e., gender is described as numbers and proportions whereas the quantitative variable i.e., age is described as mean and standard deviation.
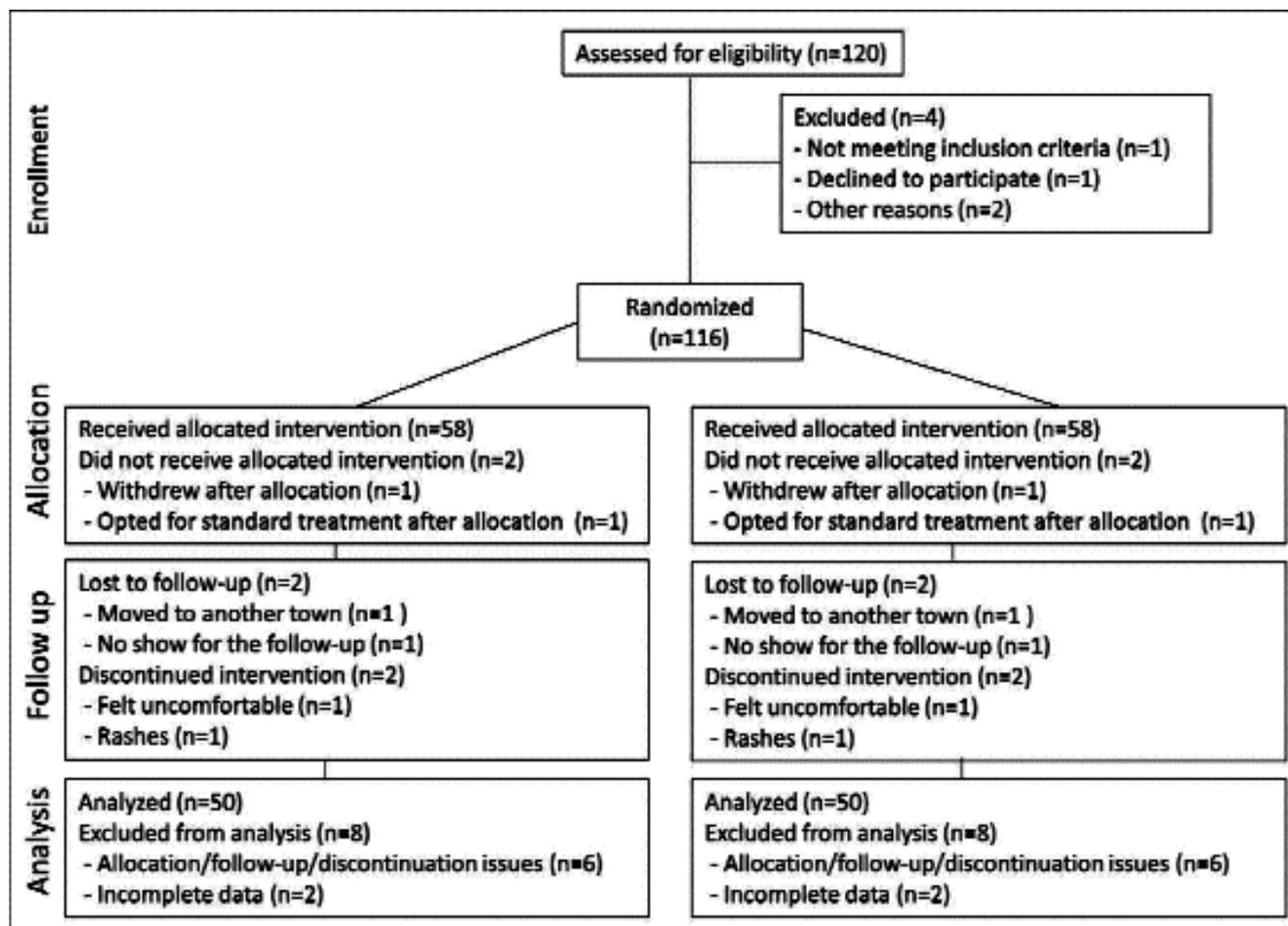
Figure: Flow diagram of the fictive randomized controlled trial.

Table-1: Example - baseline participant profile of the fictive randomized controlled trial.

	Drug B		Drug A	
	N	%	N	%
Gender				
Male	25	50.0	25	50.0
Female	25	50.0	25	50.0
	Mean	SD	Mean	SD
Age (in years)	25	5	25	5

SD: Standard deviation.

Primary analyses

For each primary and secondary outcome, present summary of outcomes such as number of participants who developed outcomes, total sample size per group and along with effect size and their 95% confidence interval or other statistics on precision. For binary outcomes, effect size is estimated as risk ratio, odds ratio, risk difference or hazard ratio while for continuous outcomes difference of means is used, along with confidence interval as an estimate of precision. All planned primary and secondary analyses should be reported regardless of their statistical significance. Both absolute (risk difference) and relative (risk ratio or odds ratio, hazard ratio) measures of effect should be presented. Usually authors present relative measures, but absolute measures provide public health significance of the findings for population under study. Table-2 describes the results of our fictive example. We have only presented absolute risk difference for simplicity reasons. For instance, the table showed that drug "B" had 30% higher efficacy than drug "A" for improvement in clinical signs (our primary outcome measure). The secondary outcome measures and safety-related variables could also be described in a similar way.

Table-2: Example - clinical efficacy and safety results of the fictive randomized controlled trial.

	Drug B		Drug A		Risk difference in %
	N	%	N	%	(95% confidence intervals)
Efficacy					
Primary outcome					
Clinical signs improved	30	60.0	15	30.0	30.0% (20.0%-40.0%)
Secondary outcome					
Subjectively felt better	35	75.0	20	40.0	35.0% (25.0%-45.0%)
Safety					
Side effects	2	4.0	2	4.0	0%

Additional analyses

Many times authors present additional analyses not pre-specified in the protocol. Multiple analyses carry risk of false significance by chance alone. Common form of additional analysis is subgroup analyses e.g., in our cases results can be presented for male and female participants separately. It has been recommended that only pre-specified analyses should be conducted and reported.[1] If difference across subgroups is of interest then test of interaction could be used or stratified analyses be reported. Tests of interactions are known to have limited power, however. For all additional analyses, authors should specify why they might have decided to conduct additional analyses.

If sample size of an RCT is large enough then it is expected that randomization will balance the characteristics of participants at baseline across groups. Sometime sample sizes are small and an imbalance of baseline characteristics is found. To account for unbalanced prognostic factors or known prognostic factors, authors adjust their analyses for baseline characteristics.[9] It is recommended that if an adjustment is performed, both unadjusted and adjusted results should be presented along with reason for adjustment, whether it was planned or decided at the time of analysis.[8]

Adherence

Adherence is the degree to which a participant correctly follows medical advice or a study participant takes the assigned treatment as prescribed. Level of adherence may affect the outcome of an intervention; low adherence may lead to low efficacy level. Furthermore, adherence also provides an indication on intervention acceptability and safety. Review of studies on oral therapeutics found that about half of the RCTs reported adherence of interventions and it was more commonly reported in negative RCTs, suggesting that reporting of adherence is incomplete and not consistent.[10] Given critical nature of this information for interpretation of results, RCTs should include information on how adherence was defined, measured and analyzed (calculation of numerator, denominators, and period off treatment e.g., drugs), and level of intervention adherence across groups and over time.

Safety and adverse effects

Overall effect of intervention is assessed as a balance between benefits and risks. In some RCTs safety may be the primary outcome of interest but even if safety or adverse events are not of primary interest, harmful effects of interventions across groups should be reported. For example, we have included the safety related information in the flow diagram and Table 2. RCTs are the best design to separate adverse/safety events that are related to conditions being treated from those from intervention though may not detect rare events. A review of trials has indicated incomplete and inconsistent reporting of adverse events.[11] Details on reporting of adverse events are provided in an extension of CONSORT statement.[12] Briefly, all adverse events assessed should be listed and defined, and assessment method should be reported. For each study group, number of participants who developed an event and total participants who were assessed and the absolute risk and number of participants withdrawn should be reported.[8]

Conclusion

The aim of the two commentaries is to provide authors an overview of what is expected in an RCT manuscript. Consistent and complete reporting using CONSORT statement is the standard everywhere when it comes to publishing an RCT. The Journal of Pakistan Medical Association supports the CONSORT statement and strongly recommends its use when submitting an RCT to this journal. We also recommend guidance and review from senior colleagues while drafting results as this improves the clarity of manuscript.

References

1. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c332.

2. Plint AC, Moher D, Morrison A, et al. Does the CONSORT checklist improve the quality of reports of randomised controlled trials? A systematic review. The Medical Journal of Australia 2006; 185: 263-7.

3. Toulmonde M, Bellera C, Mathoulin-Pelissier S, Debled M, Bui B, Italiano A. Quality of randomized controlled trials reporting in the treatment of sarcomas. Journal of clinical oncology: Official Journal of the American Society of Clinical Oncology 2011; 29: 1204-9.

4. Turner L, Shamseer L, Altman DG, Schulz KF, Moher D. Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. Systematic reviews 2012; 1: 60.

5. Milette K, Roseman M, Thombs BD. Transparency of outcome reporting and trial registration of randomized controlled trials in top psychosomatic and behavioral health journals: A systematic review. Journal of Psychosomatic Research 2011; 70: 205-17.

6. Ghimire S, Kyung E, Kang W, Kim E. Assessment of adherence to the CONSORT statement for quality of reports on randomized controlled trial abstracts from four high-impact general medical journals. Trials 2012; 13: 77.

7. Bhatti JA, Akhtar U, Azad A, Janjua NZ. Writing the introduction and methods of a controlled trial. J Pak Med Assoc 2014; 64: 720-2.

8. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Bmj 2010; 340: c869.

9. Peduzzi P, Henderson W, Hartigan P, Lavori P. Analysis of randomized controlled trials. Epidemiologic reviews 2002; 24: 26-38.

10. Zhang Z, Peluso MJ, Gross CP, Viscoli CM, Kernan WN. Adherence reporting in randomized controlled trials. Clinical trials 2013.

11. Pitrou I, Boutron I, Ahmad N, Ravaud P. Reporting of safety results in published reports of randomized controlled trials. Archives of internal medicine 2009; 169: 1756-61.

12. Ioannidis JP, Evans SJ, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Annals of internal medicine 2004; 141: 781-8.