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ORIGINAL ARTICLE

Pre-specification of statistical analysis approaches in published clinical trial protocols was inadequate

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Abstract

Objectives: Results from randomized trials can depend on the statistical analysis approach used. It is important to prespecify the analysis approach in the trial protocol to avoid selective reporting of analyses based on those which provide the most favourable results. We undertook a review of published trial protocols to assess how often the statistical analysis of the primary outcome was adequately prespecified.

Methods: We searched protocols of randomized trials indexed in PubMed in November 2016. We identified whether the following aspects of the statistical analysis approach for the primary outcome were adequately prespecified: (1) analysis population; (2) analysis model; (3) use of covariates; and (4) method of handling missing data.

Results: We identified 99 eligible protocols. Very few protocols adequately prespecified the analysis population (8/99, 8%), analysis model (27/99, 27%), covariates (40/99, 40%), or approach to handling missing data (10/99, 10%). Most protocols did not adequately predefine any of these four aspects of their statistical analysis approach (39%) or predefined only one aspect (36%). No protocols adequately predefined all four aspects of the analysis.

Conclusion: The statistical analysis approach is rarely prespecified in published trial protocols. This may allow selective reporting of results based on different analyses.

Keywords: Randomized controlled trial; Clinical trial; Statistical analysis; Pre-specification; Analysis switching

1. Introduction

Well-designed clinical trials are the gold standard for evaluating the efficacy and safety of health care interventions. It is widely agreed that the trial methodology should be prespecified in the protocol to avoid issues such as selective reporting of results [1,2]. Previous research has shown that failure to adequately prespecify trial outcomes can lead to ‘‘outcome switching,’’ where statistically significant outcomes are more likely to be reported than nonsignificant ones, leading to exaggerated treatment effect sizes and misleading conclusions [3–13].

Similar issues are faced when specifying a statistical analysis plan (SAP) for the trial [14–17]. The analysis approach should be chosen to address the study research question and involves a series of decisions, including identifying the participants to be included in the analysis, the statistical model to be used, and the method of handling missing data [1,2]. Different approaches could lead to different results and hence influence the interpretation of the trial. It is therefore important that these decisions are prespecified before seeing the trial data because lack of prespecification may affect the trial’s validity by allowing investigators to selectively report the analysis approach that provides the most favorable results [18].

The International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-E9 guidelines state that the trial protocol should contain ‘‘all the principal features of the proposed confirmatory analysis of the primary variable(s)’’ [19]. Similarly, the SPIRIT (Standard Protocol Items: Recommendations for Interventional

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What is New?

- The chosen statistical analysis approach can affect results from randomized trials. Pre-specification of the analysis approach can guard against selective reporting of analyses; however, it is not known how often the statistical analysis approach is adequately prespecified in trial protocols.
- Our review found that no protocols adequately prespecified their entire statistical analysis approach for the primary outcome. The analysis population and the approach to handling missing data had the lowest rates of pre-specification; however, the analysis model and the use of covariates were also poorly prespecified.
- An exploratory re-analysis of two trials found that changing the analysis approach based on the trial data could lead to either statistically significant or nonsignificant results, depending on what the investigator wished to show.
- Many trials may be at risk of selective reporting of statistical analyses, which could affect the interpretation of study results.

Trials) guidelines state that ''The protocol should prespecify the main (''primary'') analysis of the primary outcome, including the analysis methods to be used for statistical comparisons; precisely which trial participants will be included; and how missing data will be handled'' [2]. The aims of this study were to evaluate whether statistical analysis approaches for the primary outcome were being adequately prespecified in published trial protocols, with a particular focus on the analysis population, analysis model, use of covariates, and handling of missing data.

2. Methods

2.1. Review of published protocols

We conducted a review of published trial protocols to assess how well statistical analysis approaches were being prespecified. Protocols of randomized controlled trials conducted in humans and published in English were eligible for inclusion, regardless of therapeutic area or nature of the intervention. The main exclusion criteria were pilot and feasibility trials, and phase 1 or phase 2 trials. This was because we wanted to focus on large, phase III trials that could affect clinical practice. We also excluded articles with a primary outcome of cost-effectiveness and any articles with published results.

We identified articles in a PubMed search of titles and abstracts using the terms ''protocol'' or ''randomi*'' and excluding articles that included the terms ''pilot,'' ''feasibility,'' ''phase 1,'' ''phase one,'' ''phase i,'' ''phase 2,'' ''phase two,'' and ''phase ii'' in the title. We restricted the search to articles published in November 2016. One author (L.G.) initially screened abstracts to identify appropriate full-text articles. All full-text articles were screened independently and in duplicate by two authors (L.G. and B.C.K.) to ensure they met the inclusion criteria.

Two authors (L.G. and B.C.K.) independently extracted data for all included protocols onto a standardized, prepiloted form. We extracted information on whether the following elements were adequately predefined in relation to the primary outcome: (1) the analysis population to be used; (2) the analysis model to be used; (3) the covariates to be included in the model; and (4) the method of handling missing data. Further details on these elements are available in Table 1. Discrepancies between extractors were resolved by discussion.

For protocols that did not specify a primary outcome or specified multiple primary outcomes, we used the outcome used in the sample size calculation. If no sample size calculation was reported, or if the sample size calculation was performed for multiple primary outcomes, we used the first outcome listed in the protocol abstract.

We classified each element as either (1) adequately predefined; (2) incompletely predefined; or (3) not mentioned. Elements were classified as adequately predefined if they contained sufficient detail to allow replication by a third party and would not allow the analyst to choose the analysis approach subjectively based on the trial data. Elements were classified as incompletely predefined if some detail was included but not enough to allow replication by a third party (eg, if a per-protocol population was specified without defining under which circumstances patients would be excluded from the analysis) or if it allowed the analyst to choose the analysis approach subjectively based on the data (eg, if the analyst was to choose between multiple analysis models based on the fit of the data, but no objective or reproducible method for choosing was given). Elements were classified as not mentioned if they were not addressed at all in the text.

2.2. Exploratory re-analysis of the OPTIMISE and TRIGGER trials

We also conducted an exploratory re-analysis of two randomized trials that were recently completed by two authors (R.P. and V.J.) in order to assess the impact that changing the analysis approach could have on results. Specifically, we wished to see how extreme the difference in results for each trial could be if the analyst was choosing the analysis approach based on the trial data to obtain a specific result (to demonstrate either as large or as small of an effect as possible).

For each trial, we chose an initial reference method of analysis. We then varied different aspects of the analysis in turn, to obtain either a larger or smaller effect than that