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REVIEW ARTICLES

Optimism bias leads to inconclusive results—an empirical study

Benjamin Djulbegovic[a,b,*], Ambuj Kumar[a,b], Anja Magazin[b], Anneke T. Schroen[c], Heloisa Soares[d], Iztok Hozo[e], Mike Clarke[f], Daniel Sargent[g], Michael J. Schell[b]

[a]*Department of Medicine, Center for Evidence-based Medicine & Health Outcomes Research, University of South Florida, Tampa, FL, USA*
[b]*Department of Hematology, Health Outcomes & Behavior, Moffitt Cancer Center & Research Institute, Tampa, FL, USA*
[c]*Department of Surgery, University of Virginia, Charlottesville, VA, USA*
[d]*Department of Internal Medicine, Mount Sinai Medical Center, Miami, FL, USA*
[e]*Department of Mathematics, Indiana University North, Gary, IN, USA*
[f]*UK Cochrane Centre, National Institute for Health Research, Oxford, UK*
[g]*Department of Biostatistics, Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA*

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Abstract

Objective: Optimism bias refers to unwarranted belief in the efficacy of new therapies. We assessed the impact of optimism bias on a proportion of trials that did not answer their research question successfully and explored whether poor accrual or optimism bias is responsible for inconclusive results.

Study Design: Systematic review.

Setting: Retrospective analysis of a consecutive-series phase III randomized controlled trials (RCTs) performed under the aegis of National Cancer Institute Cooperative groups.

Results: Three hundred fifty-nine trials (374 comparisons) enrolling 150,232 patients were analyzed. Seventy percent (262 of 374) of the trials generated conclusive results according to the statistical criteria. Investigators made definitive statements related to the treatment preference in 73% (273 of 374) of studies. Investigators' judgments and statistical inferences were concordant in 75% (279 of 374) of trials. Investigators consistently overestimated their expected treatment effects but to a significantly larger extent for inconclusive trials. The median ratio of expected and observed hazard ratio or odds ratio was 1.34 (range: 0.19–15.40) in conclusive trials compared with 1.86 (range: 1.09–12.00) in inconclusive studies ($P < 0.0001$). Only 17% of the trials had treatment effects that matched original researchers' expectations.

Conclusion: Formal statistical inference is sufficient to answer the research question in 75% of RCTs. The answers to the other 25% depend mostly on subjective judgments, which at times are in conflict with statistical inference. Optimism bias significantly contributes to inconclusive results. © 2011 Elsevier Inc. All rights reserved.

Keywords: Optimism bias; Inconclusive trials; Randomized controlled trials; Bias; Study design; Systematic review

1. Introduction

In the conduct of randomized controlled trials (RCTs), ethical and scientific principles require a reasonable expectation that the research questions will be answered, thus contributing to general knowledge resulting in societal benefit [1]. The Declaration of Helsinki states that clinical trials must be designed to facilitate successful completion and, therefore, prohibits "unethical exposure of participants to the risk and burdens of human research" [2]. Trials that fail to answer the questions they were designed to answer—inconclusive trials—are contrary to one of the key rationales for RCTs, namely, to resolve disputes about competing treatment alternatives [3–7]. These trials generate little new knowledge about the relative effects of the treatments, because the research question is left unanswered and the evidence remains consistent with the hypothesis before the trial began. The proportion of RCTs in oncology that generate reasonably conclusive statements is unknown. Theoretically, two reasons can be

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* Corresponding author. Department of Medicine, Clinical Translational Science Institute, Center for Evidence-based Medicine and Health Outcome Research, University of South Florida Health Clinical Research, 13101 Bruce B. Downs Boulevard, CMS3057, Tampa, FL 33612, USA.

E-mail address: bdjulbeg@health.usf.edu (B. Djulbegovic).

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Key finding
Optimism bias refers to unwarranted belief in the efficacy of new therapies and significantly contributes to inconclusive results. Formal statistical inference alone is not sufficient to answer the research question. The answers to the research question also depend on subjective judgments, which at times are in conflict with statistical inference.

What this adds to what was known?
How often and why results from randomized clinical trials are inconclusive and whether there is a concordance between statistical inferences and investigators' global judgments in phase III randomized controlled trials is not known. This is the first empirical study to show the reasons for inconclusive findings.

What is the implication and what should change now?
Trial design should not rely on an intuitive approach but should include a detailed rationale for the chosen effect size, ideally based on systematic review of the existing evidence on the topic.

offered as explanations for publications of inconclusive trials: (1) inadequate patient accrual [8] and (2) optimism bias—an unwarranted belief in the efficacy of new treatments [9]. By overestimating the treatment effect of a particular therapy, trials are designed with insufficient power to detect the actual, smaller treatment effects between tested therapies.

In determining whether a trial provides conclusive results, researchers usually use two inferential approaches: (1) hypothesis-driven, formal statistical or mathematical rules aimed to assess the impact of the experimental treatment on the primary outcome of interest in comparison with that of a control and (2) global, subjective assessments of the relative merits of the treatments, which are based on an integration of various factors, including data from non−primary endpoints and external factors, such as treatment toxicity, ease of application, resource use, and others. Thus, the overall judgment on the merits of a trial's results takes into account all relevant observations, many of which may have not been anticipated a priori. Information on the extent to which these two inferential approaches influence published conclusions in clinical trials is lacking.

We sought to examine how frequently completed phase III oncology trials generate conclusive results, quantify the impact of optimism bias on trial results and assess the nature of inferential processes underlying the conclusions drawn from a trial. Given the important role of the National Cancer Institute (NCI)-funded Clinical Trials Cooperative Groups in advancing cancer care, we elected to focus our study on phase III oncology trials performed by these groups.

2. Methods

We studied all consecutive phase III RCTs conducted, completed, and published between 1955 and 2006 by eight NCI-sponsored cooperative oncology groups (NCI-COG): Children's Oncology Group, National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, North Central Cancer Treatment Group, Gynecology Oncology Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, and Southwest Oncology Group. Details regarding publication status, quality, and overall distribution of outcomes from these trials have been reported elsewhere [10−13]. Trials for which full protocols were not available or trials with missing data on the expected and observed treatment effects or on patient accrual were excluded. We also excluded trials involving multiple comparisons (12%), because our analysis would have required the reuse of data from the multiple treatment groups, thereby violating the independence criterion for statistical analysis. RCTs that were closed early because of poor accrual (arbitrarily defined as the trials that accrued less than 40% of the predicted accrual) [10,13] were also excluded.

2.1. Determination of trial conclusiveness

Trials were categorized as conclusive or inconclusive based on two criteria: statistical and investigators' judgments.

2.1.1. Statistical criteria

Conclusive trials included trials with a statistically significant result. Conclusive trials also included "true-negative" trials, in which the observed effect and the 95% confidence interval (CI) were entirely within the predetermined limit of equivalence. Conversely, inconclusive trials were defined as having the treatment effect and the 95% CI crossing the line of no difference and both limits of predetermined equivalence. There is debate about whether results that favor one treatment over another but whose 95% CIs cross the line of no difference and only one line of equivalence should be considered conclusive or inconclusive [14]. We took a conservative approach and categorized these trials as conclusive, labeling them as "true negatives" regardless of the direction of the effect. Thus, we considered statistically significant (favoring new or standard treatment) and true-negative results as conclusive findings and all other results to be inconclusive. Figure 1 illustrates the methods used to determine the designation of conclusive and inconclusive trials.

Because minimally important (clinically meaningful) treatment differences were rarely specified in the protocols, we based the predetermined limits of equivalence on published estimates related to what can be considered small, moderate, or large treatment effects in oncology [15]. We defined a small

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