The uncertainty principle and industry-sponsored research

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Summary

Background Reporting of pharmaceutical-industry-sponsored randomised clinical trials often result in biased findings, either due to selective reporting of studies with non-equivalent arms or publication of low-quality papers, wherein unfavourable results are incompletely described. A randomised trial should be conducted only if there is substantial uncertainty about the relative value of one treatment versus another. Studies in which intervention and control are thought to be non-equivalent violates the uncertainty principle.

Methods We examined the quality of 136 published randomised trials that focused on one disease category (multiple myeloma) and adherence to the uncertainty principle. To evaluate whether the uncertainty principle was upheld, we compared the number of studies favouring experimental treatments over standard ones. We analysed data according to the source of funding.

Findings Trials funded solely or in part by 35 profit-making organisations had a trend toward higher quality scores (mean 2·94 [SD 1·3]; median 3) than randomised trials supported by 95 governmental or other non-profit organisations (2·4 [0·8]; 2; p=0·06). Overall, the uncertainty principle was upheld, with 44% of randomised trials favouring standard treatments and 56% innovative treatments (p=0·17); mean and median preference evaluation scores were 3·7 (1·0) and 4. However, when the analysis was done according to the source of funding, studies funded by non-profit organisations maintained equipoise favouring new therapies over standard ones (47% *vs* 53%; p=0·608) to a greater extent than randomised trials supported solely or in part by profit-making organisations (74% *vs* 26%; p=0·004).

Interpretation The reported bias in research sponsored by the pharmaceutical industry may be a consequence of violations of the uncertainty principle. Sponsors of clinical trials should be encouraged to report all results and to choose appropriate comparative controls.

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Introduction

There is concern that clinical trials sponsored by the pharmaceutical industry result in biased findings.[1,2] Two reasons have been suggested. First, the quality of research sponsored by profit-making firms may be poor. For example, low-quality trials overestimate therapeutic benefit by an average of 34%.[3] Second, it could be that industry will sponsor only those research projects that are likely to be positive, thus violating the uncertainty principle—a fundamental scientific and ethical principle for running randomised clinical trials.[4,5] The uncertainty principle, or equipoise, states that the patient should be enrolled in a randomised controlled trial only if there is substantial uncertainty ("equal bet")[4–9] about which of the trial treatments would benefit a patient most. To distinguish between these possibilities we assessed the influence of the source of funding on the quality of randomised trials and whether the uncertainty principle was adhered to in their conduct.

Methods

Trials

We reviewed therapeutic studies in patients with multiple myeloma. By focusing on one disease, existing knowledge that plays a key role in the planning and design of the study can be better ascertained. Using the Cochrane search strategy, we identified all randomised trials for multiple myeloma from the period from 1996 to 1998.[10] 113 articles on 136 trials were identified. The quality of each trial was assessed with the scale of Jadad and colleagues.[3,11] This scale has a score from 0 to 5 and a score of or lower than 2 is poor quality.[3]

Equipoise

Despite the importance of the uncertainty principle for the design and conduct of randomised trials, no empiric measure has been developed to assess equipoise. We hypothesise that there must exist some relation between equipoise and ultimate outcome of these trials. If the uncertainty principle is observed, we would expect over time to find no significant difference in the number of results favouring experimental treatments versus standard ones.[4] Thus, the empiric determination of the outcome of trials should serve as a surrogate measure of equipoise. For equipoise to hold, expectation of competing therapeutic alternatives must be equal in terms of balancing both benefit and harm.[4] In addition, equipoise is not necessarily the same as the expectation that a null hypothesis would be accepted or rejected.[4]

The null hypothesis is often focused on a single dimension of therapeutic intervention (eg, efficacy), while for equipoise to exist, treatment A must be equal to treatment B in the sense that differences in efficacy will be balanced by harm caused.[4,12] There is debate about the usage of "equipoise" versus the principle of "uncertainty" as an entry criterion for a randomised trial.[13] We use the terms interchangeably because they are not mutually exclusive. Equipoise simply represents the point (or distribution) of maximum uncertainty (maximum uncertainty occurs when probability of expected outcomes are equal).

The best way to find if equipoise exists is to report preferences between innovative and standard therapies in the manner that the original investigators reported them.[14] This approach captures the estimated trade-off between efficacy and toxicity of competing therapies better than analysis focusing on formal testing of a null hypothesis. We adopted the proposal of Gilbert and colleagues,[14] and Colditz and colleagues,[15] to rate the reported conclusions from each randomised trial on a six-point scale: 1=standard treatment highly preferred; 2=standard preferred to innovation; 3=about equal, innovation a disappointment; 4=about equal, innovation a success; 5=innovation preferred to standard; and 6=innovation highly preferred.

A value of 3·5 represents no difference between the two types of therapy; this point is used as an empiric measure of equipoise. We also assessed equipoise by computing the proportion of studies with a score of 3 or below versus those with a score of 4 or higher. Equipoise exists if the number of studies in which new therapies are preferred (those with a score ≥ 4) over standard therapies (those with a score ≤ 3) is similar. The unit of analysis was the randomised controlled trial. However, since some papers described more than one randomised trial, we also repeated the analysis with each article as the unit of analysis. When this was done, we assessed just the one randomised trial we felt was most important. Since this manner of analysis did not significantly change the results from the assessment whereby randomised trials were used as the unit of analysis, only the latter results are reported.

Studies were assessed by a single investigator unaware of funding source. Every effort was made to rate the study according to the original investigators' conclusions. In most cases the interpreting authors' conclusions about the values of the treatment were deduced without difficulty. However, in 16 (12%) out of 136 studies, a consensus among the investigators was used to arrive at the final rating score. In reaching consensus, the investigators were unaware of the source of funding. In addition, the first author independently validated the findings of an additional 40 (29%) reports.

The source of funding was obtained from each paper or directly from the investigators in 130 (96%) out of 136 studies. An association with a manufacturer was defined as acknowledgment of drug supplied or grant support by a pharmaceutical company. Non-manufacturer-associated trials were sponsored by federal, national, or other non-profit-making grant agencies. One paper reported two randomised controlled trials in which the first randomisation (induction treatment) was judged to be funded by a public agency and the second randomisation (maintenance with interferon) was sponsored by a pharmaceutical company. Overall, 27% of the studies were funded by commercial sponsors.

Since it has been asserted that control arms with placebo or no therapy may represent an inferior form of comparison[16] we also assessed equipoise separately for those trials with active treatment controls versus those where the comparison was either placebo or no therapy.

Statistical analyses

Standard summary measures were estimated and hypothesis testing between groups was done according to the source of funding and quality scores. The variables of interest (Jadad's score and therapeutic evaluation score) did not conform to a normal distribution ($p<0{\cdot}0001$ by Wilks-Shapiro test). Therefore, the Mann-Whitney test was used for testing the null hypothesis of no association between funding source and the measures of interest. The χ^2 test was used to test for differences in proportions. Two-sided tests of the null hypothesis and significance based on a $p\leq 0{\cdot}05$ were used throughout.

Results

The overall quality of the randomised trials was poor (mean Jadad score 2·5 [SD 1]). 53 (39%) and 45 (33%) of the trials had scores of 2 and 3, respectively, accounting for 98 (72%) of the trials. Only seven trials (5%) had the maximum score of 5.

Figures 1 and 2 show the rating scores for all trials, with 56% of the studies reporting success for innovative treatments and 44% favouring standard therapy ($p=0{\cdot}170$). The mean evaluation score was 3·7 (SD 1) with a median rating of 4, slightly favouring new therapies. Scores ranged from 2 (12%) to 6 (1·5%) with 80 (59%) of the 136 studies having a score 3 or 4, which indicates equipoise in most studies. When the analysis was done according to the source of funding, equipoise was seen in studies funded by non-profit-making organisations (53% *vs* 47%, $p=0{\cdot}608$). However, in trials supported solely or in part by commercial organisations new treatments were significantly favoured over standard treatments (74% vs 26%, $p=0{\cdot}004$,

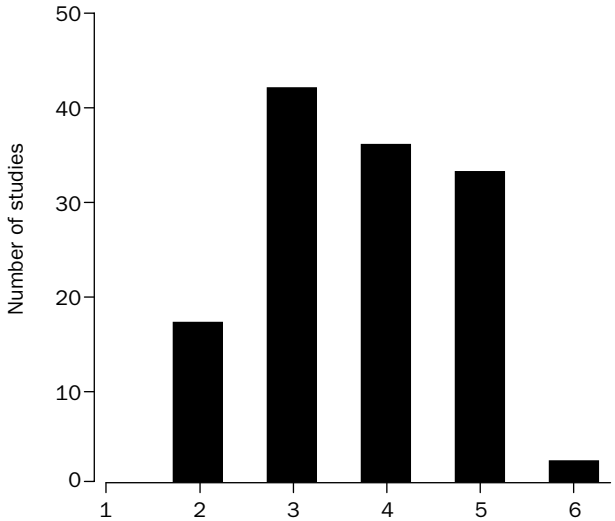

Figure 1: **Distribution of scores evaluating success of innovative therapies over standard ones in 136 randomised trials in multiple myeloma**
Scores from 4–6 denote that innovative treatments were better, while scores 1 to 3 indicate that standard treatments were preferred.

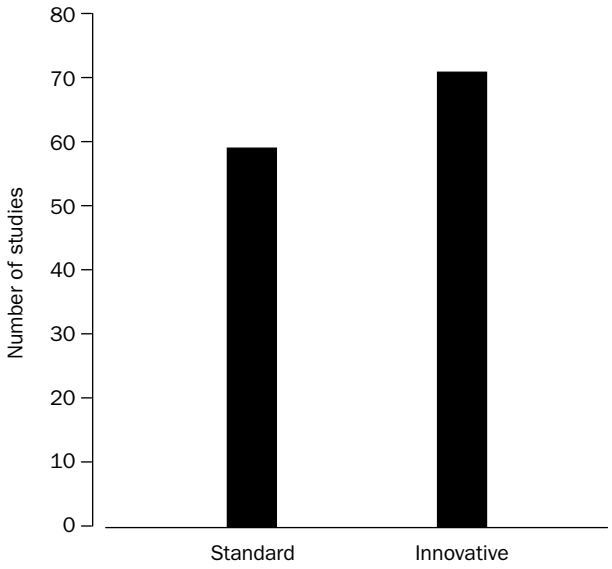

Figure 2: **Proportion of randomised trials in treatment of multiple myeloma showing success of innovative (56%) and standard (44%) therapies**
p=0·170.

figure 3, A). Similarly, the median and mean scores were significantly higher for studies funded by the pharmaceutical industry (5 *vs* 3; 4·1 [1] *vs* 3·5 [1], p=0·003).

Trials funded solely or in part by commercial organisations (n=35) had a trend towards higher quality Jadad scores (mean 2·94 [1·3], median=3) than those supported solely by governmental or other non-profit organisations (n=95, mean 2·4 [0·8]; median=2, p=0·06, figure 3, B). A greater proportion of industry-sponsored studies compared innovative treatment to either placebo or no therapy than did studies sponsored by public resources (60% *vs* 21%, p<0·001, figure 3, C). Equipoise was seen in the studies in which innovative treatments were compared with active standard therapies irrespective of the source of funding (innovative *vs* active standard: 59% *vs* 41% [p=0·133] in public-sponsored studies, and 50% *vs* 50% [p=1·00] in industry-sponsored trials). However, innovative treatments were favoured when the standard comparative treatment was placebo or no therapy (90% *vs* 10% [p<0·001] in commercially supported trials, and 70% *vs* 30% [p=0·074] in research sponsored by public funds).

Discussion

Chalmers[17] previously asked "what is the probability that new treatments will be superior to standard ones?" Gilbert and colleagues[14] reviewed 46 randomised trials that compared surgical and anaesthesia treatments. 49% of innovations were successful when compared with standard treatment. Colditz and colleagues[15] examined 36 randomised trials and found a 61% chance that a patient who received the new therapy would fare better than a patient receiving standard therapy. Machin and colleagues[18] examined 32 Medical Research Council trials. 45% of trials favoured innovative treatment at the 10% level of significance. These studies, as well as our study empirically confirm investigators often do not know in advance what they will discover,[19] reflecting adherence to the uncertainty principle in the design and conduct of randomised trials. However, our results in multiple myeloma indicate that this important principle can be violated, particularly when randomised trials are sponsored by or conducted on behalf of the pharmaceutical industry. We found similar findings in randomised trials of erythropoietin.[20]

There are at least two possible mechanisms for the observed violation of equipoise in commercially-funded studies. If violations occur because of an increased number of studies favouring innovations (positive studies), the implication is that treatments that are more efficacious than standard therapy are being tested and patients are being enrolled into trials with inferior comparative therapies.[4,16] What constitutes substandard controls can only be addressed when each trial is designed. We found that more industry-sponsored studies used placebo or no therapy as comparator than the publicly funded studies. The possibility of a substandard comparison was also highlighted in studies with fluconazole, where for-profit sponsored studies frequently compared this agent given intravenously against the oral, poorly absorbed drug nystatin, thus creating a bias in favour of fluconazole.[21,22] We are not arguing here that placebo comparisons should not be used in randomised trials;[23] we only wish to highlight that trials should not be done without attention to the uncertainty principle. Investigators should be particularly vigilant about applying the uncertainty principle when using a placebo or no-therapy control.

Potential and real conflicts of interest may operate in industry-sponsored research.[24,25] However, the bias in

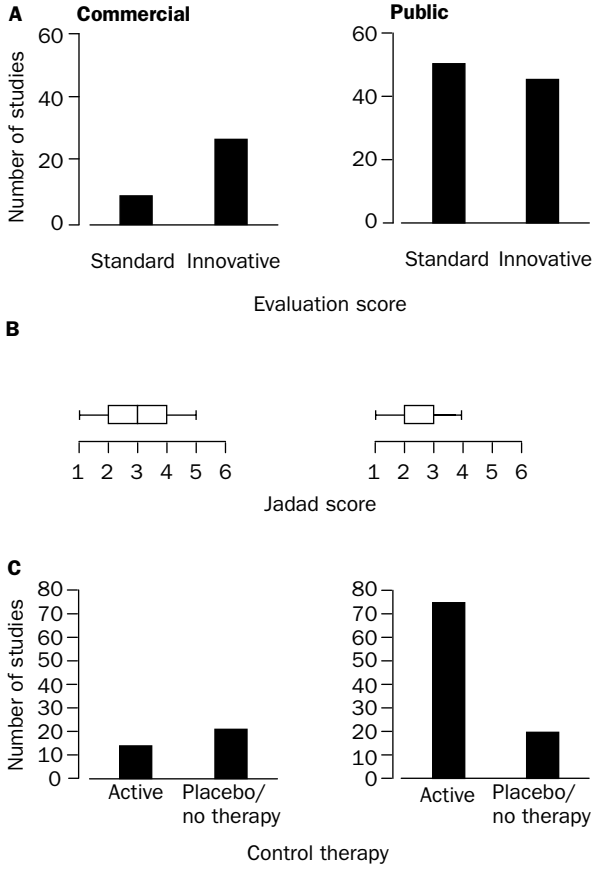

Figure 3: **Effect of funding source**
A=Proportion of trials showing success of innovative and standard therapies by source of funding. B=Quality of trials measured by the Jadad score. C=Number of trials in which control arm was placebo/no-therapy or active treatment.

research sponsored by pharmaceutical companies is not likely to be due to poor-quality studies. We found that industry-sponsored research is not of lower quality than sponsored by public resources, and may, in fact, be of even higher quality. Similar results were reported by Kjaergard and colleagues.[26] Many international, national, and local regulations are intended to ensure proper conduct in clinical trials.

The increased proportion of successful interventions among commercially-funded randomised trials more likely means that preferential support was given to trials that had a greater chance of favouring one intervention over another. Provisions about the type, design, and conduct of clinical research are easier to implement than requirements about the validity of the scientific questions that are being asked. Institutional review board approval is usually required related to the conduct of the study without review of the scientific merit of the proposed research. Since preserving the principle of equipoise is important to society and patients,[4] increased scrutiny of the scientific merit of proposed randomised trials is warranted.

Our study was retrospective and attempted to discern authors' beliefs before the studies based on interpretation of their findings and conclusions after the studies were completed. We cannot fully account for any publication bias related to restricted submission or acceptance of studies for publication.[27] Violation of the uncertainty principle among industry-sponsored studies could also be explained by the decision of a sponsor to prevent the publication of negative studies. By preferential publication of positive studies, reported outcomes may be distorted and provide false impressions about the efficacy of a given therapeutic innovation.[27] Since clinical decision-making is based on interpretation of published data, the under-reporting of clinical research has been condemned as a form of scientific misconduct.[28] Journal editors have proposed the establishment of an international registry of randomised trials to reduce the impact of under-reporting and publication bias on clinical trials.[29]

Determination of equipoise should be a quality-control measure in randomised trials. No trial should be approved without explicit consideration of the uncertainty principle.[12] Since the development and implementation of randomised trials is one of the most important achievements in medical science in the twentieth century,[5,30,31] violation of equipoise threatens the continued existence of the clinical trial system in medicine.

Contributors

This paper was conceived by Benjamin Djulbegovic and then refined in numerous discussions with Gary Lyman, Ben Djulbegovic wrote the first draft of the paper, which was then considerably improved by Gary Lyman. Mira Lacevic was responsible for data collection. Charlie Bennett and Jared Adams were responsible for obtaining data on funding and contributed to the intellectual content of the paper. Alan Cantor advised on and did most of the statistical analyses. Nicole Kuderer provided important constructive comments on the statistical and design issues, in particular during revised analysis of the paper when analyis was focused on the use of placebo as a comparator. Karen Fields critically appraised the paper and provided important suggestions particularly in terms of practical implications of this work. All authors read and approved the final version of the paper.

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