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Conducting industry-partnered trials in orthopaedic surgery

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Summary We have seen an emergence of larger scale collaborative multi-center trials in surgery. These larger trials have the advantage of increased generalisability of the results and the potential for large scale and efficient recruitment (1000 patients or more). It is estimated that the average cost of bringing a new drug to market approximates 500 million dollars. The funding limitations in most national peer-reviewed agencies provides a compelling rationale for industry co-sponsors.

To limit biases associated with industry-sponsored research, researchers should develop specific protocols to ensure accurate and transparent reporting of funding sources, design and implementation of surgical trials, manuscript preparation and the criteria for authorship.

Introduction

Randomised trials have gained popularity in surgery[3,4] and there has been greater appreciation for the limitations of non-randomised studies.[3] Randomisation offers the best method to limit bias in clinical research. Randomised trials are most commonly single center initiatives in orthopaedics.[4] Recently however, we have seen an emergence of larger scale collaborative multi-center trials in surgery. These larger trials have the advantage of increased generalisability of the results and the potential for large scale and efficient recruitment (1000 patients or more).

Investigators and the industry sponsors involved in such trials may have conflicting goals and perspectives. Also, a potential for bias on the part of clinical investigators involved in these trials exists, whether due to financial incentives, a desire for notoriety, academic pressures, or clinicians' general desire for new successful therapies for disease processes.[14,17]

Costs of research

Unfortunately, with increased complexity in the conduct of RCTs comes increased costs. The conduct

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of a high quality RCT in surgery enrolling 1000 patients or more may require in excess of 1 million dollars. It is estimated that the average cost of bringing a new drug to market approximates 500 million dollars.[13] The funding limitations in most national peer-reviewed agencies provides a compelling rationale for industry co-sponsors. Almost one in five randomised trials have industry partners further vindicating the importance of co-sponsorship in clinical research.

The costs of conducting clinical research are not small. Emmanuel et al. evaluated the clinical and non-clinical hours and costs associated with conducting a mock phase III clinical research trial. The hours were based on enrolling 20 patients in a 12-month randomised placebo-controlled trial of a new chemotherapeutic agent. On average, 4012 h (range: 1512—13,319 h) were required for a government-sponsored trial, and 3998 h (range: 1735—15,699) were required for a pharmaceutical industry-sponsored trial involving 20 subjects with 17 office visits, or approximately 200 h per subject. Thirty-two percent of the hours were devoted to non-clinical activities, such as institutional review board submission and completion of clinical reporting forms. On average, excluding overhead expenses, it cost slightly more than 6094 dollars (range: 2098—19,285 dollars) per enrolled subject for an industry-sponsored trial.[10]

Industry-sponsored trials and reporting bias

Academics are debating if industry collaborations in clinical research influences research findings and conclusions.[5,6,8,9,11,12,15] Three recent studies have demonstrated statistically significant associations between industry funding and authors' findings/conclusions of medical randomised controlled trials.[6,9,11,12] Kjaergard and Als-Nielsen reviewed 159 randomised trials published in the *British Medical Journal* across 12 medical specialties. Adjusting for study quality, sample size, type of intervention, and medical specialty they reported that industry funding was significantly associated with authors' conclusions.[11] In a recent meta-analysis, Bekelman et al. pooled 1140 original studies and found a statistically significant association between industry sponsorship and pro-industry conclusions (pooled odds ratio: 3.60, 95% confidence interval 2.63—4.91).[1] Bhandari et al. reviewed 332 randomised trial and pooled their results with those of Bekelman et al. ($N = 1140$ trials)[1] and Clifford et al. ($N = 100$ trials)[6] utilising a random effects model. Pooling was deemed appropriate due to a non-significant test of heterogeneity ($p > 0.1$), widely overlapping confidence intervals and similarity of point estimates.[2] The pooled estimate of 1572 trials provides a current estimate of the impact of industry funding on authors' conclusions [$N = 1572$ original studies, pooled odds ratio: 2.30, 95% confidence interval: 1.29—4.11, heterogeneity p value = 0.02].[2]

The failure to publish negative results is one explanation for the propensity of positive trials associated with industry funding. Unfortunately, even when an investigator has had substantial input into trial design and data interpretation, the results of the finished trial may be buried rather than published if they are unfavourable to the sponsor's product. An alternative explanation includes the possibility that industry sponsors are excessively careful and deliberate in their choice to fund research questions with the greatest possibility of revealing significant results.

Guide for conducting industry-partnered trials

Despite potential conflicts of interest, a productive and ethical relationship between investigators and industry sponsors is important. That relationship is best served by an atmosphere of honesty and openness in which concerns over integrity and credibility are unlikely. A productive and scientifically sound relationship can exist only if conflicts and investigator bias are stringently avoided.[14] These guidelines are designed to promote that form of relationship for the benefit of both investigators and industry.

Concerned about threats to the integrity of clinical trials in a research environment increasingly controlled by private interests, the International Committee of Medical Journal Editors (ICMJE) has issued revised guidelines for investigators' participation in the study design, access to data, and control over publication.[16] Schulman and colleagues interviewed officials at U.S. Medical Schools about provisions in their institutions' agreements with industry sponsors of multi-center clinical trials.[16] Of the 122 Medical Schools that are members of the Association of American Medical Colleges, 108 participated in the survey and demonstrated limited adherence to the standards embodied in the new ICMJE guidelines.

International committee of medical journal editors (ICMJE)

Committee members have outlined several recommendations pertaining specifically to industry funded trials.[7] The report states that industry sponsors