EDITORIAL

Financial conflicts of interest in clinical research

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Financial conflicts of interest are common in clinical research. For example, in a cohort of oncology drug trials, industry funded 44% of trials, and 69% of authors declared conflicts of interest [1]. For a drug company, the financial impact of a positive pivotal trial can be substantial. One investigation reported that the mean stock price of the companies funding 23 positive pivotal oncology trials increased by 14% after disclosure of the results [2]. Several dramatic cases of biased industry trials have been widely debated [3]. These often involved selective reporting of outcomes and gift/ghost authorship. Other cases involved companies attempting to intimidate authors of independent investigations [4].

Conflicts of interest do not necessarily cause biased trial results, but create the risk thereof. Unfortunately, our knowledge of what factors affect that risk, and to what extent, is incomplete. In this editorial we address the intersection between financial conflicts of interest, including industry funding, and bias in clinical research.

A conflict of interest is typically defined as “a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest” [5]. In clinical research, the primary interest is in conducting a relevant and unbiased investigation. Secondary interest typically relates to financial relations. Financial conflicts of interest arise when clinical investigators have relationships with the company that manufactures the drug or device that is the subject of the investigation. Those relationships could be in the form of study funding; monetary payments, consultancies, share ownership, or advisory board

membership; or other ways that investigators stand to gain financially from a study result, such as patents.

Bias is a systematic error in the results of individual studies or their synthesis. Bias in this technical and narrow sense should be clearly distinguished from its broader meanings of prejudiced investigator motives and “problematic” investigation.

When addressing the risk of bias in a clinical study, it may be challenging to determine which aspects of a trial should be regarded as indicators of bias, for example, whether conflicts of interest should be considered. The widely used Cochrane Risk of Bias Tool for randomized trials addresses this by including only six mechanistically defined core bias domains: generation of allocation sequence, concealment of allocation sequence, blinding of participants and treatment providers, blinding of outcome assessors, attrition, and publication bias. Financial conflict of interest is not included (though this has been debated), as it is not regarded a mechanism through which biases are introduced into trials, but a motivation behind them. The intention is to detect any bias associated with conflict of interest indirectly through one of the outlined mechanisms.

A key question is whether trials with and without financial conflicts of interest reach different results. A systematic review of 75 such comparisons reported that industry funding was associated with positive trial conclusions and more frequent statistically significant results, but it could give no clear answer to whether the size of the estimated treatment effects differed, and found no association with the assessment of conventional bias domains [6]. However, confounding in such comparisons is considerable, as the result of trials may differ for many reasons other than funding source (e.g. choice of study comparator or outcome). One included study minimized this risk of confounding by sampling comparable trials from meta-analyses. It reproduced the general

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association with positive conclusions and no clear association with size of estimated treatment effects [7]. A similar pattern was found in studies of financial conflicts of interest in systematic reviews [8]. Thus it appears that commercial funding is robustly associated with favorable conclusions but less so with estimated treatment effects.

Industry-funded trials often differ from trials not funded by industry. An industry-funded trial is often large, participants are often carefully selected, placebo is often used as comparator, and short-term surrogate outcomes are frequently used [9, 10]. In some cases, industry trials or outcomes may not be published if deemed commercially unfavorable. Trial registration and decades of debate about publication bias have improved matters to some degree, but lack of transparency and incomplete reporting of trials is still a significant problem [10, 11]. Furthermore, trial results are often over-interpreted, and spin in conclusions is commonplace [12]. Such trials, if fully reported, may not be biased in the strict sense that their estimated treatment effect is wrong, but they are often problematic in the broader sense that results do not include the most relevant outcomes or may not be directly transferable to the typical patient.

Aside from industry funding, clinical investigators' individual and institutional financial conflicts, as well as their non-financial conflicts, may also unduly influence the planning, conduct and reporting of their studies. Financial ties of principal investigators seem to be independently associated with positive clinical trial results [13]. In addition, financial conflicts of interest may bias the dissemination of study findings, such as the display of strong advocacy by investigators on social media. Moreover, conflicted investigators may inappropriately favor industry interests when acting as content experts on panels of regulatory agencies or clinical practice guidelines [14].

The most common approach to managing conflicts of interest on the part of clinical investigators is through the public reporting of relevant conflicts. Unfortunately, there is evidence of high rates of underreporting of financial conflicts of interest [15]. In addition, there is concern that simple public disclosure, particularly in the context of guideline panels, is not enough. Problems related to conflicts of interest in trials may be especially concerning in systematic reviews where several trials are combined. As one effort to counter this, a tool for addressing conflicts of interest in trials (TACIT) is under development under the auspices of the Cochrane Bias Methods Group.

The field of clinical research needs to improve its approaches to identifying and managing financial conflicts of interest. This includes the need to develop methods and tools to verify the accuracy and completeness of declared financial conflicts of interest, to further assess

the extent of bias associated with a financial relationship, and to minimize the risk of bias associated with investigator conflict of interest.

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