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Conflicts of interest in clinical practice: lessons learned from cardiovascular medicine

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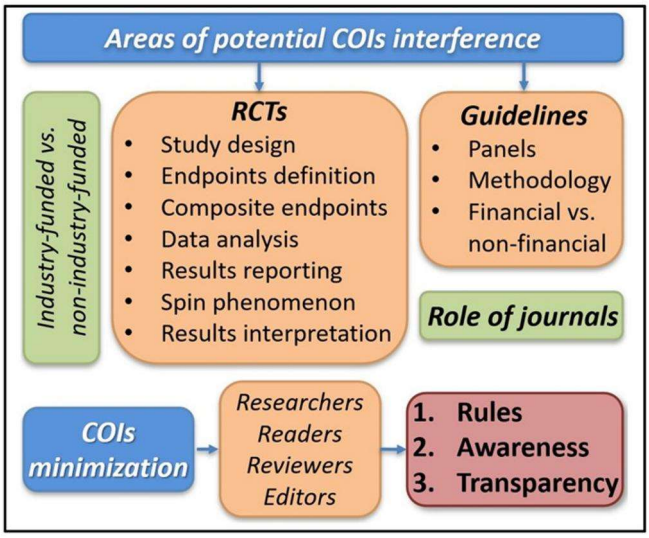
Summary

COIs in clinical research have multiple areas of interference significantly affecting any aspect of a trial conduct, from design (including endpoint definition) to results interpretation and, subsequently, influence on clinical practice guidelines. Actions to minimize COIs are essential to protect the central role of evidence-based medicine.



Legend: COIs = conflicts of interest. RCTs = randomized controlled trials.

Abstract

Cardiovascular diseases represent a major burden worldwide, and clinical trials are critical to define treatment improvements. Since various conflicts of interest (COIs) may influence trials at multiple levels, cardiovascular research represents a paradigmatic example to analyze their effects and manage them effectively to re-establish the centrality of evidence-based medicine. Despite the manifest role of industry, COIs may differently affect both sponsored and non-sponsored studies in many ways. COIs influence may start from the research question, data collection and adjudication, up to result reporting, including the spin phenomenon. Outcomes and endpoints (especially composite) choice and definitions also represent potential sources for COIs interference. Since large randomized controlled trials significantly influence international guidelines, thus impacting also clinical practice, their critical assessment for COIs is mandatory. Despite specific protocols aimed to mitigate COI influence, even scientific societies and guideline panels may not be totally free from COIs, negatively affecting their accountability and trustworthiness. Shared rules, awareness of COI mechanisms and transparency with external data access may help promoting evidence-based research and mitigate COIs impact. Managing COIs effectively should preserve public trust in the cardiovascular profession without compromising the positive relationships between investigators and industry.

Keywords: Cardiovascular research • Conflicts of interest • Randomized controlled trials • Coronary revascularization • Aortic valve replacement • Transcatheter aortic valve implantation

ABBREVIATIONS

COIs	Conflicts of interest
CPGs	Clinical practice guidelines
HF	Heart failure
ICMJE	International Committee of Medical Journal Editors
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
RCTs	Randomized controlled trials
SAVR	Surgical aortic valve replacement
TAVI	Transcatheter aortic valve implantation

INTRODUCTION

Unbiased medical research and its interpretation are paramount to improving patient care. Different types of studies, including retrospective studies, real-life registries (e.g. from electronic databases) and even randomized controlled trials (RCTs) are potentially subject to peculiar biases that may compromise their conclusions. Countless participants have accepted the risks of enrolling in RCTs, hopefully contributing to improved clinical care; thus, factors undermining this process should be identified and eliminated [1].

The primary and secondary interests of physicians intertwine with clinical practice. Patient welfare is a primary one, complemented by "promoting and protecting the integrity of research" [2]. In contrast, secondary interests and gains are more complex,

subtle and harder to identify. For example, they consist not only of financial gain but also of the desire for professional advancement and recognition for personal achievement [2]. Many of these secondary interests are bolstered by the current incentives for academic progress, which may paradoxically endanger ethical clinical practice [3].

The impact of secondary interests on clinical practice and research has long been recognized [4–6]. This article elaborates on "the elephant in the room": conflicts of interest (COIs). By revising practical examples from the cardiovascular literature, we discuss their definition, current recommendations and how they influence study design, the reporting of results and the choice of the end point, thereby affecting the public's perception of results and, potentially, of clinical practice and decision making. Lastly, we elaborate on how these conflicts can even influence clinical decisions through cardiovascular medicine practice guidelines.

Definition of conflict of interest and current recommendations

A COI is defined as "a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest" [2].

A recent review on COIs mapped medical industry ties to activities and parties in the healthcare ecosystem [7]. There is an extensive network involving the industry and research, health professional education, guideline development, clinicians and patients. These relationships flow directly and indirectly through financial and non-financial ties, and a lack of appropriate oversight and transparency characterizes this intricate network [7]. Therefore, the state of knowledge on COIs, primarily financial, is complex and potentially incomplete and should include not only individual investigators, but also their affiliated institutions.

A major tool necessary, but not sufficient, to contain COIs is the disclosure of interest [1]. Disclosures have been widely applied in the policies of medical journals since 1984, although criticisms of their inefficiencies have been discussed [1]. Transparency of COIs also depends on honest disclosures by investigators, which is unfortunately not always the case [8].

To limit the impact of COIs in research, the International Committee of Medical Journal Editors (ICMJE) has published serial recommendations from 1979 to 2021 [9]. Authors, reviewers, editorial staffs and journals should disclose all relationships that could be viewed as potential COIs in the peer-review and publication process. Editors could then use this information to guide editorial decisions. Also, the ICMJE requests information on financial relationships, e.g. grants, royalties, consulting fees, stock ownership.

Among other recommendations, the Institute of Medicine 2009 report recommended prohibitions to limit the extent to which the industry can involve researchers, such as bans related to speakers' bureaus and events directly controlled by the industry [2, 10]. This report highlights the importance of engagement of the institutions in adopting, implementing and strengthening COI policies.

In addition to financial COIs, non-financial ones can also take different forms [11]. For example, an investigator with a reputation for having developed a specific procedure may have an interest in having studies of this procedure be favourable, further branding his reputation. These non-financial COIs are more difficult to mitigate and identify. Not only do direct financial COIs need managing, but indirect financial COIs, including unrestricted research grants and donations to respective institutions/universities or research organizations, also require monitoring.

Role of study design and results reporting

The RCTs frequently require companies' sponsorships, leading to a first potential bias: the selection of topics related directly to companies' fiscal interests and not necessarily to patients' clinical interests. Sponsored studies are more likely to find results favourable to their funder [12–16]. An example by which similar RCTs with different funders perhaps contributed to different results is the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trials about the transcatheter edge-to-edge mitral repair for patients with heart failure (HF), with the first (funded by the industry owning the patent of the device) achieving statistical significance in favour of the device, differently from the latter (funded by the French public health agency) [17, 18]. Although elaborate pathophysiological explanations have been postulated for these differences, concerns about potential biases and COIs require an equally attentive assessment for each study.

Multiple trial characteristics can contribute to favourable results for the industry. When comparing 2 active treatments, the appropriate choice of the control arm is essential. However, reports have described a systematic bias in study designs of industry-funded trials [19]. For example, when comparing a new drug to an inferior control drug (comparator drug) with incorrect dosage, any positive results may be due to bias and not a true incremental effect for the new drug [20]. Higher comparator drug doses could generate adverse effects potentially favourable to the new drug [19].

Another disturbing impact that COIs can have on RCTs is associated with the dissemination of the results. Biases influence which results are published and how they are reported [21]. Industry-funded trials systematically tend to publish favourable results through many mechanisms, e.g. avoiding publication of studies with negative results, using more spin to summarize trials, conducting and separately publishing subgroup analyses, reporting only specific end points among many analysed, excluding centres with negative results in multicentric studies and incorrectly reporting adverse events [20, 22, 23]. Alternatively, industry-sponsored trials are more often multicentre, more frequently associated with protocol registration, use non-inferiority design, include higher percentages of screened patients and are published in journals with higher impact factors [16].

Does the choice of end points (and their definitions) affect results?

The choice and identification of the end points, including their definitions, play a pivotal role in study design. The end points represent trial outcome values measured for each enrolled subject. To enhance statistical power, often composite end points are chosen [24].

The definition of the end point may critically influence RCTs results, either individually or as part of a composite outcome.

Thus, in 2009 the U.S. Food and Drug Administration supported the Standardized Data Collection for Cardiovascular Trials Initiative by enlisting uniform definitions for cardiovascular and stroke outcomes [25]. This work supported more accessible data aggregation and integration from multiple trials, recognizing the pivotal role of the definitions of end points [25].

An example of how end-point definition may affect trial results is represented by the definition of periprocedural myocardial infarction (MI), contributing to the primary composite end point of the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial comparing percutaneous versus surgical revascularization in left main disease [26, 27]. This study used the Society for Cardiovascular Angiography and Interventions definition of MI, mostly based on enzymatic profile, resulting in significantly fewer MIs in the percutaneous coronary intervention (PCI) arm compared to the surgical arm. Consequently, the primary composite end point, including MI, was found non-inferior in PCI compared to coronary artery bypass grafting, although mortality was higher for PCI-treated patients [28, 29]. Moreover, several authors have shown how the rates of periprocedural MI highly depend on its definition, and the adoption of the most common universal definition of myocardial infarction, requiring also clinical and/or imaging criteria, resulted in no differences between the percutaneous and the surgical arms [30–32].

Due to the continuous improvements in cardiovascular outcomes, smaller effect sizes of new treatments have increased the challenges in trial designs [33]. Therefore, researchers are increasingly using composite end points, combining death and other relevant non-fatal outcomes into a single composite event to reach the overall event rate required for adequate statistical power [34]. However, composite end points must be managed cautiously, being subject to criticisms, including the lack of distinction between the relative clinical significance of each end point and the arbitrary choice of outcomes contributing to the composite end point. Analysis and interpretation might be misleading and may potentially negatively impact patient care [24, 33, 34]. A further demonstration is the exclusion of ischaemia-driven revascularization, despite its clinical relevance, from the primary composite end point in the EXCEL trial, differently from all previous RCTs comparing PCI versus coronary artery bypass grafting [24, 27, 33].

The addition of clinically questionable, confounding outcomes to composite end points may also inherently bias the results, favouring 1 treatment. An example is the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II trial comparing the Mitraclip system versus mitral valve surgery [35]. In this trial, the primary safety end point represented the rate of major adverse events at 30 days, comprising death and 11 more-or-less clinically relevant events. Adding a marginally relevant end point, i.e. blood transfusions, significantly affected the composite outcome [35].

Another example is represented by the PARTNER 3 (Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients With Aortic Stenosis) trial, which compared a transcatheter aortic valve implant (TAVI) versus a surgical aortic valve replacement (SAVR) in patients with aortic stenosis at low surgical risk [36]. Every previous TAVI versus SAVR trial used death and "disabling stroke" as primary outcomes. PARTNER 3 investigators added "rehospitalization rate at 1 year" to death and "any stroke" as the primary composite end point. The problems here are threefold: first, rehospitalization is not as severe an outcome as stroke or death; second, early rehospitalization will bias against SAVR, given its more invasive nature; and third, a trial set-up to produce early "positive" results for the new procedure potentially creates a cognitive anchoring bias in which clinicians become anchored to the idea of TAVI superiority, thereby giving more weight to short-term favourable outcomes rather than to long-term critical evaluation [36, 37].

The timing of the evaluation of the end points critically impacts the results. Indeed, a recent meta-analysis by Barili *et al.* [38] shows how the outcomes in large RCTs comparing TAVI versus SAVR invert after 24 months of follow-up. The same is true for the above-mentioned rehospitalization end point. This trend can be generalized to trials comparing more invasive versus less invasive treatments, where the latter have an early advantage that is lost over time, sometimes even reverting the outcome [38]. These short-term considerations might also be used by certain institutions to favour TAVI over SAVR, for instance, to optimize the reimbursement compensations per intervention, independently from the expected long-term advantage for patients [39].

Finally, Gaudino *et al.* [16] showed that in 38% of 216 RCTs on invasive cardiovascular interventions, one significant discrepancy existed between the registered and published primary outcomes, regardless of trial sponsorship. An example may be found in the GUIDE-HF (Hemodynamic-GUIDEd Management of Heart Failure) trial, comparing the CardioMEMS device monitoring versus standard care for HF. Because the primary composite end point of death, urgent HF visit and HF-related hospitalization, was not met, the authors performed a post hoc analysis of the pre-COVID era (not specified in the original protocol, but agreed to by regulatory agencies, given the exceptional circumstances of COVID-19), which resulted barely positively in favour of the CardioMEMS, due only to a significantly lower rate of hospitalizations [40].

Need for transparency and the role of industry: sponsored versus non-sponsored trials

Transparency is a broad term that covers the funding process through to data availability and analysis. Any trial requires funding to be conducted [7]. It is therefore imperative to identify and declare who is sponsoring the trial, partially or totally.

Funds for research may come from various sources, including institutional university or hospital budgets, public authorities or government granting agencies, private organizations, charities and the biomedical industry. Collaborations and interplay among doctors, researchers and biomedical companies have been historically commonplace, sometimes essential, to develop new devices and treatment alternatives [4, 15]. However, it is important to remember competing interests: one is to improve patient care, another is to maximize profits for shareholders. Therefore, it is crucial to consider the role of the sponsoring organization in trial design, data collection, analysis, site selection and rights to review the manuscript before publication [7, 41, 42].

Data analysis represents another area potentially affected by COIs. Complex data analyses possess an intrinsic variability regardless of the funding source and the best intentions of the researchers to conduct the most rigorous trials [16, 43]. Indeed, subjective analytic decisions may influence results. Although researcher degrees of freedom should be controlled through

prespecified protocols, considering that such analytic biases remain, Silberzahn *et al.* [43] commented that the best solution is transparency concerning data, methods and analytic processes to fully evaluate the presented results. Such transparent approaches would provide better insights into the published results, including the possibility to verify and reproduce the analyses [43]. The importance of data sharing is also recognized by the ICMJE, as emphasized by the data sharing statements required by publications [44]. Indeed, replication of findings guarantees true patient benefit and should be considered mandatory before device or drug approval.

Transparency in RCTs includes open access to trial data for external analysis, but also the need to disclose any type of funding and any relationship the investigators may have with industry [7]. However, the interplay between medical investigators and the biomedical industry goes well beyond research funding and includes financial and non-financial ties that should always be considered when approaching sponsored trials [7, 11].

When trials do not reach the expected primary outcomes, investigators may intentionally or not resort to "spin", defined as specific results reporting strategies (e.g. confusing statistical and clinical significance), for whatever reason, to distract the reader from statistically nonsignificant results, thereby leading to misinterpretation and, potentially, to misapplication of the trial's findings [45].

Healthcare professionals should effectively manage the risks related to the commercial influence of industries on trials for patients' safety and to ensure public trust in both the healthcare system and in the healthcare professionals involved in major trials and clinical practice guidelines (CPGs) [7, 46]. Furthermore, because our society is increasingly threatened by the spread of unverified information and a generally decreased reliance on healthcare authorities and scientific associations, protecting the independence and trustworthiness of medical research acquires an even greater significance.

The role of editors

Editors must contribute to the academic reputations of the journals they serve, extending beyond self-serving metrics such as the impact factor. Citations driven by CPGs represent an easy way to improve the impact factor and academic development; they are therefore highly desirable for journal editors. Furthermore, Gaudino *et al.* showed that industry-sponsored trials, with more favourable results on average, have more citations after publication and are generally published in higher-impact journals, potentially impacting more significantly also on the development of CPGs. Given this "virtuous circle" for metrics, it is thus in a journal's interest to accept more industry-sponsored trials [16, 19].

From the financial side, a significant source of revenue for journals is reprint orders. In a study including major British journals, industry-funded trials had much higher numbers of reprints [47]. The revenue from reprints is not necessarily trivial since it contributed to 3% of the budget of the BMJ, compared to a remarkable 41% of the Lancet budget, for 2005–2006 [48]. Nevertheless, although the current digital era has generally modified the accessibility to publications, more recent data suggest that reprint-related revenues still play a potentially relevant role in the decision-making process of certain journals [49].

Finally, editors are responsible for ensuring fair and neutral reporting of trial results. Their duty to the scientific community is to select independent reviewers, have spin removed from manuscripts, report fragility of findings when appropriate and have articles retracted when the scientific record they have produced does not align with the totality of the trial data. Although at different levels and on different aspects, both the editor-in-chief and other members of the editorial boards might have a role in influencing the above-mentioned decisions.

Conflicts of interest in practice guideline panels: the tip of the iceberg?

Although many diverging interpretations and comments arose regarding the recent results of large RCTs about myocardial revascularization and the treatment of valvular heart diseases and their interpretation, the recent publications of the North American and European guidelines for myocardial revascularization and the treatment of valvular heart diseases, respectively, have underscored the methodological bases on which panels derive clinical recommendations [46, 50, 51].

Despite the lack of generally accepted methodological standards, COIs among CPG panel members represent a well-known matter officially addressed by every scientific society, although not uniformly established. For instance, whereas the European Association for Cardio-Thoracic Surgery adopted the Institute of Medicine standards, where members with COIs must be a minority and the chair must be free from COIs, also involving a clinical methodology expert, the European Society of Cardiology requires the completion of COI forms and considers stock ownership or patents relevant to the guideline incompatible with the panel, whereas direct or indirect payments from industries are allowed up to 10,000 € [52, 53]. However, as disclosure rules for COIs have progressed, some loopholes remain, because grants to taskforce members' institutions are allowed, representing a potential unconscious bias. On the other hand, the American College of Cardiology and American Heart Association state that >50% of the members and the chair of the taskforce must have no relevant relationships with industries, and conflicted members are not allowed to vote on recommendations for which COIs exist [54].

When developing CPGs, it is crucial that a balanced proportion of all the professionals involved in treating the addressed condition have identified shared, reasonable and evidence-based recommendations [46, 55]. Such equilibrium is even more important when addressing controversial topics. For instance, when considering the CPGs for the valvular heart diseases, in the European panel, the members are equally distributed among clinical cardiologists, interventional cardiologists and cardiac surgeons, affiliated with both the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. Conversely, the North American panel is disproportionately composed of a larger number of cardiologists [46, 50, 56]. This imbalance may per se generate an uneven decision on the recommendations due to intrinsic professional COIs related to each specialist's competence. Moreover, the consensus required for issuing recommendations is also critical (e.g. simple majority versus 75% of votes).

Such methodological approaches might preclude the development of shared recommendations, as happened with the 2021 American Heart Association/American College of Cardiology/Society for Cardiovascular Angiography and Interventions coronary revascularization guidelines [51]. These guidelines have generated a considerable debate, where progressively more surgical societies worldwide expressed concerns with some

recommendations, therefore preventing their endorsement and spoiling their trustworthiness [46, 57, 58].

Because different recommendations have been developed by different panels based on the same evidence, it would be essential to consider whether other factors influence such decisions, including some indirect COIs [46]. For instance, Lenzer *et al.* [46] observed how respecting the official rules for financial COIs in CPGs panels does not prevent the panels from presenting some COIs, such as the selection performed by the committee chairs having COIs of panel members known to support a certain viewpoint instead of other members known to have diverging opinions. Methodological manuals cannot cover all these possible scenarios, and the choice of more compliant members in certain debated topics is a potential source of influence [7, 46].

Although the focus is commonly on financial COIs, non-financial ones are sometimes manifest in CPGs. Even the role of scientific societies, at times representing a "union" in defence of their specialty and thereby having unmitigable COIs, has been questioned [59]. This aspect is further biased since CPGs represent an important driver for a journal's impact factor. Therefore, scientific societies have an interest in producing the CPGs published in their affiliated journals. Perhaps a neutral, external approach, using methodologists without skin in the game, using a reproducible framework to evaluate the evidence (e.g. GRADE), could produce balanced recommendations and avoid many COIs. A further example of how scientific societies should support a rigorous methodology in research is represented by the recently published position statement regarding the VARC-3 definitions for aortic valve clinical research [60].

The ultimate goal is to provide comprehensive, rigorous, reproducible and widely accepted CPGs developed by groups of independent methodologists that present the relative strength and weaknesses of the available evidence to a balanced multidisciplinary group of stakeholders for recommendation drafting and further independent review. This approach would lead to wider endorsements by scientific societies, thereby improving the trustworthiness and appraisal of guidelines and extending the recognition of recommendations by an extensive base of clinicians belonging to different specialties, everything for the benefit of patient care.

CONCLUSIONS

This paper presents the most relevant aspects of COIs, with special emphasis on COIs in cardiovascular medicine. Although it is utopic to aim for the complete removal of COIs from research, the hard path towards minimization of COI interference should be based on 3 pillars, namely rigid international and shared rules, greater reader awareness and transparency with external data access. Knowing the different scenarios may help managing COIs without compromising the relationship between investigators and industry and preserve public trust in the cardiovascular profession.

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The manuscript is a review of literature, with no data and no data analysis. There are no data to be shared.

Author contributions

Daniele Ronco: Conceptualization; Data curation; Formal analysis; Investigation; Writing—original draft; Writing—review and editing. **Arthur M. Albuquerque:** Data curation; Writing—original draft. **Mateo Marin-Cuartas:** Investigation; Writing—review and editing. **Amedeo Anselmi:** Investigation; Writing—review and editing. **Rafael Sádaba:** Validation; Visualization; Writing—review and editing. **Fabio Barili:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Writing—review and editing. **Miguel Sousa Uva:** Conceptualization. **James M. Brophy:** Data curation; Formal analysis; Methodology; Supervision; Validation; Writing—review and editing. **Eduard Quintana:** Visualization; Writing—review and editing. **Francesco Musumeci:** Investigation; Writing—review and editing. **Jacques Tomasi:** Investigation; Visualization; Writing—review and editing. **Jean-Philippe Verhoye:** Visualization; Writing—review and editing. **John Mandrola:** Conceptualization; Investigation; Methodology; Writing—review and editing. **Victor Dayan:** Investigation; Visualization; Writing—review and editing. **Patrick O. Myers:** Validation; Visualization; Writing—review and editing. **Ovidio A. Garcia Villareal:** Investigation; Writing—review and editing. **Sanjay Kaul:** Conceptualization; Validation; Writing—review and editing. **Jorge Rodriguez-Roda Stuart:** Validation; Writing—review and editing. Milan Milojevic: Visualization. **Walter J. Gomes:** Investigation; Validation; Writing—review and editing. **Alessandro Parolari:** Conceptualization; Investigation; Project administration; Supervision; Writing—review and editing. **Rui M.S. Almeida:** Conceptualization; Project administration; Supervision; Writing—review and editing.

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Position Statement