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Physicians and Pharmaceutical Industry: Need for Transparency by Conflict of Interest Declaration and Independent Ethical Oversight

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Abstract

Aim: The collaboration between physicians and pharmaceutical industry are based on financial interests on both sides. Transparency will bring the scientific as well as social public to a position from which they are able to judge whether the physician's interest dominates over the patients' benefit.

Proposals: The declaration of any conflicting interest (CoI) must be placed on the first slide of a scientific presentation and on the last line of a published abstract. Declaring the amount of industry funding in the patient information form of all investigator-initiated clinical trials should also be considered. To limit influence of the industry on data presentation and interpretation, employees or experts acting in charge of a sponsoring company cannot be made co-authors but will only be mentioned in the acknowledgement of publications. For approval of a clinical trial the local ethics committee or the institutional review board should evaluate whether industrial funding is balanced by personal work.

Conclusion: The need to disclose will motivate physicians to keep their own interests under control. The intrinsic motivation of the profession needs support by external oversight to maintain the ethics in physician-industry interactions. (Expenses were refunded for FK, KM and DP by ERA-EDTA.)

Keywords: ethics, disclosure, conflict of interest, funding, physician-industry relationship

1. Introduction, background and objectives

Pharmaceutical funding plays an important role in medical progress. Thus, clinical and academic research has been significantly commercialized [1]. There are data to suggest that economic interest from industry may have a negative influence on the objectivity of the science, the publication of research, and even patient management as discussed for rofecoxib [2, 3]. The manufacturing company for instance had engaged "... in misleading practices to promote the prescription and usage of rofecoxib, including 'fake' journals and guidelines to 'drug reps' that minimised the adverse cardiovascular risks" [4]. Industry-sponsored reports are up to four times as likely to favour a pharmaceutical company's product compared to independently published data [5, 6].

Influence of industry interest is not always zero as in the case of the British National Institute of Clinical Excellence (NICE) where cooperation with industry is prohibited for all members. But influence can be suspected in 50–100% of other expert panels [3, 7, 8]. Such influence has been found in guidelines promoting, for instance, gabapentin or preferably recommending patented antidiabetic drugs [7, 9]. Pushing epoetins and cinacalcet, KDOQI guidelines had favoured a target haemoglobin up to 12 mg/dl and recommended calcium values less than 9.5 mg/dl (<2.38 mmol/l) against other evidence [10].

We wish to analyse the need for clear regulations and we will make new proposals for how best to disclose or – less adversarial – declare a conflict of interest (CoI). On the one side and as a consequence, it has been suggested that the dynamics of this process need to be more restricted and governed by less tolerant regulation [11]. Considerations of how ethics here could be made effective might help from another side.

2. Analysis of the present state

Regulations such as the "Physician Payment Sunshine Act" are needed but probably not sufficient to make sure that conflicts are declared and not concealed [12]. Even such measures as the proposed Center for Monitoring and Implementing Publication Ethics will only be instrumental when clear sanctions are laid down [13]. But the consequences regarding sanctioning of malpractice are unclear. While misuse and non-adherence call for legal regulations or even punishment, responsible and trustworthy actions have a foundation in ethics. Physicians must have an intrinsic interest that patients and colleagues trust what he or she is saying and doing.

In medicine generally, "... the primary interests are the health of the patient" whereas financial gain, prestige or preferences are not illegitimate but secondary interests [14]. Medical professionalism "... demands placing the interests of patients above those of the physician" [15]. Such privilege likewise no client could expect from an investment banker. According to the charter of medical professionalism, the primary patients' interests are: welfare, respect for autonomy and social justice – namely the main principles of medical ethics [15, 16]. The primacy of patient

welfare can be guaranteed only if the indication for treatment is medical, not economical. The patient's autonomy will be compromised if she/he was misled and thus consented to a therapy that appeared better than what it ended up being. Financial interests can do harm to the principles of parsimony and social justice when the more expensive intervention is not justified by evidence but favoured by a physician under pharmaceutical influence.

Economic mechanisms benefitting the market need other and special regulations in medicine in which the person who decides, benefits and pays is not one and the same. Market mechanisms do not work in medicine where the interests are not equivalent and health cannot be circulated like money, exchanged like a ware or consumed like goods. To give an example, dialysis will be mentioned here. Financial incentives will motivate adequate measures to reduce mortality and facilitate access to dialysis for all patients who need it. But such economic interest could also corrupt the physician to prematurely recruit patients for dialysis or unnecessarily maintain this treatment [17].

2.1. Need for specified regulations

Whether the interests of professionals really are secondary to the welfare of the patient must be made clear and transparent to all persons concerned. As professionals, physicians must seek patients' confidence, social trust and vocational reputation [3]. In the patient-physician relationship, ethics is the foundation of confidence, and confidence is the foundation of sustainability.

Although the percentage of physicians with any relationship to industry decreased, this relationship was still very high at 84%, ranging from a \$10 sandwich to the \$1 million research grant [3, 18, 19]. Expectations of reciprocity may be the primary reason for sponsorship by industry [20].

Due to subtle psychological effects, even small gifts might be a powerful stimulus for reciprocity [21]. Physician who received a single industry-sponsored meal had significantly higher rates of prescribing rosuvastatin, nebivolol or desvenlafaxine [19]. Research into the psychology of receiving and giving gifts indicates that more appropriate regulations would be necessary [2, 3]. Most scientists call for an open conflict of interest declaration, although some of them might fail to identify their own personal conflicting financial interest [22]. Whilst 61% of physicians had the opinion that financial incentive did not influence their own practice, only 16% believed that the same was true of their colleagues [23].

It is uniform experience that physicians and scientists do not willingly talk about their own motivations – be they economic or intellectual [21, 24]. The rigor of a study has been judged to be significantly reduced when funding came from industry compared to studies where the funding was from a government agency, for instance the National Institute of Health [25, 26]. Worldly wisdom tells patients and doctors to intuitively distrust studies funded by companies [25].

In response, it has become a prerequisite that all persons involved in the activities of the European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) adhere to the 2014 Council Regulations that were initiated by the ERA-EDTA Ethics Committee

(see Acknowledgments): the disclosure – or less adversarial – the declaration of interest (DoI) is mandatory to make transparent whether there could be a conflict of interest (CoI). This applies when presenting a talk or chairing a meeting, when working on guidelines, acting as editor or reviewer and submitting a manuscript for publication. Such declaration of interest regulations are practiced now in most medical societies.

Regulations are needed but probably not sufficient to ensure that conflicting interests are declared and not concealed [12]. Research on the tension between moral rules shows “... that collaborative settings provide fertile ground for the emergence of corruption” [27]. Physicians not always will resist to the seductive influences by industry. Regulations will only be instrumental when clear sanctions are laid down [23].

3. Proposals

Threat of scientific banning, ostracism, litigation and the law should intend to discourage concealment and deception. The German parliament, for example, is planning to issue a new anti-corruption law for all workers in the health system (StGB §299a and b). The boundaries, however, between an illegal incentive that stimulates corruption and a financial reward judged to be an adequate compensation are fluid.

Targets The economic interests of clinicians and researchers need to be more transparent to:

- establish sustainable trust and confidence in clinical science, medical practice and data published from physicians and scientists,
- enable patients', audiences' or readers' own judgments as to whether a conflict of interest exists and whether such conflict impacts on science or practice,
- discourage economic incentives but limit financial compensation to what has been invested as personal work.

The aim of legal regulations and ethical motivations should be to confine the influence of industry that could impact on clinical practice and on the conduct and reporting of medical research.

Table 1. Declaration of conflict of interest.

At first, transparency might help better the matter than pending threats to be sanctioned in the case of non-adherence to the canonical conflict of interest regulations. Transparency will help to bring the scientific as well as social public to a position from which they are able to judge whether the physician's interest dominates over the patients' benefit. Fair payment compensates for work performed, while inadequate payment tends to influence decisions with costly consequences.

Proposals To improve transparency:

1. The conflict of interest should be declared:
 - a. on the first slide of any oral presentation,
 - b. on the last line of an abstract as in all NEJM papers (**Figure 1**), and
 - c. at the beginning of official guideline statements.
2. For the sake of confidence, the dominant conflict of interest should be declared first.
3. Consider mentioning funding by industry also in the patient information form of any investigator-initiated trial.
4. Avoid employees of a company influencing the conduct of a trial and bias the presentation of data. It should be part of the primary contract that all contributions by employees or representatives of industry can only be mentioned in the acknowledgement.
5. Violation of the conflict of interest declaration rules can be efficiently sanctioned when the researcher will no longer be allowed to acquire and receive any further legal funding coming from either industry or from government.

To discourage corruption by limiting financial incentives:

1. The ethics committee must control all clinical research proposals for adequacy of funding and balanced financial compensation.
2. An ethical oversight should be established for all guideline committees.

Table 2. Proposals for declaration of interest (DoI) whether a potential conflict of interest (CoI) might exist and how to improve transparency.

With the most evident objectives in mind (**Table 1**), therefore, we suggest seven proposals on how to deal with a potential conflicting interest when presenting a talk, when publishing a paper or planning a trial (**Table 2**). More far-reaching standards than for presentations and publications will be needed for committees installed to develop trustworthy clinical practice guidelines as Richard N Shiffman has pointed out (Institute of Medicine, 2011).

3.1. Declaration of conflicts of interest (CoI)

The declaration of interests does not necessarily mean that the interests are in conflict with truth [3]. Conversely, also a declared conflict of interest can still negatively influence science and practice [28]. The subjective feeling of integrity can turn out to be a biased dependency on

an objective level [29]. In scientific journals, transparency is needed. The journal editors must judge whether a conflict of interest disclosure is correct, and otherwise reject such work [30]. Not only with regard to financial conflicts but also an intellectual conflict of interest might prevent a fair reviewing process. This can be managed only by the editor [31].

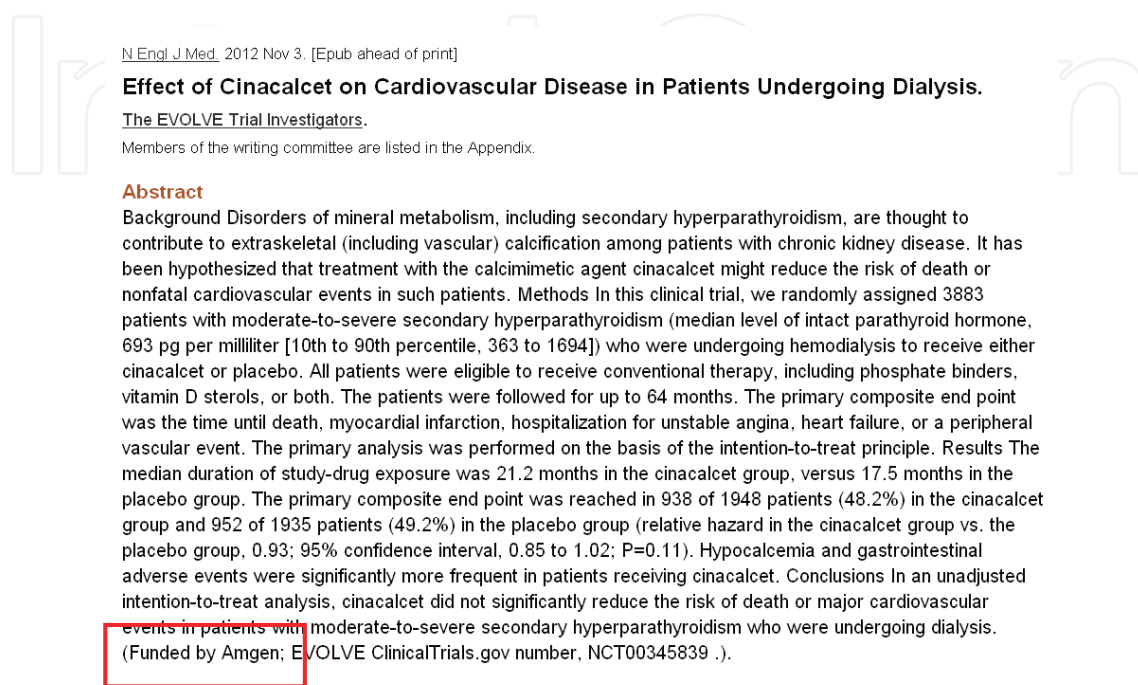


Figure 1. Funding disclosed at the end of the abstract as in all NEJM papers.

The readers and the public must have the opportunity to form their own opinions about the independence and the value of a study [29]. An unstructured list of many sponsors, although unintentional [32], could make a contributor falsely appear to the public to be both prestigious and independent. Any potentially conflicting interest should be declared in an exposed and not a hidden place (**Figure 1**) and a fair and honest interest disclosure states the potentially most important conflict first [1].

The general declaration of interests might bear the risk that a conflict could be perceived that does not exist. But such scepticism will do less harm than the growing mistrust when a real conflict can be concealed. It does not matter here whether this is only a perceived conflict or a real conflict of interest. Physicians and patients do not want to be victims of subtle suggestions [33].

To be informed, not only readers and listeners but also patients need complete transparency. Therefore, it should be considered that the amount of financial funding by the industry must also be stated for each included subject in the patient information form of any investigator-initiated trial (**Table 2**). If not stated for each included patient, the total amount must be declared at least for the complete study. In any case, the disclosure is needed whether the money goes to the institution or into the pockets of the investigator. Mistrust will spread and

neglected sustainability will come back in the end. A damaged reputation ultimately results, as has been discussed with the examples of gene therapy, rofecoxib, new antidiabetics or oseltamivir [3, 34].

Declaration of interest rules are not yet sufficiently specified. Besides being blamed by publicity, one sanctioning instrument might be most efficient: a researcher could be excluded from receiving any further legal sponsoring, be it from industry or from government. But academic institutions dislike inflicting such ultimate and most efficient sanctioning instruments since these harm the institution itself.

3.2. Authorship

To publish purely industry-driven research, the name of a highly recognized scientist can be misrepresented as an author. Ghost, guest or gift authors might make a company look like a great research partner or a paper look like a good science [12]. On the other side, a great scientific and ethical problem is posed when individuals participate in research, data analysis and/or writing of a manuscript but are not named or disclosed in the author byline or acknowledgements [35]. Some ethics experts maintain that placing employees of a company on the list of co-authors will make them accountable and reduce the role of ghost-writers (Susan L Norris, Howard Brody).

If included in the list as co-authors, however, employees or experts acting in charge of pharmaceutical companies can influence the results. As discussed for epoetin or for some psychopharmacological trials, drug company employees could significantly guide the presentation of data [36, 37]. The influence of a co-author could even be more problematic than that of a ghost-author or a ghost-writer. The analysis of 198 trials in three psychiatric journals found that the involvement of a drug company employee was even stronger associated with the interpretation of study outcome than the financial sponsorship [36].

To limit the subtle dominance of companies, the probably better solution could be first to only consult independent, not the companies' statisticians. Furthermore, the contribution to a study by employees or representatives of the industry should exclusively but explicitly be mentioned in the acknowledgements [38]. This does not preclude employees' scientific work from being published independently by themselves. Employees can publish their own papers but should not be made co-authors of investigator-initiated trials. This rule must be clarified by contract from the beginning of the cooperation (**Table 2**).

3.3. Ethical oversight

In consequence, clear guidelines, rules and even laws regarding how to motivate for integrity and to control for misconduct need to be released. We propose to establish both academic and legal measures to meet this target. Also in such research that was publicly funded by a government agency, misleading influences might endanger research integrity: plagiarism, falsification and fabrication of data, fraud, and violation of good scientific practice reflect the other growing debate on misconduct in research and science [39, 40].

Intrinsic virtue prompts the professionals to not let themselves be corrupted [3]. But such virtue should be encouraged and affirmed. The oversight by an ethics committee might refine such virtue. The order to disclose all industry interactions had a salutary effect: transparency facilitated the complete abstinence from the addictive power exerted by industry sponsoring; after enactment of this order all members of the Medicines Agency of the German Physicians Association AkdÄ completely ceased all collaborations with industry [41]. Transparency regulations and oversight ethics have not only a prophylactic but also a curative potential when applied to the physician-industry relationship.

Between the basic confidence in personal virtue of the physicians and the deterrent legal threat by law there is a role for the ethics committees. For all experts with a mandate to release guidelines an ethical oversight has already been postulated [42]. This oversight will demotivate any concealment and manipulations. Such a committee will also be able to correct misconduct and personal failure. This committee will approve whether the financial compensation is in balance with personal work.

Financial incentives will be discouraged by such an institution before the law comes into action. Such an ethics committees and institutional review boards have long been established to approve any clinical trial for the risk-benefit balance. It should be made an obligation to such ethics committees to guarantee also the balance between financial compensation and personal work (**Table 2**).

4. Conclusion

Material goods such as medicinal products or new therapeutic agents can best be manufactured and distributed by market mechanisms; but social and personal relations should still be regulated by moral values [43]. Protection is needed for an independent medical and academic sector where both the patient-physician relationship and integrity of research are “sacrosanct” [1]. True science must not be free from any interest, be it economic or emancipatory [44]. In order, however, to maintain academic integrity and to comply with the fiduciary duty of the medical profession, it is in the interest of the credibility of each scientist and every physician to check herself/himself for possible conflicts of interest and to limit such influence. While patients defend their personal identity, physicians must fight for their moral integrity.

Money will do damage to physicians’ reputations especially when it makes them resemble a company lackey [3]. Many physicians feel ashamed when their collaboration with industry is disclosed. Physicians will be motivated to keep their own interests under better control by the need to disclose any CoI and make their interests transparent. A disappointing response to the conflicting interests has been identified as “moral disengagement operations” such as justification, euphemistic labelling, diffusion of responsibility, sharing blame, minimizing risks and victim dehumanization [45].

Where patients can no longer trust medicine, controllers and lawyers will dominate the scene [46]. Transparency consequently allows for more tolerant regulation because the ethical

principles are proactive and not restrictive. On the patients' side, in addition, transparency about financial stimuli might also bring down some illusionary hopes and wishes back to reality.

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Transparency

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