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National Council of Ethics for the Life Sciences

**Opinion and Recommendations concerning
Declaration of Interest and Conflict of Interest in Health
and Biomedical Research**

(July 2013)



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

MEMORANDUM

Rapporteurs: Ana Sofia Carvalho, João Ramalho-Santos, Miguel Oliveira da Silva.

PRELIMINARY NOTE: This Memorandum is an instrument of introductory reflection on the concurring opinion, and is the sole responsibility of its authors. As such, it has not been voted on by the full CNECV.

1. INTRODUCTORY NOTES

It is an undeniable reality that current health care faces important and complex challenges as never before, thanks to an unparalleled increase in both complexity and cost, which a context of economic crisis has exacerbated. These challenges include, among others, the sustainability of the National Health Service, the high price and complexity of treatments, complementary means of diagnosis and drug provision and pressure to cut costs in health care. In comparison, and from a less thorough perspective, the issue of conflict of interest could be considered a matter of lesser importance. However, none of the challenges described above can be properly undertaken without reflecting deeply on the theme of conflict of interest. Society has got to trust in the health care which is on offer, in the scientific results that are transmitted, in the institutions that educate the professionals, in those institutions that regulate the practice of medicine, and in the healthcare industry, and not be inappropriately confronted with growing distrust concerning the financial interests of both health professionals and the several health care industries and partners involved.

This is not the first time the CNECV has made pronouncements on the issue of conflicts of interest and the necessity to make the respective statement. While this approach had not yet taken the form of Memorandum and Official Opinion - as is the present case - this theme had already been the object of reflection on two occasions: in 2008 as a chapter of the book *Biomedical Research* (Lobo Antunes, 2008) and in 2012 in Opinion 64/2012/CNECV concerning a Decision-making protocol for financing the cost of medicines. It is also worth underlining the study undertaken by APIFARMA, which resulted in the publication of a code of ethics, which had been the subject of a protocol with the Medical Association. More recently, in 2013, the Ministry of Health, within the framework of a decree law concerning the status of medicinal products, introduced the requirement for a compulsory declaration for health professionals and patient associations. Furthermore, in a subsequent resolution, 25 euros is stipulated as the threshold beyond which all offers received from industry must be disclosed to INFARMED.



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

Based on the recurring failure of previous regulations - "in a way it would almost be enough to comply with a signed protocol never put into practice" (Antunes, 2008) - many think that it is not sufficient to continue to have a greater or lesser acquis and regulations to change this situation, but that what is necessary is to create a system of effective penalties for the respective breach.

A conflict of interest in the areas under consideration comprises a set of conditions in which a professional decision concerning a primary interest (such as the patient's welfare or the results obtained from specific scientific research) may be unduly influenced by a secondary interest (such as financial gain or profit) (Thompson, 1993).

The primary interest is determined by higher moral values: the professional ethics of a doctor, a researcher, a teacher, or another specialized professional. The primary interest is thus one that guarantees the best welfare of the patient / research subject, research integrity and excellence in education. The primary interests include the promotion and protection of scientific integrity, of the best welfare of the patient and of the quality of medical education. These, which may be simply referred to as medical professionalism, are often designated as ends or objectives (to promote patient wellbeing), such as obligations (the obligation to promote patient wellbeing), or rights (the right of the patient to have a doctor who promotes their welfare) (Lo & Field, 2009).

The second main element of a conflict of interest is the secondary interest. The secondary interest may, in some situations, not be illegitimate in itself and might even be an integral part of the profession. Nevertheless, the relative weight of these secondary interests in the final decision can never place in jeopardy the primary interest in question. The secondary interests, in this case, are unacceptable when they acquire a greater weight than the main interest in professional decision-making.

The secondary interest related to the financial component has been the most visible aspect of this problem. However, other secondary interests, of equal or greater importance, and sometimes even harmful, such as favouritism towards relatives, friends or co-religionists, the desire for prestige and power, institutional or personal quarrels and jealousies, which are more subjective and not easy to identify objectively, have significant consequences which it is important to pay attention to.

Not all conflicts in the field of medicine are conflicts between a primary and a secondary interest (Lo & Field, 2009). In different situations the professionals in this area are faced with the need to decide between different courses of action where, on frequent occasions, two or more conflicting values will be found. These conflicts, the so-called conflicts of obligation, represent tensions between different primary interests, between different values or ethical positions. The so-called conflicts of commitment are closer to what is meant by conflict of



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

interest. This might involve a careful weighing-up of different responsibilities in the case of health care providers or researchers taking on external commitments, such as voluntary work, teaching or research within or without the institution. These conflicts, similarly to those previously listed, in most cases represent a conflict between different primary interests: between the provision of health care to the patient and biomedical research, between the provision of health care to the patient and medical education, and between scientific research and teaching. Thus, in order to circumvent this problem, the various institutions must have clear institutional policies and objectives that will prevent any future conflicts.

The conflicting interests of health professionals and researchers pose a threat to the integrity of scientific research, the objectivity of medical education, the quality of health care and society's trust in medicine and scientific research. Continuing and tolerated behaviour regarding conflict of values, which often acquires the status of normality, frequently commences at undergraduate level (Spelsberg, 2009). It is therefore important to emphasize that the discussion concerning conflict of interest, due to its considerable importance, should not be considered a mere trend, with obscure recommendations and often with proposals that lack justification (Kottow, 2010). On the contrary, such reflection should be at the forefront of the debate about health care, the ethics of research, medical education and bioethics.

Different authors and important social players in the area of health and other areas have argued that little or nothing changes with general formal declarations, to which the public have no or only limited access, and which are not very specific and are difficult to interpret (both for those who draw them up and those who read them). Thus, it is necessary to overcome this shortfall, to get to the bottom of the issue, to develop a civic and ethical culture of accountability as a way of life, and not as a requirement imposed from above, which from an individual or collective moral standpoint may not be accepted. Despite the consensus that conflicts of interest cannot be eliminated entirely, and despite there being some well-known commendable efforts to address this issue, our goal is to develop a set of rules which enable us to manage these in a rational and ethical manner (Kachuck, 2011), so as to enable us to maintain society's trust in science, in researchers and health professionals, supporting all initiatives which aim at creating greater accountability and transparency at this level.

As outlined by Lobo Antunes (2007), it is no longer possible to ignore the paradox that emerges from the conflict between two moral principles: altruism and self-interest, which in its most extreme form is just pure selfishness. The right balance between these two opposing values constitutes one of the toughest challenges for the medical profession. On the one hand, personal interest fosters values such as the guarantee of self-satisfaction, academic or professional career advancement, public recognition and financial comfort. On the other hand, altruism requires the promotion of those same values, albeit for the benefit of others, and if



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

necessary, by sacrificing our own values. It is in this unstable and rickety balance that the issue of conflict of interest must be analysed.

2. CONFLICT OF INTEREST IN MEDICAL EDUCATION AND IN THE TEACHING OF PROFESSIONALS FROM OTHER AREAS OF LIFE SCIENCES AND HEALTH

The final mission of medical education is to prepare physicians to provide effective and safe care, of high quality, efficient, timely, accessible and focused on what is best for the patient. The aim of the mission is also to prepare doctors critically to evaluate scientific evidence, keeping abreast of scientific advances throughout their professional lives. Ideally, these two elements are included in the formal curriculum, both of medical teaching and of teaching activity that other professionals carry out relating to the provision of care or scientific research in the areas of Life Sciences and Health.

On the other hand, this training should also include ethics, research methodology and scientific integrity, in order to harmonize the approach of all professionals involved. This is important when one considers the multidisciplinary composition of most teams. However, these elements are influenced by the informal and / or hidden curriculum, the students, teachers and senior researchers bearing an undeniable responsibility in the acceptance and manifestation of certain types of behaviour and practices.

Currently, the role of industry in the sponsorship of education/postgraduate medical training is important and complex. It is therefore important to regulate with transparency and sincerity the contact that health professionals have with industry. Suffice it to say that, viewed objectively, however good the intentions and political programmes of public officials often are, it would prove very difficult to implement and complete the postgraduate training of junior doctors and many specialists if there were no support (often self-interested and potentially skewed) from industry. Also important is the support for participation - at congresses, conferences or international symposia of high scientific quality. In these cases the number of those who directly or indirectly participate just because of the afore-mentioned sponsorship is extremely high. In fact, this opportunity for meetings and scientific discussion at the highest level represents a gain at the level of skills and training of health professionals, and this added asset is not inconsiderable.

However, given the difficulty of disentangling clearly and objectively what it is that constitutes educational skills and what should be considered subtle forms of commercial bias, the number of experts who have suggested significant changes in this relationship between industry and continuing education activities / programmes has been increasing (Steinman et al., 2010). Thus



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

it may be desirable that the support for postgraduate training is not meted out on an individual basis, in accordance with the not always transparent criterion of industry, but in an institutionalized way, with clear and transparent rules, in line with the professional interests and related areas of researchers, technicians and clinicians. Given the constant changes in this area, support at this level that may come from other sources will also be considered relevant, such as instrumentation companies, insurance companies and banking or financial institutions with influence in this area, drug dispensing companies, or companies specializing in the promotion of events, among others.

It is important to underline the connection, often barely institutionalized and hardly transparent, of university professors and senior researchers with industry and the media. Because of this, training and research institutions must have objective standards and policies for the link between human resources and industry, in order to prevent scientific excellence being used in the marketing employed by the industry.

Finally, it is worth pointing out that this type of procedure has also been expanding into undergraduate education, in particular by the granting of various sponsorships to student associations or bodies, which may result in trivializing the process before its nature and consequences have been completely absorbed by future professionals.

3. CONFLICT OF INTEREST IN RESEARCH WITH HUMANS AND CLINICAL TRIALS

Health interest declarations are intended to prevent and control less transparent practices that may lead to favouritism, fraud and corruption, expressing both in an individual and public way a culture of transparency - in this case in scientific research and biomedicine - which enables excellence and maintains public confidence in science.

The role of biomedical research in the discovery of new or improved tests / treatments / drugs for improving individual and public health cannot be disputed. According to a report published by the British House of Commons, "Approximately 75% of clinical trials published in *The Lancet*, the *New England Journal of Medicine* (NEJM) and the *Journal of the American Medical Association* (JAMA) are sponsored by industry" (Abramson & Starfield, 2005). Accordingly, and as previously mentioned in relation to teaching, in this area we must also consider not only concerns about the financial relationships between industry and researchers, but also the potential benefits of such relationships. These research partnerships between industry, academia and government are essential for the discovery and development of new drugs and medical devices, and the concomitant prevention, diagnosis and treatment of various health problems; nor must there be any stigma automatically associated with the professionals involved in these activities. Nevertheless, it is crucial that citizens, patients and their relatives,



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

doctors, researchers and those responsible for the shaping of public policies can be assured of the scientific validity of this research.

Until about 20 years ago, or perhaps less, the institutionalized practice of declarations of interest did not ethically form part of scientists' activity routines: there was no reference to them in articles (not even scientific journals had any well- defined policies in this respect), and in scientific communications it was not common for such declarations of interest to be indicated. In short, in science, one was dealing with a different ethical paradigm. The need felt to make these relationships explicit and to regulate them by means of declarations of interest presupposes that not always do those involved (including in these areas) regulate themselves, that is to say, they neither act nor interact in an ethically spontaneous manner -as the history of post- Second World War Bioethics up to the present day demonstrates (Willowbrook, Tuskegee, the South Korea stem cell fraud, to name some examples). In any event, there is always a legitimate discussion about what is the right standard that requires prudence ethics in each case.

Relationships between industry and biomedical research in terms of financing have grown markedly in the last few decades, the largest source of funding for biomedical research in the United States currently exceeding the funds made available by the National Institute of Health (NIH). Despite the benefits, relationships with industry can create conflicts of interest that can have a negative impact on the goals of medical research. One of the fundamental assumptions of scientific research is that the information, data, and methods should be universally accessible. So when a piece of research is carried out with a commercial purpose in mind and with the intention of safeguarding the commercial value of the object of that research, which may be patentable, this sharing is often compromised. Access to data is another concern. In some industry-sponsored research, the researcher does not have full access to the data, the handling and aggregating of these being the responsibility of the company's biostatistics departments (Lo & Field, 2009). This can raise doubts about the data's veracity or the results presented. Aware of the problems of integrity associated with this type of requirement, some scientific journals have decided to lay down restrictions and not publish the results of industry-funded studies, in case restrictions on full access to the data are imposed (DeAngelis et al., 2001). Due to multiple relationships of researchers with industry and various stories of fraud and corruption, a culture of transparency and accountability has been advocated of which (including in science) the obligation to publish declaration of interests is an integral part.

Several studies have shown that many clinicians do not voluntarily reveal the support they receive from industry. In a 2007 study in the USA amongst orthopaedic surgeons who carry out hip and knee replacement surgery, 71.2% willingly reported having received payments from the manufacturer of the prostheses involved. Among the reasons for non-disclosure of financial support, 38.9% reported that the payment was not related to the topic of the



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

presentation made at that meeting, while 12.3% said they had misunderstood the requirements for the declaration (Okike, 2009).

Several systematic reviews have pointed to a disturbing trend; clinical trials funded by industry are more likely to produce results that benefit industry (Lo, 2000; Lexchin et al., 2003). In the same vein, with even more significant consequences, other studies have underlined the fact that some report findings on the effects of a certain drug were presented as positive even when the experimental results did not support that conclusion (Djulgovic et al. 2000). Some of the examples attention was drawn to include: (1) published clinical trials suggested that selective serotonin reuptake inhibitors had a favourable risk-benefit profile ratio in children with depression. However, when unpublished data were taken into account, the results showed the opposite tendency, the risks outweighing the benefits; (2) the results of clinical trials with paroxetine that demonstrated an increased risk of suicide in adolescents or inefficacy of the drug in this group of patients have not been published; (3) the manufacturer of aprotinin, a drug used in cardiac surgery, withheld the data showing proof that the use of this same drug increased the risk of kidney failure, myocardial infarction and heart failure; (4) the results of a clinical trial, which compared the combined use of statin and ezetimibe with the use of a statin used separately in individuals with high cholesterol levels, and which showed that no differences existed in the wall thickness of the carotid artery in both groups, were not published (Lo & Field, 2009).

Several suggestions have been made to justify this fact: in the first place, companies seek to invest in products which are potentially effective and safe; thus only the drugs deemed likely to succeed were selected to enter the clinical trial phase; in the second place, the researchers, persuaded of the drug's efficacy by individual research, may tend to develop financial relationships with the promoter of the clinical trial; in the third place, the studies in this area may be designed and / or undertaken with less rigour or be designed but not conducted according to the experimental protocol; fourthly, advertisers can be conditioned to accept the publication of study findings with favourable results. The scope of this type of procedure is also conditioned by the fact that the publication of scientific research findings in general (irrespective of their origin or funding source) favours positive results, and is resistant to the dissemination of inconclusive ones, which often prevents the available literature from adequately reflecting the actual state of the art (Sandercock, 2012; Janot et al., 2013).

Another issue deserving of consideration is ghost authorship of scientific articles. In this type of authorship, regarded as ethically problematical from the point of view of scientific integrity, the author(s) connected to the Healthcare industry (or other relevant actors) are not identified as authors of the article to circumvent the conflict of interest declaration. Thus, when it comes to the publication of the results, many of the trials that have a significant number of authors linked to the industry appear only with the names of researchers linked to research centres and / or universities.



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

4. CONFLICT OF INTEREST IN HEALTH CARE PRACTICE

It is commonly assumed that doctors and other health professionals must put the interests of patients above all others. However, the truth is that this value is often compromised by social, economic and cultural nuances, and as emphasized by Lobo Antunes (2007), by the ubiquity of doctors' work, which quite often serves non-clinical objectives. In spite of the doctor-patient relationship being the noblest and most traditional duty, it is "pure hypocrisy to affirm that it dominates all other professional duties of the physician." As Pellegrino and Relman (1999) stress, "... often the ethical goals have been mixed with protection of self-interest, with privileges and prerogatives. The suppression of self-interest is the characteristic that distinguishes between a real profession and other occupations."

The financial relationship with industry is not intrinsic to medical practice and therefore should be avoided whenever it causes conflict of interest. These relationships create a conflict of interest when physicians: (1) accept gifts from industry, including meals and drug samples; (2) participate in promotional acts on behalf of companies; or (3) have a financial interest in a medical products firm whose wares they prescribe and / or recommend.

Furthermore, conflicts of interest may arise from the way health care professionals are reimbursed for the service they provide. These conflicts, which often appear when remuneration for a particular service is involved, can generate amongst these professionals concerns of a different nature and have posed significant challenges to health policies and the consequent efforts to control, limit or eliminate such concerns. The highest levels of payment for procedures (e.g. surgery, invasive procedures, diagnostic imaging and chemotherapy) when compared with the level of remuneration for other types of medical care (for example, medical assessments and counselling or incentive systems for specific acts, some of questionable interest), have contributed to an escalation in the use of invasive procedures. Because of this, one's secondary interest (i.e. higher remuneration for the procedure provided) has the potential to skew one's primary interest, the best welfare of one's patients. This kind of conflict poses the ethical question at two different levels: on the one hand, at the level of individual welfare, the patient receives unnecessary services which as a result cause unnecessary expenditure, while on the other hand, at the level of welfare in general, society, increasingly faced with budgetary constraints on healthcare, is overburdened with needless expenses.

Referral of patients to another health unit in which the doctor him/herself provides services (self-referral) or to units in which "partners" work (clearly situations in which professional competence is not the main consideration), for appointments, examinations or interventions,



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

has often been cited as a common practice in Portuguese medicine. One of the reasons that may contribute to such a situation could be related to the practice of medicine within the NHS alongside private medical practice, a situation that various health professionals proclaim that they will regulate, but which even today continues to be the target of sharp criticism. It is worth stressing that this form of conflict assumes less importance when the request is made by the patient him-/herself, freely and independently. By way of illustration, we can instance the cases of patients who either by their own means or by grants or health insurance, choose to transfer to private health care as a means of circumventing the waiting list for elective surgery/ appointment or shortening the waiting time for additional examinations.

Marketing is undoubtedly a major expense for firms and other entities with activity in this area. Their representatives use a variety of interpersonal techniques, including offers, to establish relationships with physicians and to promote their products. In addition, companies have information on the prescribing practices of each doctor and can use this to monitor the effects of their relationship. The approval and marketing of the vaccine for the human papilloma virus and cervical cancer was a concrete example of the use of health professionals for the marketing of products. The project involved hundreds of doctors and nurses trained by the company who received various financial rewards and gifts in exchange for conversations and communicating information to other professionals (Lo & Field, 2009).

The participation of physicians in clinical trials conveys important benefits at various levels; the recruitment of participants, the representativeness of the sample and the trial costs can benefit from the research being conducted in the context of health care. As regards clinical trials, the majority of patients who are recruited in principle ignore the declarations of interest of the respective researchers, not even imagining that these (the individual researchers themselves and / or the institutions which exercise functions) in the overwhelming majority of cases receive subsidies from industry to conduct such clinical trials. Several authors, with the aim of increasing transparency, have argued that patients who agree to participate in clinical trials must be acquainted with researchers' declarations of interest. These must be included on the information sheet or consent form to be distributed to research participants. In this way, not only is the integrity of scientific research preserved (Weinfurt, 2009), but also the autonomy of the trial participant is maximised.

In the same way, any payments made to the media (or their agents) by those involved in scientific research or health care, in order to increase their media presence, with eventual benefits at other levels (enlistment of patients, participation in trials, influencing public opinion, etc.) should also be the object of scrutiny.

5. CONFLICT OF INSTITUTIONAL INTERESTS

Previously, we examined the conflict of interests that occurs at an individual level. However, it is also important to consider the conflict of interests that can occur at an institutional level.



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

This form of conflict of institutional interests involves situations that are as serious as those related to individual conflicts. They arise when the financial interests of the institution, or its directors, can endanger and influence the decisions that involve that institution's primary interests. Some of the relations which institutions maintain with industry can generate significant benefits in terms of patient care and scientific research. Nevertheless, as in the case of the conflicts earlier described, here too the danger zone between what constitute the benefits and undue influence on decision-making is sometimes very tenuous.

In universities and research centres (whether public or private) such conflicts can occur in several cases: (1) when the aim of the research is to apply for a patent; (2) when the institution has financial interests in companies incubated in that institution's space (or in companies which still maintain a relationship with the said institution); (3) when the institutions seek and receive company funding; (4) when the institutions themselves provide services directly.

In institutions that provide health care, conflicts of interest also arise when the hospital is sponsored by a particular industry in order to provide support for patients with a specific disease, but when access to these services is limited to patients who are treated with drugs sold by that same company. It is also important to state that some professional associations and patient advocacy groups rely on medical supply companies for a significant portion of their total revenue and for specific activities (e.g. continuing medical education and/or medical and scientific advice), and there are potential social benefits resulting from this activity, provided that it is carried out with transparency and avoids situations of potential conflict of interest.

Dealing with conflict of institutional interests may be more difficult in some respects than dealing with conflict of individual interests, since the regulatory bodies (usually university senates, academic or hospital boards) are the same bodies that make decisions regarding benefits. Another aspect that often makes it difficult to regulate this kind of conflict is based on the fact that decisions whether to accept or reject a particular benefit may be more easily understood as serving the institution. However, it is precisely because this argument is so plausible (and often valid) that conflicts of interest at an institutional level are so often ignored. Thus, it is crucial to carry out a careful assessment as to whether these prejudice or promote the institution's main duties.

6. CONFLICT IN THE DEVELOPMENT OF CLINICAL GUIDELINE STANDARDS

Clinical guidelines are at the crossroads of biomedical research, education and clinical practice. Ideally, and as published in Opinion 64/2012/CNECV with regard to a Discussion Model for financing the cost of medicines, they should be based "*on a critical evaluation of scientific*



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

evidence, and on the relative clinical benefit when compared with current standards. There should be an analysis of the impact on the improvement and control of the chronically ill and an evaluation of all available alternatives." Undoubtedly, one of the greatest difficulties that arises in the development of these standards is related to the lack of research in some areas that could ultimately result in very comprehensive rules and recommendations. Therefore, clinical experience remains a significant and indispensable element in the development of clinical guidelines.

The financial relationships previously mentioned, the fact that these standards rely on specialists, who also often receive similar requests from industry, can create conflict of interest and pose a risk of undue influence. Therefore, organizations and physicians who publish standard rules should publicize the document of the guidelines they have followed in their preparation, the clinical context for which they are intended, the authors' credentials and conflicting interests, and their qualifications, experience and training.

7. CONFLICT OF INTEREST IN SCIENTIFIC RESEARCH IN THE LIFE SCIENCES NOT IMPLYING ANY INVOLVEMENT OF PATIENTS OR USE OF HUMAN SAMPLES

Potential conflicts of interest in Life Sciences research assume a much more complex significance from a bioethical standpoint when they imply the involvement of patients, or the use of human samples. However, there are other instances in which one can identify potential conflicts in research undertaken with other types of biological materials, whether they be cells in culture, laboratory animals, biological samples or environment/ecology-related studies. In general, the recommendations of an ethical nature that should be proposed regarding the respective declarations of interest in these cases will be similar, although they will assume particular importance when it comes to research on patients.

Given the nature of contemporary research, situations that embody potential conflicts of interest in the Health and Life Sciences can seem almost inevitable, considering that several institutions are sponsored by companies with an interest in the outcome of the research, or considering that it may prove difficult to assemble and appoint suitable sufficiently knowledgeable panels to evaluate, for example, studies related to industry without the vast majority of experts in this field having to declare conflicts of interest that could potentially affect the process, either due to connections with the company concerned, or with its competitors (Angell, 2005; Kassirer, 2005). The self-correcting mechanisms of scientific research, in terms of the need for reproducibility, are often invoked as a security blanket in terms of minimizing the potential effects of undeclared interests (Ramalho-Santos, 2007). However, beyond the ethical question of the possible waste of funds, and of undermining public confidence, of particular importance are situations affecting studies with implications



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

for human health (e.g. non-publication of serious side effects in clinical trials; Curfman et al., 2006), or those which normally only take place once, and which can have long-term social consequences (e.g. environmental impact studies of a large urban or agri-industrial project). The mechanisms for dealing with potential conflicts of interest take many forms, but to a large extent entail a (usually voluntary) declaration of connections which might imply a conflict, and which are, or are not, investigated and validated by sponsors or evaluators of scientific activity. They also entail the establishment of assessment panels that minimize the potential effects of eventual interests on the part of these same entities.

Although no total uniformity exists between countries, institutions, funding agencies or scientific journals that publish research findings in life sciences, there is a clear underlying trend to consider the interests involved in scientific research as an important issue worth taking into account, as indicated by the existence of guidelines for the identification and prevention of conflicts of interest, based on different types of declarations of interest, although this process varies from country to country, and from organization to organization, and in particular depends to a large extent on voluntary participation and transparency of those involved (Davidoff et al., 2001; ERC, 2007, 2010, Blum et al., 2009; WAME, 2009; CSE, 2012; MRC, 2012; FCT, 2012, 2013; COPE, 2013, ICMJE, 2013; IoM, 2013; NIH, 2013).

Curiously, this concern does not seem to be shared with the same vehemence in the economic-financial academic research domain, in which authors of different types of studies do not have to disclose the agencies, banks, insurers or companies that fund them (or do so very infrequently and unsystematically), mainly through consulting agreements, which can clearly hide potential conflicts of interest, and have consequences for the global economy (Carrick-Hagenbarth & Epstein, 2012). Fragmentation in the European Community, not only from the standpoint of criteria and mechanisms for declaration of interest, but also regarding how to deal with them consistently, must be a cause for concern (Bosch, 2010).

In very general terms the potential conflicts of interest can be divided into different types (related to their nature) and different categories (related to their relevance at any particular time). To be more specific, they may be considered as either financial or non-financial interests, and as interests that may influence the results of a study, or interests that could affect the subsequent evaluation of these results.

In theory, interests of a financial nature are the easiest to identify, and are those whose potential impact can be assessed, provided that there are clear instructions in this regard, and transparency on the part of those involved. These interests involve financial sponsorship of jobs/projects by entities with a direct interest in the research results, whether they be (e.g.) companies wishing to corroborate the effectiveness (or non-toxicity) of therapeutic agents and equipment in different contexts and biological systems, or agro-industrial companies wishing



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

to prove the efficiency (or non-hazardousness), and the environmental impact of substances / waste products, of development projects for an area / region, or of extraction / production methods. They also include the granting of projects or contracts (with the capital gains that this implies) on the part of donors to individuals or institutions not based on scientific criteria, but for personal or family reasons.

We can also cite indirect financial considerations, such as the free allocation of reagents, equipment, or other materials for the purpose of conducting a given study; sponsorship for participation in conferences or for the provision of promotional materials, and also the participation of researchers in a company through allocation of shares or consulting agreements, for example). The evaluation of these latter potential conflicts of interest will depend on the effective link being made *a priori* or *a posteriori* to the study in question.

Non-financial interests may potentially be more difficult to identify, and involve instances in which issues of a non-scientific nature can crop up, but which relate to personal or social connections. These can interfere with the completion of a study, for example, unduly enabling / hindering access to specific material (place, samples, databases), or they can consist of a system of reciprocities in the evaluation of research projects / academic theses (whether positive or negative in nature) without the evaluator excusing her/himself from the process when the researchers are collaborators or competitors.

From another perspective, the impact of potential conflicts of interest may be different depending on when this is relevant, particularly if it is before the commencement of the study, or if it deals with its results. Thus, there may be potential conflicts related to the granting of a study or funding (whether or not competition is involved, e.g. through a bidding process) to a researcher or institution based on non-scientific criteria, such as personal, social or family relationships, or ideological in nature, for example in the sense of choosing a researcher linked to the study sponsor or with a pre-disposition to reach a particular conclusion desired by that sponsor. Problems related to the evaluation / publication of a piece of work can also occur, if it is carried out by organizations or researchers with potential interests which are of relevance to the study or its authors.

Regarding the methods for dealing with conflict of interest in the Life Sciences, more or less detailed criteria exist for the self-presentation of the respective statements by researchers prior to submission of projects, but above all for articles for publication, about situations embodying possible potential conflicts [of interest], whether of a financial or non-financial nature. These criteria are available at the majority of funding agencies, albeit with widely varying degrees of thoroughness (MRC, 2012; FCT, 2012, 2013; IOM, 2013; NIH, 2013) and more explicitly, in associations that bring together editors of specialized journals for publication of scientific results (WAME, 2009; CSE, 2012; COPE, 2013; ICMJE, 2013). It should



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

be stressed that although the declaration of interest by authors of academic papers published in accordance with the standards mentioned above is mandatory, the information disclosed is voluntary, and apart from cases of complaint / fraud with potential *a posteriori* consequences for those researchers involved, no validation mechanisms appear to exist, although an attempt has been made to involve the institutions that employ or finance researchers in the analysis, verification and resolution of any problems which might arise.

Still on the subject of publication of scientific results, a recent study (Bosch et al., 2013) demonstrated that the need felt by top scientific journals to identify authors' conflicts of interest of a financial nature is clearly seen as essential, applying to 90 % of publications. Perhaps surprisingly, 70% of publications are equally concerned with declarations of interest of a non-financial nature, suggesting that these have attained a higher profile. One concern of note is that the same study mentions that only 39% of the publications called for declarations of interest on the part of their editors, that is to say, by the very person who is ultimately responsible for evaluating and deciding whether a given contribution will be published or not, thereby suggesting a discrimination between those researchers who produce scientific work and those who evaluate it, which does not seem ethically defensible.

8. MODEL OF DECLARATION OF INTERESTS

The United States (USA) Committee on Conflict of Interest in Medical Research, Education, and Practice suggests which ethical criteria to take into account in the implementation of public declaration of interest models (Lo & Field, 2009). First comes the criterion of proportionality, which requires that policies, whether preventive or corrective, are efficient and effective in divulging serious conflicts of interest. The second ethical criterion demands that ethical statements are transparent. Transparency is essential for determining whether the declarations of interest are available not only to those who are subject to them (e.g. physicians, researchers, academics, authors of scientific articles and members of evaluation panels), but also to other stakeholders, including the public. Confidentiality and privacy protection rights place some limits on the information that could be available to a wider audience. On the other hand, the explanation of institutional or national policies relating to declarations of interest should be explained to all those who are directly affected. The final criterion, based on the principle of justice, is that of equity. On the one hand, this requires that policies concerning declarations of conflict of interest are applied to all doctors or researchers without exception, and on the other hand, it requires that individuals in different



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

institutions [but] who are in similar situations, are treated in the same manner. Otherwise, the ethical sustainability of policies for implementation will be called into question, since the decisions can be considered arbitrary.

In the analysis of and discussions about the effectiveness of declarations of interest - notwithstanding the enormous diversity of their contents - it is generally agreed that, aside from their positive aspects, which encourage the adoption of ethical standards and transparency, efficacy and efficiency are often questionable, not reaching the intended or desired goal (Spelsberg, 2009). In this context, the discussion revolves around common policies among different institutions and means of scientific diffusion, with similar models for the disclosure of potential conflicts of interest, and with penalties and sanctions of similar scope and size.

Questions related to the reliability and accuracy of the declaration are also issues being debated (Marcovitch, 2009), requiring validation by credible bodies.

It is unrealistic to expect that the declaration of itself will increase transparency and ethicality in science, biomedicine and public health. The declaration of interest should be an integral part of anti-corruption policies which leads to the promotion of transparency and a civic and moral culture.

In this regard it is important to emphasize the need for professional codes of conduct (not only for health professionals, but also for the healthcare industry, patient associations, scientific societies) which really work, effective protocols, a public register of every clinical trial and other research activities (including post-marketing studies) with publication of all relevant results, the continuing education of health professionals which is not dependent on industry, annual public reports concerning progress in the struggle for transparency and the fight against corruption and fraud (Spelsberg 2009).

The enormous diversity of models of declaration of interest (e.g. in scientific journals) is one of the obstacles to the development of a more uniform policy which would enable homogeneous and comparable results to be obtained in this area. In this sense, various scientific journals have agreed that the same model of declaration of interests should be shared by the authors of articles in these journals (Drazen, 2010). Even though the impracticability of a single, uniform declaration model is assured - given the diversity of the areas involved - it is nevertheless important to avoid unnecessary duplication and define the various fields and *modus operandi* of the respective databases (Lichter, 2012)

Another issue that has been the subject of intense discussions is related to the frequency with which the declarations of interest should be made. There is a conflict of *systematic* interests (e.g. an accumulation of functions in a healthcare and teaching institution involving overlapping timetables) and other *Ad hoc* interests that involve merely occasional occurrences



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

(e.g. having a close relative as a student and not wanting to examine him/her). In the case of disclosure of conflict of systematic or ongoing interest (e.g. regular conference and congress attendances at the invitation of industry), it is arguable with what frequency such a declaration should be updated.

In the case of disclosure of conflict, whether systematic or sporadic, it is important to know whether such a declaration of interest should or should not appear in an accessible form on the electronic page of the institution (or simply on that of INFARMED), and in what detail it should be reported (financial sums involved) and what type of protagonists should make this declaration. Following the discussion above, we find different positions on who should have access to the declaration of interests. While some advocate maximum transparency, maximum detail and full access for anyone at all, others argue for a happy medium, with some caution that can avoid uncontrolled voyeurism. It being accepted that the President / Board of the institution should be aware of the declarations, can any members of the public also have uncontrolled access to them? Is it sufficient to mention that one has been sponsored to attend a conference, or must one declare the amount that one has been sponsored for? And such an amount having been disclosed, should the knowledge of it be restricted or not?

If it is agreed that health professionals must make a declaration of interests - doctors, pharmacists/chemists, nurses, dieticians, physiotherapists, psychologists - all other stakeholders in decisions, dissemination and analysis regarding health issues should also do the same: politicians and their advisers, hospital administrators and their aides, those in charge of health management, health care journalists. Recently, the literature has placed particular emphasis on the importance of journalists' declarations of interest when writing about health or medicine, so that their impartiality and objectivity remain above suspicion (Dentzer, 2009; Lipworth 2012).

Although spontaneous accountability is always preferable, we should not forget to consider, as a last resort and when the failure of a civic and moral culture of transparency is clear (when the declaration is systematically absent, incomplete or fraudulent), the application of sanctions with concrete consequences for those involved (Spelsberg, 2009; Steinbrook, 2009; Lobo Antunes 2008).

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NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

RECOMMENDATIONS

Considering

- That the principle of responsibility is the moral basis for reflection concerning conflict of interest;
- The Code of Ethics for different professionals in the areas of life sciences and health;
- That the main goal of the health professional should be the maintenance and improvement of public health, whether considered individually or collectively;
- That the greatest responsibility of any health professional is always to seek the best interest of the patient;
- The scientific progress and search for truth that research and scientific and biomedical practice allow;
- The need for transparency in the "ethical pact" between the health professional and the patient and between the researcher and the subject of research, in the relationships of all participants in the area of health ¹;
- The need for public confidence in science as a highly prestigious social enterprise and in the respective health professionals;
- That relationships with industry or other stakeholders are ethically unacceptable whenever they undermine the relationship of trust between doctor and patient or between researcher and research subject;
- The importance of guidelines in establishing practices which help to prevent, disclose and understand conflict of interest situations;
- The difference between a declaration of interest and a situation in which a conflict of interest occurs, in which case decision-making may be compromised;
- The importance of ensuring the exemption, impartiality and independence of all stakeholders through awareness-raising and public knowledge of their interests;
- That very general and invalidated formal declarations of interest are insufficient and can even prove misleading, a more detailed declaration of interest being preferable to one that is too succinct;
- That such declarations, in themselves, do not necessarily eliminate conflict of interest situations, and their respective causes and consequences;
- That the individual interests of professional development should as far as possible be integrated and supported institutionally, in an unambiguous manner;



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

- That the accumulation of different functions with decision-making power in the same person may lead to conflict of interest situations and compromise the independence of the decision;
- That power-sharing reduces the margin of discretion and of potential conflict of interest;

The National Council of Ethics for the Life Sciences (CNECV) is of the OPINION that:

1. Declarations of interests of all relevant stakeholders in the area of life sciences and health (including scientific societies, professional associations, patient associations and healthcare journalists) should be mandatory, as an instrument which upholds the principle of responsibility, public accountability and transparency of professional practice.

2. Whoever undertakes, authorizes or evaluates studies, assignments, projects, dissertations, as well as teaching and research institutions or study cycles, must equally make declarations of interest.

3. Such declarations should be updated whenever there is sponsorship:

a) for any public scientific contribution or communication (oral or written);

b) for any report, news or opinion article concerning health or scientific research, in the scientific (or other type of) press.

4. Health professionals:

a) must refuse offers of significant value (defined by law), without this affecting the legitimate payment for services rendered by companies or entities with relevant interests in healthcare;

b) must not make public presentations or publish scientific articles which unduly benefit the healthcare industry, which are conditioned by it or contain substantial portions written by someone who is not identified as the author or duly recognized as such:

c) must refuse the provision of consultancy services not based on written contracts.

5. Declarations of interest must be made public, and must be easily accessible on the electronic page(s) of the health, education or research institution(s) in question.

6. Health professionals or researchers who have participated in the promotion of any method, procedure, device or drug that scientific evidence will prove to be ineffective or inadequate have a moral obligation to disseminate this information.

7. Participation in postgraduate training should be at an institutional level in accordance with researchers' and health care providers' professional and other related interests.

8. Institutions of higher education and research (medical schools, schools specializing in life sciences and health, biomedicine and biotechnology) must establish rules of conduct for their



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

teachers and researchers and include in their formal curricula courses that enable students to acquire skills in this area.

9. All researchers submitting articles and presenting papers with industrial sponsorship, or the support of any other patron or funder, should refer to that support in the article, presentation or material for scientific dissemination in question.

10. Researchers' declarations of interest in the clinical area should be included in the information given to the subject of the study for the purpose of free and transparent informed consent.

11. In the case of declarations of interest involving financial sums (subsidies, grants, travel, accommodation, advice, payments), these should be detailed and the management / chair of the respective institution should be cognisant of them.

12. Prior to the undertaking of studies and evaluation of projects and results thereof, a detailed declaration of interest must be made (listing all the potential relevant financial and non-financial interests).

13. University Deans/Senates, academic management boards, research centre management (public and private) and hospital boards must take particular care to make clear in their reports of accounts or activities the patronage from which they benefit.

14. Whenever universities and research institutions have financial interests in companies incubated in the same space, they must make a declaration of interest.

15. Healthcare professionals who hold management positions in public health administration and who also perform activities in private institutions must provide a declaration of interest before their appointment.

16. In principle, those who occupy management positions in health organisations should not accumulate other management posts in the same or other health institutions (or any that are linked to such institutions). Furthermore, anyone who is responsible for the career management of close relatives who are subordinate to them must, as far as possible, using common sense, avoid such situations.

17. Members of working groups that produce clinical practice guidelines, as well as committee members, pre-contractual procedure review boards and consultants who support the respective juries or participate in the selection, evaluation, and issuing of guidelines in the area of medical products and devices within the framework of the institutions and services of the National Health Service, as well as of other services of the Ministry of Health, must publicise their respective declarations of interest. In the setting up of these groups it must be ensured:

- a) that amongst their members there are a majority of elements without conflict of interest;
- b) that the group's President is not subject to any conflict of interest;



NATIONAL COUNCIL OF ETHICS FOR THE LIFE SCIENCES

c) that elements that have financial and / or commercial relations with companies that produce drugs or devices that may be affected by production rules are banned;

d) that declarations of interest are disclosed in the public arena.

18. The management policy of the institution with regard to payment of bonuses and incentives, including evaluation and outsourced services, must be properly publicized.

19. "Guidelines" and formularies should be prepared and disseminated on websites of relevant institutions and agencies for research in life sciences, such as the Ministry of Health (e.g. INFARMED DGS) or the Ministry of Education and Science (e.g. Foundation for Science and Technology, Agency for the Accreditation and Evaluation of Higher Education (A3ES)), seeking homogenization and consistency, wherever possible from a European perspective.

20. The members of Ethics Committees must, at each meeting, make the respective declaration of interest in relation to the planned items on the agenda, and should not participate in the discussion and voting on these points.

21. The analysis and management of the declarations must form part of institutional ethics committees' work.

22. The truthfulness and completeness of the declarations can be verified by a body that might be set up for this purpose.

23. False or incomplete declarations of interest must be subject to sanction. Likewise, failure to refuse to participate in a decision -making process where there is a conflict of interest should also be sanctionable.

Lisbon, July 17, 2013.

President: Miguel Oliveira da Silva.

Ana Sofia Carvalho, João Ramalho-Santos and Miguel Oliveira da Silva acted as rapporteurs.

Approved at the plenary session on July 17, 2013, present at which, in addition to the President, were the following members: Agostinho Almeida Santos; Ana Sofia Carvalho; Carolino Monteiro; Francisco Carvalho Guerra; Isabel Santos; João Ramalho-Santos; José Germano de Sousa; José Freitas Hare; Lucília Nunes; Michel Renaud; Pedro Nunes; Rita Lobo Xavier; Rosalvo Almeida.

Hearings. In the context of this recommendation, the following people were heard:

Dr. Guilherme d'Oliveira Martins, President of the Court of Auditors and Chairman of the Council for Prevention of Corruption;

Dr. José Tavares, Official Adviser for the Court of Auditors;

Prof. Jorge Miranda, Emeritus Professor, Faculty of Law, University of Lisbon (FDUL) and the Catholic University of Portugal (UCP).