HELLENIC NATIONAL

BIOETHICS COMMISSION

REPORT ON

CONFLICT OF INTEREST IN BIOMEDICAL RESEARCH

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1. Introduction

In a former Opinion the Hellenic National Bioethics Commission dealt with the ethics of drug clinical studies and other therapeutic procedures. Particular issues concerning the lack of credibility for several studies, due to the financial interests of the sponsor, were already identified in that document.

With the present report, it is attempted to probe deep into the issue of conflict of interest, since it is a serious matter commonly encountered by the physician/researcher. In addition, the credibility of clinical studies is now at the forefront of public interest, not only due to the high cost of medical products, but also because the demand of rapid and effective new treatments is imminent (a recent example is the H1N1 influenza virus).

Progress in biomedical technology changes medicine with an extremely high pace. In the past, biomedical research was mainly conducted in Universities and large hospitals, as opposed to the present situation, where pharmaceutical companies and the pharmaceutical industry have taken the reins. Large companies eagerly convert scientific results into "pharmaceutical products" or into biomedical materials, aiming at financial profits of course. Relationships between physicians and pharmaceutical industries generate -rightly or wrongly- suspicions both to the society and the State. The publicity -often unfounded– which is given in such a relationship has a serious effect on the accountability of health workers, especially when legal entanglements arise.

Sponsoring medical research is initially desirable. There is no doubt that many of the new discoveries, both in the field of pharmacology and biotechnology, are a result of the combination of knowledge -generated in Universities or research organizations-, and the private sector which affords the implementation of such discoveries. The integrity of research, meaning the persistence in drawing results with a valid scientific and ethical methodology, is yet a matter of great concern. To pose the problem schematically, it is a matter of how the researcher would be able to reconcile in practice the ideal of scientific truth with the commercial pursuits of the industry, which sponsors research. A number of cases are reported in the literature, and concern is expressed[1] regarding the involvement of the industry in the potential illegitimate interaction of researchers or institutions with the "sponsors".

Several particular questions, relevant to this subject, may arise:

1) What is the extend and the outcome of an illegitimate influence interfering?
2) Is it possible for the average physician and citizen to show absolute confidence in the scientific "findings" of a research study?
3) Is there a possibility that the general financial deterioration of academic institutions or public hospitals, causing incapability to support independently research programs, would lead to a lack in the complete control of results?
4) Does the search for accuracy in research results discourage sponsors from funding, due to high cost (e.g. because of possible replication of an experiment producing negative results)?

2. Financial data

During the past years, the industry has increased respectfully the funds on clinical research. Data from the USA show that in the 1980s, 68% of funds for Phase II and III clinical studies derived from the government and only 32% from the pharmaceutical companies, whereas in 2000 the relevant percentages were reversed, i.e. 38% of funds was from governmental grants and 62% from pharmaceutical companies. Similarly, in the United Kingdom, 70% of the research outlay stems from pharmaceutical industries and only 30% from other sources.

It is estimated that the cost of drugs is increasing in a two-digit percentage rate, and is already up to $162.4 billion in the USA[2]. The pharmaceutical industries spend 35% of their income for "sale and advertising" expenses. An illustrative, extensive research in the USA in 2010 reported that out of 2.938 participating physicians (primary care physicians, specialized cardiologists, anesthetists, general surgeons and psychiatrists), 83.6% declared they had some kind of relationship with pharmaceutical and medical-device companies, in the form of financial aid, travel expenses, meals and professional services[3]. The estimated amount spent by the pharmaceutical industries on "sale and advertising" outlay is $8.000-15.000 per physician[1].

Another study in the USA in 2004, revealed that 44 pharmaceutical companies spent $2.47 billion on sponsorships. The average production cost for a new drug is between $300-600 million. Out of the total $6 billion spent on "research", $3.3 billion are actually into spent on research itself.

The pharmaceutical companies have additional reasons to urgently seek approval of a product. It has been estimated that due to "industrial espionage", "competitive" industries are very eager to secure the first approval of the product, whatever the consequences. Each day delaying the product approval costs on average $1.3 billion to the industry[2].

This results in rapid drug approval, without the appropriate evaluation of long-term results (on safety and efficacy), with whatever that implies. A recent example is the withdrawal of Avastatin, a drug that had been "prematurely and unnecessarily" approved by the Food and Drug Association (FDA) for use by patients in an advanced stage of breast cancer, a drug approval that proved to be rather hasty, as showed by four subsequent clinical studies examining its safety and efficiency. All four studies proved that this drug not only didn't offer any advantage to women with breast cancer, but also, in many cases, caused adverse side effects putting the patients' life in danger.

Suspicions are generated by the fact that when a study is funded by a non-profit Institution, the negative results rise up to 38%, whereas when the study is supported by private grants the figure comes up to 5%.

Some claim that the reason why industry-sponsored research shows more positive results, derives from the fact that financial resources are available to conduct studies with a large number of participating patients (large sample size), leading to a high possibility of finding statistically significant differences. Another reason is the use of preliminary data-results, allowing for better planning of a clinical study and increasing the possibility of positive results[4].

The first argument refers to the question whether a statistically significant difference is of clinical value as well. Regarding the second argument, we should consider that most of the preliminary data derive from laboratory animal studies and often cannot be directly applied to humans.

In addition, it is surprising that different clinical studies come up with contradictory results, depending on the funding company. During an evaluation of previous clinical studies on second generation drugs used to treat mental diseases, such as schizophrenia, Heres and his colleagues examined 9 different clinical studies testing the efficacy of the two following substances: olanzapine and risperidone[5]. They discovered that 5 of the above mentioned studies were sponsored by the company producing olanzapine -and their results were in favor of this substance- while 3 out of 4 studies sponsored by the producer company of risperidone, were also in favor of this particular drug. Similarly, several studies conducting direct comparison of statins, were more likely to be in favor of a drug, which was produced by the sponsor company, against other drugs[6].

3. Research misconduct

The term research misconduct refers to:

(a) Data fabrication, i.e. creating non-existent or fictitious results during the recording or publication process.

(b) Data falsification, i.e., modification or concealment of critical results.

(c) Plagiarism, i.e. repetition of referencing results, opinions, ideas or research methods, without the appropriate reference to the person who used them or reported them originally.

Specifically, it is worth noting:

a. Quality of methodology

Although some people believe that clinical studies sponsored by the pharmaceutical industry are associated with poor methodological quality[7], most of the authors stress that research protocols sponsored by the private sector are no less methodological[8] and in fact, show better quality of methodology[5,9].

b. Inappropriate selection of dose and administration route

It is observed that in clinical studies where two drugs are directly compared, the sponsor's drug is administered in high doses to show better effectiveness or in low doses to show fewer side effects. Administration of unequal doses violates the scientific principle of "clinical equipoise", representing that a subject may be enrolled in a clinical study only if there is true uncertainty about which of the study arms is most likely to benefit the patient[10]. For instance, in 13 studies comparing the antifungals fluconazole and amphotericin B in cancer patients who are vulnerable to fungal infections due to low white blood cell counts, 80% of the patients had the drug administered orally in suspension, which shows poor absorption, not as an injection. Conducting such clinical studies not only leads to misinformation but is also unethical, since the lack of therapeutic utility, endangers the patients and prolongs their pain.

c. Selective publication

Occasionally, industries intervene and prevent publication of negative results about their product which is under trial. Such interference is reported by almost 20% of researchers[11]. On the contrary, industries ensure that clinical studies with positive results are mentioned in more than one reference in the literature. An illustrative example is a study revealing that the results from 6 different clinical studies testing duloxetine were used in more than 20 publications[12].

d. Different interpretation of results

It is observed that industries interpret and present the results of a clinical study in different ways depending on whether they aim to publish them or submit them to the competent authorities. According to the existing literature, 94% of the clinical studies showed positive results, whereas according to the US Food and Drug Administration (FDA) only 51% of the clinical studies had positive results[13].

e. Discrepancy between results and conclusions

Although the results reported in some studies are accurate, it is common that authors misrepresent their meaning and draw more favorable conclusions compared to what the results can really support. For instance, 19 out of 22 clinical studies of non-steroidal anti-inflammatory drugs (NSAIDS) concluded that the drug manufactured by the sponsor was less toxic compared to others, but in fact such a conclusion could only be drawn by the results of 12 clinical studies[14].

f. "Authors on demand"

"Authors on demand" are exclusively employed to interpret the results of a clinical study and write up manuscripts that are in favor of the drug manufactured by the sponsor. The company, i.e. the drug manufacturer, hires a prestigious academic or physician to sign the manuscript as an author. When the manuscript reaches the publication stage, there is no reference to the original role of the "author on demand". There are multiple references in the literature about "authors on demand", some of which are analyzed in the paper by Dunbar and Tallman[15].

"Authors on demand" are not only used in order to ensure that positive results of clinical studies are reported, but also to create doubts about studies that showed negative results. A good example of such a case is the clinical study "Heart and Estrogen/progestin Replacement Study, (HERS)". The study concluded that administration of hormones to women with coronary heart disease offered no advantage to secondary prevention[16]. Publication of the study was followed by "manuscripts on demand" which questioned the results of the study, supporting that hormone therapy had a protective effect[17].

g. "Seeding studies"

Finally, conducting clinical studies after a drug is approved may be another way of misleading the public. In many cases, clinical studies conducted after the drug release solely intend to establish the drug on the market – to be more frequently prescribed by physicians and become better known amongst patients – and not to answer a scientific question.

4. Types of sponsorship

Sponsorships of clinical research can be classified into five categories (Table 1).

Table 1: Categories of sponsorship.

1st	Free pharmaceutical products
2nd	Gifts, meals, tickets to cultural events
3rd	Travel (tickets, accommodation etc.) Conference registrations etc.
4th	Counselling services, lecture fees
5th	Recruitment of patients in research

Figures from 2004 and 2005 show that ¾ of researchers having a financial relationship with the pharmaceutical industry, received sponsorships within the established limits[18], i.e. below $10.000 annually. A relationship with a commercial company operating in healthcare is reported by 5.9%-6.2% of researchers. In addition, when the results were presented in prestigious fora, the researchers received more frequent and higher sponsorship. The largest proportion of the above mentioned researchers originated from the USA (9.2%) compared to researchers from other countries (4.2%).

5. Conflict of interest

An internal conflict of interest may emerge in case the researcher has financial interests from publishing favorable research results about a pharmaceutical or biotechnology product and yet, he/she must honestly manage the scientific truth.

However, in addition to individual researchers, conflict of interest may emerge in Institutions carrying out research, when the financial interest of an Institution or the Institutional officers/board members may possibly influence the process of design,

execution, assessment and announcement of results, neglecting the integrity of the clinical study.

Conflict of interest may be schematically represented as having the healthcare industries and commercial companies on side, and the bodies carrying out research, either in the individual level of a researcher or in the level of the officers, on the other side. Simultaneously, the scientific journals publishing research results and the private healthcare using the new products, are also implicated. The patients, who volunteer to participate in a clinical study, stand in between.

It is reasonable for researchers, specialized in implementing research projects, to be more commonly associated with pharmaceutical companies, compared to those who do not deal with research. This mutual relationship creates the conditions for conflict of interest[19].

The pharmaceutical industries have any reason to seek participation of major centers in research, because:

a) Industries lack the necessary infrastructure and experience for such studies.

b) Institutions ensure patient/volunteer participation.

c) Institutions have the necessary status that will contribute to confidence in the pharmaceutical product.

According to some experts, the relation between academic Institutions and the pharmaceutical industries creates problems which become increasingly complex[20], not only to researchers but also to academic Institutions, due to the suspicion surrounding their moral integrity and the transparency of research[21].

“Cooperation”, may be in the form of: direct research funding from the industry, provision of technical knowledge from the Institution to the industry, academic “coverage” of the industry, student scholarships and product recognition by the Institutions. In 1994, the industries offered $1.5 million funding to USA Universities, for use in 6.000 research projects[8].

Publication of favorable research results to a high impact scientific journal is a positive step towards the establishment of a drug or any other healthcare product. Subsequently,

some companies seek "improvement" of their results, as indicated by the fact that 59% of pharmaceutical industries sponsored scientists who work for scientific societies and issue guidelines on how not to affect research results[8].

The private sector comprises the final stage in the availability of a drug. There is an increasing number of private healthcare physicians participating in clinical studies, either as "researchers" in non-profit centers or as patient providers. In the USA, the number of the above mentioned physicians is increasing[21]. Medical advisors visit more often private-sector physicians. It has been estimated that every physician has more than 16 visits per month[21].

6. Measures in the USA

The cooperation – partnership between academic Institutions and the private sector is, in general, promoted by modern health systems[22]. According to the law in the USA, researchers are encouraged to cooperate with the private initiative in research[11].

In order to deal with the conflict of interest phenomenon, Universities and the State have generated plans on establishing control mechanisms. In 2001 the Association of American Universities (AAU), expressed concerns about the possibility of conflict of interest phenomena, and submitted relevant proposals[23]. In parallel, in 2001 and 2002, the Association of American Medical Colleges (AAMC) published guidelines under the title "Protecting Subjects, Preserving Trust, Promoting Progress"[24].

In 2006, due to the increasing scandals concerning the NIH (National Institution of Health) in the USA, AAMC and AAU[25] organized a Task Force to introduce management practices with which "the community conducting biomedical research could benefit from precise rules of priorities and values concerning conflict of interest issues between individuals and different Institutions".

The Task Force, consisting of reliable and experienced members of Universities and hospitals, submitted a report in 2008 entitled "Protecting Patients, Preserving Integrity, Advancing Health: A report of the AAMC – AAU Advisory Committee on Financial Conflicts of Interest in Human Subjects Research, February 2008". In 2001, the

General Accounting Office (USA), addressed its concerns about the conflict of interest phenomena in institutions conducting clinical research[26].

A common component to all the above mentioned recommendations is the obligation of all individuals potentially involved in relevant cases during the design, conduct, assessment or announcement of research results, to disclose or notify of any relationship with the industry.

A. *Declaration* means provision of relevant information by the "researcher" to the responsible internal authorities of the Institution, such as the "Conflict of Interest Committee" (CIC) and subsequently, notification to the Committee of Research Control (CRC) of the Institution.

B. *Notification* (or disclosure), means notification to third parties, besides the Institution, such as the patient interested, the accredited responsible State authorities, the scientific societies or journals where the research results are intended for publication.

There are three main aims of "Declaration" and "Notification"[27].

1. The comprehensive knowledge of possible relationships allows the participating patients or healthy volunteers to exercise informed choice on the right to autonomy. A condition to exercise this right, is that the "Notification" includes all the details of the "reconciliation". The clarity and timeliness of the notification are prerequisites.

2. To protect the researcher from potential legal entanglements. Although currently there is no legal obligation to reveal the sponsors, nevertheless, the researchers may be involved in legal matters[28]. Existence of a declaration facilitates transparency.

3. A third aim, is the moral prevention of researchers and Institutions providing health services to receive sponsorships, especially high subsidies[28].

The fact that a researcher submitting the Declaration / Notification feels that he/she is vulnerable to criticism over the "transaction", acts as a deterrent. Approximately half of the academic centers state that granting the declaration has become mandatory in

research. This declaration may be independent or may be included in the informed consent form.

The declaration must include the following details:

i. First name and Surname of the researcher.

ii. Name of the Institute.

iii. Type of sponsorship.

iv. Amount of sponsorship*.

v. Sponsoring company / industry.

vi. Approval of the CRC.

A relevant study revealed that approximately 50% of Institutions accept the establishment of a declaration[16]. However, half of them wish to include it in the informed consent form, whereas the remaining prefer to inform the participating patients orally. In addition, unanimity does don exist on the extend of details to be disclosed, and many support that the sponsor's name is adequate. Others claim that the disclosure must be complete and include, not only the sponsor's name and type of sponsorship, but also the amount, and the participant must be informed of any possible effects of the sponsorship on the research outcome, suggesting an honest discussion between the researcher and the patient.

A declaration must also be submitted for a 1st stage research, where there are no human participants, but is intended to move to the 2nd clinical stage within the next 12 months. In that case, it is within the authority of the "CIC" to decide on whether the rules concerning the clinical study also apply to the preclinical stage of the study.

"Disclosure" of the relationship must be submitted to persons or authorities outside the Institution, such as:

- The responsible State authorities.
- The sponsors.

* The US Public Health Service (P.S.H) set the upper limit of <$10.000/annum. P.S.H. 42. CER, §50603.

- The “editorial” board of the scientific journal where the research is submitted for publication.
- The conference organizing or scientific committee or professional bodies, where the research is announced (conferences etc.).
- Everyone participating in the study.

Depending on the rules of each Institution, the “disclosure” may include details concerning the type and amount of sponsorship. The CRC could provide such a document. The document must include an assurance that the Protocol/Disclosure has been approved by the CIC, and state that the sponsorship does not compromise the patient’s health.

An additional recommendation is that the patient participating in research is informed about the fact that the matter has been addressed and approved by the Special Ethics Committee of the Institution and that the research does not compromise his/her health. Therefore, the disclosure may be posted on the Institutional website.

Compliance with the above mentioned, is mainly shown by the Academic Centers, whereas there is no clear picture of what is the case outside Academia. It is evident that there is no unanimity especially concerning the extend of disclosure. However, 89% of the Institutions suggest that the disclosure must include any possible participation of husbands/housewives, parents or children[18]. Regarding scientific journals, it is reported that 43% apply a policy of compulsory disclosure.

Questions are generated by the fact that only a small proportion of scientific journals and non-academic hospitals ask for a declaration of possible sponsorships. Questions are also generated by the tendency to inform orally, which may lead to confusion about a matter that demands complete transparency.

Every Institution undertaking a clinical study, accepts the regulation of the applied “research policy”, which includes all the commitments imposed by the State and the authorized “National Committees”. The president and the members of the control bodies (CIC and CRC), must also submit a disclosure. A study[29] showed that 36% of Committee members admitted they had at least one relationship with the industry in the past, although 85.5% of them stated that this would not compromise their judgment.

However, considering that the control of patient safety is within the authority of the above mentioned Committee, its members owe to be free and above any suspicion, as laid down by law in some US states[30].

Especially for the CIC, it must be noted that it is composed by senior members of the Institution, who are experienced in their field and are independent of the Institutional administration. Two members outside the Institution, with similar qualifications, participate in the Committee. The members themselves must not create conditions for conflict of interest, otherwise, they are revoked immediately. Members must also submit a "declaration". There is close cooperation and mutual information between the CICs. The CIC is responsible for reporting the incident to the authorized bodies and analyzing the type of relationship in detail. In cases concerning the Institution/industry relationship, the Committee examines whether the sponsorships belong to the provided exemptions and the extend to which it could compromise research integrity.

The declaration is submitted to a) the responsible State authorities, b) the Institution' s administration, c) the sponsors, d) the researchers and e) the publishers of scientific press, at least once per year. Every Institution has the freedom to adopt its own rules, according to the principles and philosophy governing its operation, but it must aim to minimize irregularities.

Each recommendation of the Committee, positive or negative, must be completely justified. In addition, the Institutional administrations are encouraged to make available to the public, the media and the State the measures adopted to protect the patients and their right to autonomy.

The CICs scrutinize every case of possible conflict of interest, but without prejudice that every sponsorship is necessarily reprehensible and harms the patient. The judgment takes into account: a) the amount of sponsorship, b) the Institution/sponsor relationship and its possible effect on research, c) the researcher/sponsor relationship. Subsequently, it is decided whether the research will be continued, discontinued or modified.

Institutional conflict of interest may emerge when the financial interests of the Institution or one of its members acting as a representative, may affect in any way the design, execution, assessment and announcement of research results. However, a study by

Campbell *et al.* showed that 42.3% of the RCR members do not always adhere to the principle "Conflict of Interest".

Industrial "sponsorship" may appear in various forms such as "donations", staff training, counseling offered to the industry by the Institutional members, legal ownership of shares for products resulting from research as well as mutual bonds or interest and dividends resulting from[*], or various combinations of the above mentioned.

The CIC must be aware of which of its members implicated in research, fall within the conflict of interest provisions. The committee must also determine the general policy to be followed in such cases, while it has the duty to report any type of sponsorship resulting form signing an agreement with the industry.

Exceptions are:

a. Contributions of any amount, derived from legitimate business of the Institution.

b. Payments to the Institution, resulting from the "cost", as provided in the contract signed between the Institution and the sponsor.

c. Salaries or compensations for services provided for research by the Institution, and are provided in the relevant contract.

d. Financial aids – sponsorships by the State or non-profit charitable organizations.

"Donations" are examined by the Committee with scrutiny, since they may fall within the relevant prohibitions.

The Institution must establish: a) the responsible authority where the CIC will refer to in a case of conflict of interest, b) a procedure to be followed when members of the administration have a relationship that may compromise their judgment. Cases where conflict of interest may emerge from a private company sponsorship to an Institution include:

a. Sponsorships from companies to the Institution, independent from the undertaken research.

b Dividends from investments resulting from licensing and commercialization of research products of >$50.000.

[*] Equity holding, Equity interest, Mutual funds, Stock options etc.

7. Collaborative clinical studies

Over the past years, there is an extensive discussion about collaborative clinical studies, i.e. studies in which two or more companies cooperate to test the efficacy and safety of biomedical products with similar action. With this approach, the companies share the expenses, patient recruitment/participation is faster (patients are not divided into separated clinical studies by different companies), a single control group is necessary, the duration of the clinical study is reduced, and the use of a common protocol with well defined parameters allows direct comparison and production of robust and convincing results[31].

Such collaborative studies may be conducted in order to test similar therapies by different pharmaceutical companies against the same disease, or a combination of different therapies that detect different pathways or mechanisms of disease. A good example in the recent literature is the "Cardiac Arrhythmia Suppression Trial", which was funded by the National Institutes of Health. During this study there was a direct comparison of three antiarrhythmic drugs from different companies, testing their efficacy to reduce arrhythmic death after a myocardial infarction[32]. It was proved that two out of the three approved drugs are associated with increased mortality instead of decreasing it. If three different clinical studies were conducted, more time would be necessary for completing the studies, they would cost more and it would be impossible to reach such a clear result. Collaborative clinical studies are advantageous not only for faster and less costly research, but they could potentially limit conflict of interest, since more individuals, from different companies are implicated.

8. The ethical issues

a. The basic values

Pursuing the truth justifies the freedom of research from an ethical point of view. Indeed, the value of the later -acknowledged as a fundamental right- would be pointless if not connected to a rational method revealing the laws and phenomena of nature and society. The development of civilization, along with everyday human activity in any field,

would, in reality, be unthinkable without the pursuit of truth, i.e. without freedom of research.

Starting with the above admission, we must however consider how the search for truth is practically organised in a moral-social environment, where other values also matter. It is certain, for example, that research activity is subject to some restrictions, such as respect of the person's dignity, protection of public health, protection of the environment. In the end, these restrictions correspond to respective values, which -under certain circumstances– rule out entire areas of research activity: in this context, "truth" is believed to have an excessive cost to our social coexistence, so excessive that it does not worth favouring against other values. Nonetheless, such restrictions are rather "external" on research, enforced upon it without refuting its value, setting, in a way, "geographical" boundaries on the field in which it develops.

The financial restrictions of research have a different quality. In principle they don't question the field of research -or the subject of a specific research- but they set limits on the resources attributed to the production of results. Consequently, the sponsor of a clinical study on a new pharmaceutical product is interested in: a) attributing a certain pre-calculated amount of money for this specific research and b) having specific positive results from this investment, i.e. results that will allow a patent, and subsequently, launch the product in the market.

Under these two facts, the value of truth is relative. Actually, exactly because the results are under examination, it is, by definition, impossible to estimate the cost which must be attributed so that they are accurate and indisputable. Therefore, possible failures due to the fact that "nature chooses otherwise" and not because of poor execution of the research protocol, cannot be assessed in advance. It is worth noting that the financial commitments of research do not mean that possible negative results must be definitely avoided, but they mean that the negative results cannot burden the cost. Furthermore, funding a research with negative results, although it can prove to be scientifically useful, it is financially unprofitable.

The financial commitments, especially in clinical research, would not be of such an importance, if the basic funding resource was not the industry. It must be highlighted that research on new drugs (conventional or -even more- biotechnology products)

requires a particularly high investment and also involves a high risk of failure. Under these circumstances, the private sector is nearly the only choice -if one exempts public resources from the E.U. or international organizations- as it can undertake the cost and risk. Respectively, nevertheless, it imposes financial commitments on the freedom of research, which will guarantee reciprocation from the market, i.e. profit from the production and distribution of the final product.

The commercial pursuits of industry, through its involvement in clinical research, are not ethically indifferent. Financial freedom in a democratic society is also of moral value, as it creates decisive motives for the satisfaction of needs, basic or not. This element cannot be set aside in our argumentation, i.e. the pursuit of profit from the production and distribution of innovative products cannot be considered by definition "suspicious" for interfering with clinical studies results. Undoubtedly, undertaking the business risk is already a factor promoting biomedical research.

The third value we must take under consideration at this point, is the one of health. The "pursuit of truth" by the researcher, along with the pursuit of financial profit by the sponsor, does not concern any biotic need, but the value of health. Therefore, the new product expected by the research activity must satisfy -with efficacy and safety– a basic need with unquestionable priority. Thus, it is not morally indifferent whether we will attempt to satisfy or not that need. In this sense, a clinical study also derives its moral status from the nature of its purpose -it does not constitute a kind of research out of scientific "curiosity" or simply to gain knowledge without a social meaning.

Therefore, "freedom of research with simultaneous financial reciprocation, for a product of social significance" summarizes all the ethical aspects of the matter in question.

b. Balancing the goods

Certainly, extracting conclusions from a clinical trial is not compatible in any way with some extreme actions -e.g. withholding crucial data, constructing positive results, concealing negative results -which might have been caused by the sponsor's pressure on the researcher. In these cases, consciously misleading the scientific community along with

the public leads to disregard of the value of scientific truth, by prioritising the pursuit of an economic "efficiency" based on illicit profit.

From the point of freedom, abandoning the goal of truth equates with a substantial elimination of the freedom of research, in the sense that the researcher does not act unobstructed but is subjected to external pressure in order to present prefabricated results. Moreover, when it comes to financial freedom, one must consider an important issue. Indeed, the pursuit of profit by means of deceit ignores the basic social aspect of this freedom, i.e. that its moral status derives from the fact that, after all, it actually aims at satisfying the necessaries of life. In this context, the pursuit of profit is not a morally accepted exercise of financial freedom, even if it benefits the sponsor of a clinical trial, since it does not relate to the satisfaction of necessaries. The interest of this argumentation purely concentrates on the ethical aspect of the issue and does not relate to probable financial or other type of damages (e.g. legal penalties) that a business might suffer after exposing the deceit for purposes of profit.

Beyond the above mentioned, however, an actual balancing between the interest of truth and the business interests is theoretically necessary only when the researchers discover findings that are not crucial for the efficiency and safety of the drug tested during a clinical trial. In this case, the business' interest for concluding the trial and publishing the results prevails, even if the above findings are not included in the results.

As a conclusion, the goal of serving health imposes, as a rule, that the researcher's pursuit of the true results does not retreat before the sponsor's business interest. In other words, the sponsor is morally obliged to undertake the risk that a clinical trial might lead to results that are not satisfactory, with the respective cost, precisely because the specific need to serve health weighs more.

These observations do not relate with the choice of a trial's objective, i.e. whether it is ethically justifiable to prefer conducting trials for certain diseases instead of others. The matter is definitely critical, especially when it concerns substantial disregard of rare diseases ("orphan" drugs), as well as high competition in the production of drugs for specific diseases, that often leads to scientifically unreliable clinical trial results. However, financial freedom does not allow a moral control on the private sector (pharmaceutical industry), which would result in enforcing research in certain areas of clinical trials,

ignoring the element of business profit (and business risk respectively). It is basically the responsibility of the state -or the public funding for biomedical research- to satisfy similar needs, with fair criteria.

9. The law

Accordingly to the above data, it is important at this point to examine the involvement of law in the argumentation concerning conflict of interest.

The law is particularly concerned, primarily, with the issue of responsibility of the physician/researcher on one hand and the financier on the other hand. Preliminarily, however, we must define the constitutional context, in which the matter of liability lies, especially in the field of medical research.

a. The Constitutional context

There are mainly three provisions of interest in the Constitution: art. 16 par.1 which regulates freedom of research (and equates with the unobstructed pursuit of truth by any scientist), art. 5 par. 1 which regulates financial freedom under the reservation that the "Constitution", "the rights of others" and "public morals" are respected (and equates with the pursuit of financial profit by the sponsor of a trial) and moreover, art. 21 par. 3 which regulates health as a social right under the state's care.

This last provision is crucial in resolving a conflict between the previous two, a conflict of interest in clinical research.

b. The physician's/researcher's liability

From a legal point of view, the liability of the physician as a researcher is defined both by the general provisions of criminal and civil law (especially those concerning contract and torts) and by the special provisions concerning "scientific research" in the 7th (Z') chapter (art. 24-27) of the Medical Code of Ethics (law 3418/2005). In these special provisions, apart from obligations concerning the planning of a clinical trial (also found in

texts such as the Oviedo Convention or the 2001/20/EU Directive, as in force in our country), other special obligations of the physicians/researchers are regulated:

- publishing the results of a trial to the medical community by priority, so that they can be subjected to scientific critique and
- revealing the sponsor of the trial.

Law 3418/2005 completes the above with the general provision of art. 6 par. 4, which forbids the physician "to serve, depend on or be a part of businesses which manufacture or merchandise drugs".

In the context of the EU Directive 2001/20, the National Committee of Ethics for Clinical Trials -among others- takes the researcher's "adequacy" into account (art. 6 par. 3e Medical Directorate 3/89292/2003), along with the "guidelines for good medical practice", as must be followed in that specific facility and by those specific researchers (art. 6 par. 4 Medical Directorate 3a/79602/2007).[*]

These provisions result in a commitment of the physician/researcher to the medical society. This commitment, however, is not connected to medical liability towards the patient taking part in a clinical research, i.e. it cannot be converted to criminal or civil liability of the physician during the relevant medical actions.[**]

However, liability towards the patient can arise from other provisions that concern planning of a clinical study, in our case, provided that they are ignored e.g. for reasons of "accelerating" the process, in order to come up directly with commercially exploitable results. Thus, if there is pressure to deviate from the terms of a patient's valid consent, the doctor's relevant liability arises (criminal -depending on the case-, civil and disciplinary).

In conclusion, the current legislation "shields" the physician's/researcher's scientific independence with liability provisions, in the sense that they can be raised against possible pressure from the sponsor's part. Vice versa, the law does not justify a physician's own spontaneous disregard of the rules of science and ethics in favor of financial purposes, when the later can result in harming the patient's interests. In this case, there is

[*] It is worth mentioning that explicit reference in the issue of conflict of interests is made by our legislation concerning the inspectors of clinical studies (art. 21 par. 7 Medical Directorate 3a/79602/2007), as well as the members of the National Ethics Committee (art. 3 Medical Directorate 3a69150/2004).

[**] It is, on the other hand, connected to the physician's disciplinary liability.

medical error, an intentional one, either due to a poor choice or practice of the medical action in question (according to rules of science) or due to a defiance of some rule of ethics (e.g. providing information to the patient).

c. The sponsor's liability

Another interesting side for legislation is the liability of the sponsor, as a commercial enterprise. The general context is defined by the legislation concerning the liability of providers of goods and services and the consumers' protection.[*]

Based on the relevant regulations, a business trading new products in the market - as for example a pharmaceutical industry launching a new pharmaceutical product- is responsible for the product's quality (i.e. whether it responds to the need it is meant to satisfy), as well as for informing the consumer (in this case, the patients) adequately about the efficacy (in this case, the therapeutic factors) and the safety (in this case, the possible side effects of a drug). In case a business launches defective products -e.g. drugs based on misleading results of clinical studies or new drugs with significant differences than the established ones, also based on unreliable clinical trials, it can be compelled to compensate, apart from possible administrative penalties (fines, license removal).

Therefore, from this point of view, the law opts in favor of searching for scientifically valid results in clinical research, independently from purely financial purposes. Indeed, it is interesting that the above mentioned legislation concerns providers of all kinds of products and services towards the public, as consumers in general. There is no special relevant legislation for products and services concerning health or consumers respectively (i.e. mostly patients). Even so, however, the businesses' liability is specified. De lege ferenda it could be argued that, in view of the Constitution's art. 21 par. 3, it is necessary to adopt a special -stricter- legislation about the commercial liability of businesses in the field of healthcare products in order to operate -amongst others- as a dissuasive factor in cases of conflict of interest in clinical research.

[*] See especially art. 7 of law 2251/1994.

10. Conclusion – Control mechanisms in our country

The possibility of conflict of interest in clinical research has already been regulated by the relevant legislation. The Ministerial Decision of 2003, by which the 2001/20 Commission Directive about clinical studies of medicine was incorporated, adopts a certain form of control of this possibility by the National Ethics Committee for Clinical Studies, to which research protocols are submitted in order to get approval in terms of ethical adequacy[*].

Beyond that, the constant control by the appointed authorities of the National Organization for Medicines on the course of a clinical study in terms of scientific adequacy, may reveal unjustified gaps and omissions, which can lead to misleading results due to "acceleration" and financial purposes.

The ethical, as well as the technical (scientific), adequacy of a clinical study are the sponsor's responsibility, who therefore must be inspected by the appointed authorities of the National Organization for Medicines for the possibility of conflict of interest. The responsibility of inspecting the physician/researcher, as a rule, belongs to the disciplinary powers of both the hospital where the clinical study is taking place and the corresponding medical association, mostly on the basis of provisions of law 3418/2005 mentioned earlier.

It is however pointed out that the current control system does not include, for the time being, the most crucial mechanism, i.e. the hospital research ethics committees, an established institution in most countries, which is able to spot and deter phenomena of conflict of interest in their "source". This institution –in which the Hellenic National Bioethics Commission has been repeatedly referred to -is still inactive even though it has been regulated by our legislation (law 2071/1992).

[*] See art. 6 par. 3 of Ministerial Decision Medical Directorate 3/89292/2003.
See also art. 11 par. 4 of the relevant Ministerial Decision Medical Directorate 3a/7567/2008 (2003/94 Commission Directive for rules of good manufacturing of medicinal products).

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