R. Dr. Ovídio Pires de Campos, 255
São Paulo Brasil
Phone/Fax: +55 11 2661-6400

POLICY FOR CONFLICT OF INTEREST IN CLINICAL RESEARCH

FROM FMUSP-HC SYSTEM

I - INTRODUCTION

Currently, the world's most important universities and research institutions has already settled policies and rules to deal with conflicts of interest, in order to avoid that professional conduct may be influenced by an external interest, to the detriment of the ethical practice of medicine. It is believed that the observance of strict ethical principles, in addition to qualify the researcher's work, allows the proper management of conflicts of interests in clinical research.

Thus, the most of international bodies that finance, with the intervention of Fundação Faculdade de Medicina - FFM, researches developed by researchers from Faculdade de Medicina da Universidade de São Paulo - FMUSP and from Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – HCFMUSP, (in human beings or not), have required, as indispensable document for those financing feasibility, the presentation of a Policy for Conflict of Interests.

In clinical research, the conflict of interest arises when one or more of the process participants are connected to institutions or interests that might harm the fairness of the investigation or restrict the competence and impartiality for evaluation.

In Brazil, the ethic aspects of research activities in human beings are regulated by **Resolution CNS No. 466/12,** (which revoked Resolution CNS 196/96) - Directives and Norms Regulating Research on Human Beings and by subsequent complementary resolutions, which requires as designation from the National Commission for Ethics in Research – CONEP, on item IX 8, analyze and monitor, direct and indirectly, protocols of researched with conflicts of interests that may impair or prevent the fair local analysis.

Thus, all the researches in human beings must be submitted to the appreciation of a Research Ethical Committee (CEP), whose function is to guarantee and protect the integrity and rights of the volunteers participating in the research; to evaluate whether the project is feasible; to verify the conformance of TCLE, the guarantees offered to the study participants and the eventual conflicts of interests, making them co-responsible for the research projects they approve.

The credibility of any medical professional performing care, education (conveying scientific information) or research functions depends on the

integrity, objectivity and clarity with which relationships that may represent potential conflicts of interest may occur.

In clinical research, there is a great potential for conflict of interests and, even for the researcher, the identification of these conflicts may not be very clear. There are many aspects to be considered, with implications that affect all the agents involved in the process: The subject of the research, the researcher, the institution where the research is carried out, the sponsor, the ethics committees, the regulatory agencies, the scientific community and society in general.

The conclusion is that conflicts of interest are commonly held and inevitable in academic life. The challenge is not to eradicate them, but to recognize and manage them properly, by **prior declaration** of any type of conflict of interest, whether it is real, potential or apparent.

The purpose of this document, therefore, is to present the arguments and provide some subsidies for the Institution, through the Clinical Research Center / Clinical Board, to discuss the feasibility of creating a Policy for Conflict of Interest, involving its collaborators and partners, and among them, the Foundations of Support (FFM e FZ).

II - DEFINITION OF CONFLICT OF INTERESTS

Conflict of interests can be defined as a clash between personal interests and the primary obligations of an individual who holds a position of trust (Houaiss) [1] or, more specifically, as a set of conditions that make professional judgment concerning a primary interest, such as the patient well-being or the validity of a research, tend to be improperly affected by a secondary interest such as financial gain[2].

In other words, conflict of interest is understood as a condition in which the professional conduct may be influenced by an external interest, which, typically (although, not necessarily), results in financial gain to the detriment of the ethical practice of medicine.

The conflict of interest may exist directly with the individual exercising a particular activity, as well as with people with whom this individual shares financial gain (spouse or dependent, for example).

III - NATURE OF CONFLICTS TO BE DECLARED

In clinical research, there is a great potential for conflict of interest, which may be financial, direct and/or indirect, and not financial, such as a search for professional prestige, the need to present a scientific production, personal relationships, political and ideological interests, religious interests, etc. Financial interests are the ones that draw more attention, at first, and may include, among others: consultancies; participation in companies; positions in the board of directors or management of institutions (remunerated or not); receipt of fees; received or pending concessions or patents; research funds; payment of trips and lectures; support for congresses; gifts and loans. Indirect

financial interests, although more difficult to identify, are also important. For example, a medical center may attract more patients and gain prestige and publicity if it has an innovative modality of treatment or diagnosis.[3]

In case of doubt, whether there is a conflict or not, it must be declared.

1. Employment relationship;
2. Consultancy or participation in Counseling Teams (Advisory Boards);
3. Fees for conferences, scientific articles or participation in events;
4. Payment for the leadership of Research Projects;
5. Participation in legal proceedings as Official Expert or Assistant Expert;
6. Ownership of specific Shares (except when part of an investment fund that is not controlled by the individual);
7. Grants for conducting lectures, congresses, scientific meetings, continued medical education programs;
8. Remuneration in the form of gifts, food, sponsorship of travel, accommodation, registrations in congresses or scientific or promotional events.

IV - LEGISLATION

The first regulation on health research in Brazil was established by the National Health Council (CNS) through CNS Resolution No. 1 of June 1988. This document addressed ethical aspects of researches, biosafety and health surveillance. Currently, the ethical aspects of human research activities in Brazil are regulated by the **CNS Resolution No. 466/12,** (which revoked CNS Resolution 196/96) (Guidelines and Norms for Research in Humans) of December 2012 and by the subsequent complimentary resolutions. CONEP (National Commission for Research Ethics) and the CEPs (Committees for Research Ethics), which have the primary function of ensuring and safeguarding the integrity and rights of volunteers participating in research.[5] It should be emphasized that the ethical review of any research proposal on human beings shall not be dissociated from its scientific analysis. CEPs also have the right to evaluate the budgets of the research projects submitted for their consideration.[6] As a consequence of these CNS resolutions, the first sanitary legislation on clinical research was created in our country, the Ordinance No. 911 of the National Health Surveillance Secretariat (SVS), published in 1998, revoked by RDC 39/08, currently in force.

SVS was replaced by ANVISA (National Health Surveillance Agency), which became responsible for the sanitary regulation of clinical trials in Brazil.[7] According to **CNS Resolution No. 466/12**, CEPs will always be multi and transdisciplinary, not having more than the half of its members belonging to the same professional category, having people of both sexes. Its constitution should include the participation of health, exact sciences, social and human sciences professionals, including, for example, jurists, theologians, sociologists, philosophers, bioethicists and at least one member of the society representing the users of the institution.[6]

CEPs have double care with the protection of vulnerable groups, i.e. those with reduced self-determination. That is the case of children under 18, pregnant women, poor populations, indigenous populations, prisoners, military officers,

religious people, civil servants, students, mentally disabled, incapable, and elderly. In the opinion issued, CEP assesses whether the project is feasible, verifies the adequacy of the TCLE (Informed Consent Form), the guarantees offered to study participants and eventual conflicts of interest. It is already customary for editors of scientific journals, both international and national, to request authors to express all the existent interests. This is a practice that it is also beginning to be observed, albeit in an incipient way, by the organizing committees of some medical congresses. It is believed that the observance of strict ethical principles, besides qualifying the work of the researcher, allows the proper management of conflicts of interests in clinical research.

It is highlighted that the Comitê Internacional de Editores de Periódicos Médicos (International Committee of Medical Journal Editors) set rules to conduct the conflicts of interests (table 1).[4] It should be recognized, however, that the conflicts of interest are commonly held and inevitable in academic life.

Table 1 – Rules for the management of conflict of interests (ICMJE)

Definition	There is a conflict of interest when a participant of a review process by pairs has connections and/or activities (financing, personal relationships, academic competition, intellectual passion) that may improperly influence in his/her judgment.
Authors	They must declare finance conflicts or other conflicts of interests that might cause biases to their works. They must specify on the manuscript every financing and other connection with the work.
Reviewers	They must declare financial conflicts of interest to the editors or refuse, if it is appropriate. Do not use reviewed manuscript data at their own interest.
Editorial staff	The ones who hold the final decisions must not have any financial commitment on the subjects they judge. The ones who contribute for editorial decisions must provide an updated description of their financial interests to the editors.

Font: International Committee of Medical Journal Editors®

V - EVALUATION PROCEDURES

There is a conflicting interest when the professional conduct concerning a primary interest (such as the validity of a research) can be influenced by a secondary interest (such as financial gain or personal rivalry).

Establishing the obligation to submit a previous declaration of the conflict (actual, potential or apparent) by completing a questionnaire would be an effective way of assessing the possible interference of the declared interest in the activity in question. This evaluation would be carried out by the local CEP, as provisioned in the national legislation.

Researchers would not be necessarily refused only for the occurrence of declared conflicting interests, but an observation would be published about having or not conflicting interests.

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V.1 - MODEL OF DECLARATION

The declaration is made prior to the activity in question, in writing (in a scientific paper, in the annals of a scientific meeting, or as a written document to be delivered to participants prior to a presentation). It is believed that in order to make the best decision on how to deal with a publication, it is necessary to be aware of any conflicting interest that the authors may have. Works will not be refused only because conflicting interests have been declared by the authors, but a declaration about whether or not they have conflicting interests will be published.

1. *For the past five years have you, as a physical person, legal entity member or representative, accepted the following from a company or organization that may otherwise benefit or be financially impaired by the results of your study or the findings of your review, editorial or letter?*

a) Refund for attendance at symposium?
Yes ( ) *No ( )*

b) Fees for presentation, conference and lecture?
Yes ( ) *No ( )*

c) Fees for organizing teaching activity?
Yes ( ) *No ( )*

d) Funding for conducting research?
Yes ( ) *No ( )*

e) Resources or financial support for team member?
Yes ( ) *No ( )*

f) Fees for consulting?
Yes ( ) *No ( )*

2. *During the last five years, have you been employed by a company or organization that could, otherwise, benefit or be financially impaired by the results of your study, scientific work, or publication?*
Yes ( ) *No ( )*

3. *Do you have policies or actions in a company or organization that may, otherwise, benefit or be financially impaired by the results of your study, scientific work, or publication?*
Yes ( ) *No ( )*

4. *Have you served as an official judicial expert or assistant on the subject of your study, scientific work or publication?*
Yes ( ) *No ( )*

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5. *Did you receive remuneration in the form of gifts, food, travel sponsorship, accommodation, registrations at congresses or scientific or promotional events?*

Yes ( ) *No ( )*

6. *Do you have any other conflicting interest(s)? If yes, please specify.*

Yes ( ) *No ( )*

Specify:

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*In case you have answered "**yes**" to any of the six questions above, it is considered that you may have any conflicting interest and it must be declared mandatorily.*

A DECLARATION OF CONFLICT must be written and published in the issued document. For example: Conflicting interests: "Author 1" was refunded by a particular company, for attending many conferences. "Author 2" was paid by a particular company to coordinate educational programs and her research registration was paid by the company. "Author 3" has company's shares.

*In case there are **no** affirmative answers to any of the six questions above, the following will be published: "Conflicting Interests: not declared".*

VI - CEP ATTRIBUTIONS AND SUPPORT FOUNDATIONS (FFM E FZ)

CEP shall evaluate all disclosures of conflicting interests declared and give its opinion regarding the refusal or not of the investigator.

FFM/FZ, in turn, will begin the preparation of the respective agreement and other measures applicable to it upon presentation by the interested party, of CEP determination regarding the evaluation of the presented conflict(s) of interest.

VII - APPLICABILITY

As informed in the document "Proposal for Guidelines for Policy Regulation of Conflicts of Interest", it is considered that certain practices are incompatible with clinical research standards and should be prohibited. These include:

1. Payment of fees for disclosure, promotion or addition to an experiment;
2. Bonus for achieving goals;
3. Payments contingent on results of a particular research; and
4. Research contracts in which the sponsor has the ability to override the decision of the primary investigator or executive committee to publish or present the results of the experiment.

The primary investigator is the individual (or individuals) with primary responsibility for the development of the protocol, the conduct of the experiment and the interpretation and dissemination of the experiment data. There may be more than one primary investigator in a multifaceted experiment with distinct and separate subsections from the protocol. In this case, leading researchers at any single site in a multi-site experiment are also considered to be primary investigators for the purposes of this policy.

During the course of a clinical trial (i.e., from the addition of the first patient to the publication of a substantial analysis of the experiment results, either as a summary in a presentation reviewed by parts or as an article in a journal reviewed by pairs), the primary investigators, for that experiment, should not receive:

1. Shares or counterpart capital in the sponsor of the experiment (except when diversified fund not controlled by the covered individual);
2. Royalties or licensing fees (prospective or realized) of the product or new treatment being investigated (prospective or realized) or licensing fees (prospective or realized) of the product or new treatment being investigated;
3. Patents for the product or new treatment being investigated (Note: If it is discovered after the experiment that the product or treatment is in production and that the primary investigator wants to file a patent, he or she should abandon his leading part in the experiment);
4. Position or function, board member or sponsor employee of an experiment (Note: individuals may serve on the sponsor's advice for a scientific experiment as long as the sponsor does not remunerate them);
5. Trips paid by the experiment sponsor to attend scientific or educational meetings, not including trips to meetings of researchers related to the conduct of the experiment.

VIII- PENALTIES

Possible penalties could be applied to those who violate established guidelines.

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