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EDITORIAL

SEEKING HARMONIZATION AND QUALITY IN CLINICAL TRIALS

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Sharing the experience among the different component institutes of Hospital das Clínicas, São Paulo University Medical School (HCFMUSP) was one of the main goals of the First Symposium on Clinical Research, held in September 28th, 2005 in São Paulo. The meeting brought together some of the main investigators of the institution to address the basic concepts regarding clinical trial participation. Issues such as the challenge of developing a new drug through the 4 phases (I to IV), the principles of the International Conference on Harmonization/Good Clinical Practices (ICH-GCP), and the importance of protocol design were discussed. The value and meaning of informed consent, known in Brazil as TCLE ("Termo de consentimento livre e esclarecido") was also addressed. Deficient and inconsistent TCLE writting are still a major reason of disapproval of trial protocolos by Ethics Committees (EC) in Brazil and in other countries. The symposium was part of an effort to harmonize and improve all clinical trial-related procedures in the institution, the largest academic public hospital in Latin America. In order to consistently increase the participation in clinical studies, clear rules and guidelines are mandatory. The main drivers of such a process are the commitment of the Board of Directors, the strong background of research and qualification of institution's investigators, and certainly, commitment to a fair process by the team during the implementation.

Clinical trials are essential to the development of beneficial treatments. Human testing must be preceded by preclinical or laboratory research, which typically involves years of experiments. If this stage is successful, sponsoring companies must provide data to the Food and Drug Administration (FDA-USA), or similar agencies in other countries, requesting approval for an Investigational New Drug (IND) process.[1] The clinical testing of experimental drugs usually goes through 3 phases, with each successive phase involving a larger number of patients. Phase I studies are primarily concerned with safety and possible side effects; normally performed over a few months in a small number of healthy volunteers, and designed to determine absorption, distribution, metabolism, and excretion data (ADME studies). Phase II may last up to 2 or 3 years and enroll several hundred patients, no longer healthy volunteers. Most Phase II trials are randomized, double-blinded, with one group receiving the experimental drug, while another group receives standard treatment or placebo (control group). The last pre-approval phase (Phase III) typically lasts several years; the new drug/procedure is tested in up to several thousand patients, depending on the field and/or the disease. Theses studies are usually multicentric, randomized and double-blinded and should provide a deeper understanding of the drug effectiveness and benefits as well as the range of the most common side effects. Upon satisfactory completion with all relevant items and issues solved, the company can request formal approval by the agency through a process called, in the USA, New Drug Application (NDA). Upon approval, companies obtain authorization for commercialization and can continue conducting late Phase III or Phase IV studies.[2] The patient's rights and safety are protected in that: (a) the researcher must obtain approval from an Institutional Review Board (or an Ethics Committee), normally composed of physicians and lay people and (b) every participating subject must sign an informed consent, which details the nature of the trial and everything that may happen to the him or her during the study.

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The introduction of international guidelines for Good Clinical Practices (ICH-GCP) in 1996 and the development of quality infrastructure for research in a wider range of countries opened broad opportunities to the whole community of investigators to participate in clinical trials. Institutions must adapt to these changes to maintain and improve their attractiveness as a base for industry-sponsored clinical research. When deciding where to place multicenter international clinical studies, 3 factors, namely speed, quality, and cost of research are the main concerns. None of these parameters is independent, and final decision will depend on a judgment about overall cost-effectiveness for a particular project. Several working groups in the developed world have studied how industry, academia, and government can positively influence these factors.[3] They have identified solutions to a number of important issues that should be interesting to know and to learn from.

There is a growing pressure on the pharmaceutical industry to reduce product development times. An important element in the process is the time to include the first patient (known as FPI). Removal of current and anticipated impediments to research should be hence implemented as follows: (i) responsibilities of each player in protocol approval must be clear; wherever possible, processes should run in parallel and reviews should be complete within a defined period of time, all keeping in line with international and national provisions; (ii) joint training initiatives to improve the quality of submissions to ECs, with development of training tools by the medical societies and local clinical research teams. The First Symposium for Clinical Research of the HCFMUSP was indeed a step in this direction.

Regarding quality, an important consideration for prospective clinical trial partners, 2 major areas can be identified: a) organizational quality, which encompasses the ability of centers to recruit participants efficiently, and b) internal quality, or the ability to conduct research in a proper and ethical fashion to agreed-upon standards. The application of the ICH-GCP guidelines for trials with medicine-licensing purposes increases the administrative burden associated with clinical research.[3] This in turn reduces the time available to investigators to recruit and examine trial participants. Consequently many sites have failed to recruit a single patient, and few have met recruitment targets.

The development of clinical research networks is seen as a positive contribution to improvement and has been implemented in several countries, including Brazil.[4] The Brazilian government has established requirements for choosing research centers linked to teaching hospitals to be included in the National Network for Clinical Trials. HCFMUSP was one of the sites selected in this process, and the networking process is already under way.

Government and University have their own research goals. However, most of the required infrastructure for their clinical research is common to that needed by industry; therefore research infrastructure should be shared. The same is true regarding training programs on GCP. Additionally, discussion has revealed a number of areas where government and pharmaceutical industry interests would be better served by closer collaboration and where a clear understanding of the responsibilities of both parties might improve the efficiency and competitiveness of the research process. Research partnerships have been agreed upon in several developed countries as a vehicle for advancing these aspirations.

It must be emphasized that the aim of the work in International Harmonization of Clinical Trials is to improve the health and well being of people around the world. Particularly, in Brazil, it is intended to ensure that we remain at, or moves to the forefront of clinical research in terms of scientific quality, speed of start-up, and cost efficiency. Success also depends upon increasing public knowledge of clinical trials, through information about ongoing research and development, and upon a careful operation of patient consent arrangements. A guide to collaboration in research and development between the government and other research funders could bring together the principles of these collaborative partnerships.

Research protocols may be developed by university government, industry, or others, and should be recorded in a Clinical Trial Register. In any case, there must be clear agreement on sponsorship, funding, access to data, publication/reporting of findings, and intellectual property rights, ensuring that the steering mechanism has sufficient independence to prevent conflicts of interest from arising. In the complex environment of a major university such as FMUSP, many situations arise that may be, or may appear to be, conflicts of interest among employees, investigators

and sponsors. Complete disclosure and expeditious review of such potential conflicts is in the best interest of staff, investigators, and administration. All parties should recognize that disclosure of personal financial interests is vital to continued public confidence in science, even though this may appear to be a little uncomfortable. [5] It should be made quite clear that all parties would benefit from greater transparency and creativity in the management of conflicts of interest. Dialogue must be initiated or improved through inclusion of such topics at national meetings and into student training programs. Conflict disclosure does not imply that anyone is behaving improperly; and certainly, most conflicts can be managed.[6] In March 2002, the Annals of Internal Medicine published guidelines for individual physicians and institutions, strongly recommending that institutions establish their internal policies.[7]

The outcome of this work would set the stage for improved cooperation and competitiveness. As stated by 2005 Economy Nobel Prize winners Robert Aumann and Thomas Schelling, "a minimum of cooperation is a prerequisite for a prosperous society".[8] In his book, *The Strategy of Conflict* (1960),[9] Schelling emphasized the fact that almost all multiperson-decision problems contain a mixture of conflicting and common interests. Regarding conflict, commitment, and cooperation, he also mentions that in the presence of a conflict of interests each party usually seeks an agreement that is as favorable as possible. Yet, any agreement is better for both parties than no agreement at all. A more appropriate question might be "what is a fair outcome for all parties?" Some conflicts of interest may appear so strong as to be insoluble. However, cooperation is a kind of equilibrium obtained over the long-term, despite short-term conflicts.[8] Therefore, it is important to understand the other side, because all sides will become, more than ever, inclined to cooperate whenever they face a given situation.[9-10] There is a lesson for all in the game theory, and it does not matter which field we are talking about.

EM BUSCA DA HARMONIZAÇÃO E QUALIDADE NOS ESTUDOS CLÍNICOS

Dividir a experiência clínica dos diferentes institutos pertencentes ao Complexo HCFMUSP foi um dos principais objetivos do I Simpósio de Pesquisa Clínica, que aconteceu em 28 de setembro último, em São Paulo. No evento estiveram presentes alguns dos principais pesquisadores da instituição, a fim de abordar os conceitos básicos relacionados à participação em estudos clínicos. Temas como: o desafio de desenvolver um novo medicamento, através das quatro fases clínicas (I a IV), os princípios da Conferência Internacional de Harmonização e as Boas Práticas Clínicas (ICH-GCP) e a importância do adequado desenho do protocolo foram discutidos. O valor e o significado do termo de consentimento livre e esclarecido (TCLE), como é conhecido no Brasil, foram também comentados. Inconsistências no TCLE são, ainda, a maior razão de reprovação nos Comitês de Ética em Pesquisa (CEPs) no Brasil e em outros países. O Simpósio foi uma das ações relacionadas ao processo de harmonização referente às pesquisas clínicas que está em andamento no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, o maior hospital público acadêmico da América Latina. Com o objetivo de consistentemente aumentar a participação em estudos clínicos, regras claras e diretrizes são mandatórias. Os principais condutores de um processo como este são: o comprometimento da direção da instituição, o antecedente de experiência em pesquisa e a qualificação dos pesquisadores da instituição, assim como o seguimento, pelo time, de um processo "razoável" e respeitoso durante a implementação.

Estudos clínicos são essenciais para o desenvolvimento de melhores opções de tratamentos. Antes de se iniciar os testes em seres humanos, extensa experimentação pré-clínica deve ser conduzida em animais e em laboratório, o que

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