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CONSTRUCTION OF ETHICS IN CLINICAL RESEARCH – CLINICAL TRIALS REGISTRATION

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ABSTRACT: Scientific development that has been achieved through decades finds in clinical research a great possibility of translating findings to human health application. Evidence given by clinical trials allows everyone to have access to the best health services. However, the millionaire world of pharmaceutical industries has stained clinical research with doubt and improbability. Study results (fruits of controlled clinical trials) and scientific publications (selective, manipulated and with wrong conclusions) led to an inappropriate clinical practice, favoring the involved economic aspect. In 2005, the International Committee of Medical Journal Editors (ICMJE), supported by the World Association of Medical Editors, started demanding as a requisite for publication that all clinical trials be registered at the database ClinicalTrials.gov. In 2006, the World Health Organization (WHO) created the International Clinical Trial Registry Platform (ICTRP), which gathers several registry centers from all over the world, and required that all researchers and pharmaceutical industries register clinical trials. Such obligatory registration has progressed and will extend to all scientific journals indexed in all worldwide databases. Registration of clinical trials means another step of clinical research towards transparency, ethics and impartiality, resulting in real evidence to the forthcoming changes in clinical practice as well as in the health situation.

CONFLICTS OF INTEREST: There is no conflict.

KEY WORDS: biomedical research, clinical trials, ethics, drug information services, World Health Organization.

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INTRODUCTION

Clinical research faces a decisive moment. The great progress in basic biomedical research and the advances in genomics, proteomics, bioinformatics, molecular modeling and experimental models of diseases had few repercussions for clinical practice. There is lack of epidemiological and etiopathological information, low harmonized prevention, diagnostics and interventional protocols as well as poor treatment quality and cost-effectiveness control. The association of the academic research development with the economic interests made the XXI century the "Century of Biology" (2).

Now, Medicine leads the transference of biological knowledge, which is already atrophied, to the benefit of public health (6). The bridge for such transference is clinical research, which is defined as "hypothesis-driven, patient-oriented studies that are generally peer-reviewed and are commonly, but not exclusively, conducted in medical schools and teaching hospitals. Physician-scientists play a key role in the conception, design, and performance of such research, which often occurs in physicians' offices and clinics" (2). In clinical trials – clinical research projects with prospective assignment of subjects to the study of cause-and-effect relationship between intervention and outcome – new scientific approaches, drugs, techniques and technologies are tested for the first time in humans. As a result, the medical community favors "Good Clinical Practices", providing health services based on the best efficacy evidence available at scientific knowledge archives.

Altruistic study subjects believe that their participation in clinical trials contributes to advances in science and public health and trust that investigators are able to control possible risks. Together with the medical community, they hope that clinical trial entrepreneurs (sponsors and researchers) conduct the study in an ethical manner, being honest, disclosing complete data and revealing all results, including those that were not favorable, thus helping to improve human health.

However, the interest of pharmaceutical industry and public health investment managers, and the involved political, social and bioethical aspects made clinical research a target of suspicion and criticism. The world's ten largest pharmaceutical markets are responsible for more than 450 billion dollars of annual sales (9) and Latin America has shown an increase in sales superior to that of several worldwide markets. Brazil is among the five countries in this region with the highest growth potential (15). Which is the reality of such millionaire world? Should we really believe

in clinical research? Do the proposal and published results from clinical trials reflect the best treatments? How can we overcome the problem of economic interests with detriment of the best, real evidence?

Until recently, there was selective publication of clinical trials, intentional or not, which distorted the available evidence for clinical practice support. Researchers and editors were enthusiastic about results indicating positive effects of new treatments or equivalence between two different treatments. The same did not occur with negative or inconclusive results. Besides, a great part of the studies (60%) were only shown at scientific meetings and were not published (11). In a study about combination chemotherapy for ovary cancer, for example, a clinical decision based on published results (p=0.02) could be paradoxical when compared with a decision based on the total of registered studies (p=0.25) (13). Negative or inconclusive results were not considered for clinical practice.

Despite the existing scientific interest, negative results could risk economic interests and thus took second place, being hidden and not published. The CLASS study (12) showed less gastrointestinal toxic effects of the COX-2 inhibitor “celecoxib” when compared with other non-hormonal anti-inflammatory drugs in six months of analysis. However, when the complete study was disclosed, with endpoint of 12 months, there was no such difference (8). Complete information about the clinical trials outcome is generally less published than data proposed at the beginning of the study, and desired results are published more (58%) than undesired ones (50%) (5).

Changes in clinical practice must be the fruit of many studies and meta-analyses, as well as of a consensus, but not of selected results. When conducting clinical trials, investigators cannot influence the opinion of patients, doctors, researchers and other professionals responsible for the elaboration of consensual results and protocols, or support managers.

The solution for this problem was to register every clinical trial before its beginning, allowing the collection of essential scientific parameters and the monitoring of clinical trials by every one at any time, in order to certify that all results are published. This has happened in the United States since 1997, guided by “Food and Drug Administration Modernization Act (Modernization Act), section 113”, which created the Clinical Trials Data Bank, regularizing thus the registration of clinical trials with drugs that would be studied and commercialized in that country (3).

However, nothing happened until a press release in June 2004 revealing that

GlaxoSmithKline suppressed negative results in children and teenagers in the study of the antidepressant “paroxetine” (14). Such fact made public the need for the registration of clinical trials. The studies and their results had to be completely disclosed including safe and effective data to restore public confidence in participating in clinical trials. GlaxoSmithKline itself started launching a public domain registry in the Internet to display complete information about their products and experiments (10).

In September 2004, together with 11 renowned scientific journals, the International Committee of Medical Journals Editors (ICMJE) established as prerequisite for publication the registration of clinical trials whose prospective assignment started from July 1, 2005. Those initiated before such date should be registered before publication, until September 13, 2005 (1). This proposal was also accepted by World Association of Medical Editors from July 22, 2005 (16).

On May 19, 2006, WHO impelled researchers and companies to register prospective interventional studies in humans at the International Clinical Trial Registry Platform (ICTRP–http://www.who.int/ictrp), which is constituted of a network structure (Register Network), gathering information in a standardized manner from Collaborating Registers. Collaborators that fulfill several requisites can become Primary Registers or Partner Registers, which send their data to ICTRP via Primary Register. The obtained data are made available to the public at the International Search Portal (http://www.who.int/trialsearch/) (18).

Today, ICTRP has four primary registry centers: 1) Australian Clinical Trial Registry, 2) Chinese Clinical Trial Register, 3) Clinical Trial Registry (India), and 4) International Standard Randomized Controlled Trial Number Register (England). Although not registered as a Primary Register, ClinicalTrials.gov, the largest existing registry database counting on more than 40,000 registered trials and more than 200 new registrations per week (19), has its data available at International Search Portal–WHO. Several Partner Registers and other registers under evaluation are available at the same portal (17).

In May 2007, BIREME (Virtual Health Library) recommended that editors of journals indexed in the databases LILACS (Latin American and Caribbean Center on Health Sciences Information) and SciELO (Scientific Electronic Library Online) include in the “Instructions to the Authors” the responsibility for clinical trials registration, as stated by WHO and ICMJE. The registration identification number must be displayed at the

end of the abstract (4).

In June 2007, ICMJE reevaluated its registration politics and also started to accept registration done at any of WHO Primary Register Platforms. Clinical trial is then defined by WHO: “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions (drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes) to evaluate the effects on health outcomes (any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events)”. Such measures will be valid from July 1, 2008. Still in discussion is the proposal of registering clinical trial results at the same platform (7).

In Latin America, the most advanced initiative is the Latin American Clinical Trials Register (http://www.latinrec.org/index.htm) which was created with the support by Iberoamerican Cochrane Collaboration and congregates the following countries: Argentine, Chile, Colombia, Costa Rica, Cuba, Ecuador, Guatemala, Mexico, Peru and Venezuela. In Brazil, the Research Ethics Committees [Comitês de Ética em Pesquisa–CEP] and the National Research Ethics Committee [Comissão Nacional de Ética em Pesquisa–CONEP] had already established several requisites for the submission of clinical trials. Undoubtedly, such requisites also meet the necessary conditions for the registration at any platform. However, the system was not created for such function and there are still some difficulties in establishing a national network for these data.

The Brazilian National Clinical Research Network in School Hospitals [Rede Nacional de Pesquisa Clínica em Hospitais Universitários–RNPC], which was created in April 2005 by a joint action of the Brazilian Ministry of Health, Science and Technology and the Funding Authority for Studies and Projects [Financiadora de Estudos e Pesquisas–FINEP], has discussed and disclosed the registration process of national clinical trials as one of its goals in the implementation of the National Clinical Research [Pesquisa Clínica Nacional]. Meanwhile, Brazilian clinical trials need to be registered at ClinicalTrials.gov or at any Primary or Partner Registers available at WHO International Clinical Trial Register Platform until the National Register is created.

This route reflects the efforts by the scientific community in disclosing proposals and research results in an ethical, clear and impartial manner to the society, thus making

possible for everyone to contribute to human health improvement. Citing Kant, about moral reflection: “act according to a maxim which can likewise be valid as a universal law”.

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