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Registration of clinical trials: the international discussion and the possible positions to be taken by Brazil

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José da Rocha Carvalheiro
Vice-Presidente de Pesquisa e Desenvolvimento Tecnológico of Fundação Oswaldo Cruz, Rio de Janeiro, Brasil
jrcarval@fiocruz.br

Cristiane Quental
Escola Nacional de Saúde Pública Sérgio Arouca of Fundação Oswaldo Cruz, Rio de Janeiro, Brasil
cquental@fiocruz.br

Abstract
The purpose of this text is to present the discussions about the registration of clinical trials which are currently underway worldwide and discuss the possibilities for international insertion available to Brazil. Clinical trials are one of the most valuable sources of evidence about the effectiveness and safety of health interventions. However, this evidence is disseminated mainly through scientific journals and is therefore subject to the so-called *publication bias*: articles which present statistically significant results, obtained through large-scale, good quality studies and which are favorable for the industry, have a higher chance of being published. Registering clinical trial protocols in public databases, from their outset, has been proposed as an alternative solution to minimize this problem. A register of clinical trials has been defended for many other reasons – ethical, health, scientific and economic. However, there is no consensus on the principles which should govern these registers or how to operationalize them, due to the divergent interests of researchers, the pharmaceutical industry, government and society.

Keywords
Clinical research, clinical trials, health interventions, registration, databases

Introduction

A clinical trial is a prospective investigation, which evaluates the effect of any deliberate intervention, directed towards human beings, on its clinical parameters (KRLEZA-JERIC et al., 2005). In this sense, clinical trials are one of the most valuable sources of evidence about the effectiveness and safety of health interventions (SIM, 2006).

However, this evidence is disseminated mainly through scientific journals, which gives rise to the so-called *publication bias* in the analysis which is made of the available results. Journals, for obvious reasons, cannot publish all the trials carried out in the world. They must choose to present articles which attract the attention of their readers and are interesting to them. They therefore give priority to articles which present statistically significant results, obtained through large-scale, good quality studies. On the other hand, they must carry articles which are of interest to the pharmaceutical industry, which orders thousands of

copies for distribution to doctors. As a result, when a researcher submits an article for publication, he or she also chooses which results to include, from among those which were accumulated, in a *selective reporting* process (REVEIZ et al., 2006).

In the case of Brazil – and other Latin American countries – the question of the language of publication and the fact that the majority of its journals are not indexed by the large databases such as MEDLINE, further reduces international access to the trials carried out in the country (REVEIZ et al., 2006), which are of great importance to countries in a similar situation.

Registering clinical trial protocols in public databases, at the beginning of the trials, has been proposed as an alternative solution to minimize this problem. A register of clinical trials has been defended for many other reasons – ethical, health, scientific and economic. Registration would be an ethical obligation to those who participated in the trial, who hope to contribute to the progress of scientific knowledge. It would also be a way of guaranteeing access by doctors and patients to information about trials which are recruiting participants. It would also provide patients, doctors, researchers, ethics committees and sponsors with information about trials which have already taken place and those which are currently underway, thereby avoiding the risks of unnecessary exposure to interventions which have already been studied, avoiding the duplication of efforts and driving the progress of scientific knowledge and cooperation between research groups (KRLEZA-JERIC et al., 2005).

CUERVO et al. (2006) also highlight the importance of the registration of clinical trials for planning research, as it allows the identification of the gaps in existing knowledge in different areas and research trends in the field of study, as well as of specialists in the different areas. It is worth pointing out that since technological research and development activities are considered to be the basis of innovation in health industries, this information is valuable both to companies and to policymakers concerned with the promotion of innovation.

Although the benefits of the registration of clinical trials have been under consideration for years, the question began to attract more attention from 2004 onwards, when a lawsuit was filed against the pharmaceutical company GlaxoSmithKline by the Attorney-General of New York for withholding negative evidence involving its paroxetine anti-depressant drug, sold as Paxil in the United States and Seroxat in Great Britain (KRLEZA-JERIC, 2005). According to DYER (2004), the Attorney-General had an internal company memorandum from 1998 which stated that it would be "commercially unacceptable to admit that paroxetine did not work in children and that the company would have to manage the dissemination of these data in order to minimize any negative impact".

The case intensified the debate about the need to set up a database which could register all clinical trials from their outset. But although there have been many initiatives to set up registers and to encourage the public registration of clinical trials around the world, there is no consensus on the principles which should govern these registries or how to operationalize them, due to the divergent interests of researchers, the pharmaceutical industry, government and society.

The article presents the debate currently underway worldwide and discusses the possibilities for international insertion available to Brazil.

Main initiatives for the promotion of a register of clinical trials

One of the pioneering initiatives originated in the Canadian Institutes of Health Research, which began to require the registration of all trials it funded after the episode with GlaxoSmithKline (CUERVO et al., 2006) and convened an open meeting in Ottawa to which it invited those interested in contributing to the development of a plan for a global register of clinical trials. The debates led to the creation of the Ottawa Group to take the discussion forwards on an international level (OTTAWA GROUP, 2007). The Ottawa Declaration – Part I (KRLEZA-JERIC et al., 2005), which was published in several journals, calls for the registration of all clinical trials approved by ethics committees and health authorities, and that each one be given a unique global identification number. Registration should take place before the recruitment of participants to the study, making information about the protocol available to the public, with this information being updated any time changes are made. It also calls for the registration of trial results, as soon as they are available, as well as information on harmful effects. However, the release of results to the public may await the publication of the results, which should be mentioned in the database. (Part II of the Ottawa Declaration, which deals with the principles of operationalization of international trial registration, is publicly available on the Ottawa Group's website (http://ottawagroup.ohri.ca). Part III, which focuses on the reporting of results, is under development.)

The Group argues that registration should be a legal requirement, but urges journal editors to request the unique registration number for the publication of articles relating to trials and ethics committees to support the procedure.

This proposal received key backing from the International Committee of Medical Journal Editors (ICMJE) which announced in September 2004 that its affiliated journals would begin to accept for publication only those trials which were registered in public databases following certain criteria: access by the public without charge, managed by non profit-making organizations, and offering electronic searches. Each record should include a unique identification number, details of the intervention in question, the comparison established, the hypothesis being studied, the definition

of the variables of primary and secondary outcomes, the criteria for inclusion, the timetable, the number of subjects, the sources of funding, and contact information for the main researcher (DE ANGELIS et al., 2004). This was the decisive factor which led to studies being registered more systematically (ZARIN et al., 2005). This ruling was followed by many other journals, including those affiliated to Bireme (the Latin American and Caribbean Center on Health Sciences Information, run by the Pan-American Health Organization (PAHO)), through indexing in the LILACS and SciELO databases, which announced that from August 2007 onwards it would also make prior registration a condition for the publication of articles about clinical trials (BIREME, 2006).

In November 2004 a Ministerial Summit took place in Mexico City about health research. The Mexico Declaration, signed by the ministers of health of 52 countries, recognizes that the results of good quality research should be accessible, in order to effectively inform health policy and decision-making in healthcare. It also recognizes that the results of research should be published, documented in registers and other internationally accessible formats, and synthesized through systematic reviews of the totality of research results available, to lay the foundations for an evidence-based approach to health. It urges the World Health Organization (WHO) to facilitate the integration of an international network of registers of clinical trials, guaranteeing a single access portal and the identification of trials without ambiguity (MINISTERIAL SUMMIT, 2004).

The WHO accepts the mission based on an understanding that its neutral and global nature inspires greater confidence in the public. Its role as the world authority on health, and its central role in coordination and regulation equip it to take on the task (SIM, 2006). In actual fact, the WHO had already been discussing the issue and after wide international consultation, it launched a proposal for the creation of an International Clinical Trials Registry Platform (ICTRP) in May 2005. This is presented in the following section.

The WHO proposal

The WHO argues that all trials should be registered. It proposes to lead the process of regulating the registers of clinical trials at international level, to make possible cooperation between them through the formation of a network, accessible from a single portal, where each trial would be given a unique identification number which would allow it to be monitored throughout its duration.

One of the cornerstones of the proposal is therefore a minimum set of information, which must be recorded about each trial, set out in Table 1.

According to SIM (2006), there are hundreds of trial registration databases in existence in the world, which vary in scope (focusing on a specific disease, country or funder) and aims (administrative

Table 1 – Data set for registration in the ICTRP

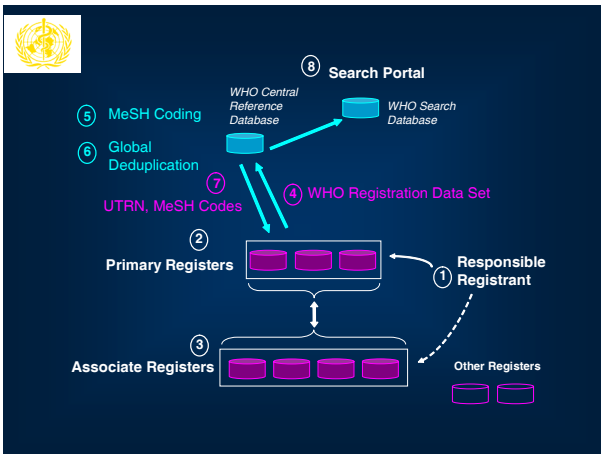
1.	*Primary register trial number*
2.	*Trial registration date*
3.	*Secondary IDs*
4.	*Sources of monetary or material support*
5.	*Primary sponsor*
6.	*Secondary sponsor(s)*
7.	*Contact for public queries*
8.	*Contact for scientific queries*
9.	*Public title of the study*
10.	*Scientific title*
11.	*Countries of recruitment*
12.	*Health condition or problems studied*
13.	Intervention(s)
14.	*Key inclusion and exclusion criteria*
15.	*Study type*
16.	*Date of the first enrollment*
17.	*Target sample size*
18.	*Recruitment status*
19.	*Primary outcomes*
20.	*Key secondary outcomes*

Source: WHO, 2007

monitoring, patient recruitment, scientific analysis etc.). The WHO recognizes that each one of them has its application, and that it is not realistic to think in terms of a single database which would work for all of them. For this reason, it proposes a hierarchical structure for connecting them, described in Figure 1.

In this hierarchy, Associate Registers would send their information to the Primary Registers, which would be responsible for the task of "deduplication" of registers (identification of trials registered in more than one database) and translation into English, where

Figure 1 – Structure of the ICTRP proposed by the WHO



Fonte: SIM, 2006.

necessary, because all the information must be made available in English. The ICTRP would be a meta-register linking up the information registered in these Primary Registers.

Questions under discussion

There are different opinions about the nature of the registration of clinical trials and the reach it should have. The first controversial question which arises relates to the actual definition of which trials should be registered. While the Ottawa Group and the WHO propose that all trials should be registered, the pharmaceutical industry suggests that trials of an exploratory nature, carried out in the initial stages of research, should be exempt from the register, since their only purpose is to generate working hypotheses. Registration would directly affect their competitiveness without effectively contributing medical knowledge, and the results would not be relevant to help inform clinical practice (KRLEZA-JERIC, 2005). The ICMJE followed this second rationale, defining a trial as any research project that prospectively assigns human subjects to intervention to study the cause-and-effect relationship between a medical intervention and a health outcome. "Studies designed for other purposes, such as the study of pharmakocinetics or toxicity (such as phase 1 trials) are exempt" (DE ANGELIS et al., 2004). These arguments contrast with the recent events which led to the death of a person during a phase 1 trial in London, which illustrate the need to register all trials (HEALTH CANADA, 2006).

The pharmaceutical industry also requests that five of the twenty items which make up the basic set of information proposed by the WHO have their dissemination delayed - the official scientific title of the study, the interventions, the primary outcomes, the key secondary outcomes and the size of the sample – as these items are more sensitive for competition. The Ottawa Group is vehemently opposed to this proposal, and stresses that the WHO proposal already excludes some items which the Ottawa Declaration considered to be crucial. These are all already included in the ClinicalTrials.gov database, which the industry should be used to by now (KRLEZA-JERIC, 2005). It argues that since one of the fields relates to the unique identification number, and nine of them are administrative, all that would remain is a minimum set of ten variables which describe the study and that without the five main ones, the description would become absolutely generic and pointless. While it could still be used for the inclusion of patients in trials, such a register would not meet the ethical and scientific objectives (KRLEZA-JERIC, 2005).

The WHO proposal is to only assign a unique registration number to those who fill out the full twenty items (although it may consider the disclosure of some of them at a later stage). The experience of ClinicalTrials.gov, the world's largest register with around 39,000 registered trials (maintained by the National Library of Medicine of the National Institutes of Health in the United States of America), described in ZARIN et al. (2005), shows that the quality of this information can be rather poor, even considering that ClinicalTrials.gov accepts the information as it is registered. In the period from May to October 2005, the field relating to the main measurement variable of the trial was filled in only 76% of trials sponsored by industry, and the quality of the data left something to be desired, as Table 2 shows.

However there are also disagreements about the model used by the system. The WHO proposal is for a hierarchical structure, where the registration of the trials would be carried out in secondary, national or regional registers, which would be consolidated by primary registers. ClinicalTrials.gov proposes the opposite: that trials be registered first in the primary databases, which would distribute the records of interest to the secondary databases. They believe that consolidation is labor-intensive and would not guarantee the quality of the data. On the other hand, Current Controlled Trials (www.controlled-trials.com), the second largest register in the world, set up in England by researchers dedicated primarily to systematic review and organized by the Current Science Group publishing house, with more than five thousand trials listed, is a meta-register, organized in a structure similar to that proposed by the WHO. It brings together various other registers and has a unique trial numbering scheme, the International Standard Randomized Controlled Trial Number (ISRCTN).

Table 2 - Primary outcome measure

Em 76% of industry trials had entries. But:
• 17% Vague
• 19% Domain without specific measure
• 23% Specific measure without time frame
• 10% Time frame without specific measure
• 31% Specific measure and time frame

Source: Zarin et al. (2005)

International adhesion to the proposal is fundamental given the lack of mechanisms to make registration compulsory. Although there is some legislation in force and several draft bills currently underway in the world in this respect, the largest incentive for registration remain the conditions imposed by journals for publishing articles. It is a time for negotiation and seeking institutional support, because registration is voluntary.

It should be stressed, however, that any limitation on the availability of information would result in a limitation on the efficiency of Clinical Trials Registers, and thus would represent a possible functional and ethical breach. (BOISSEL et al., 1993).

Movements in the Americas / Alternatives for the Brazilian position

The WHO proposal, supported by PAHO, has gained support in the Americas. The Latin American Ongoing Clinical Trial Register (LATINREC) has been set up by the Colombian arm of the Ibero-American Cochrane Network, an independent health information organization which brings together twelve collaborating centers in ten Latin American countries (Argentina, Chile, Colombia, Costa Rica, Cuba, Ecuador, Guatemala, Mexico, Peru and Venezuela), coordinated by the center in Barcelona. This register is about to become operational, following the ICTRP requirements. Along with ClinicalTrials.gov that would make two registers in the Americas.

Canada has also agreed to the proposal but is discussing how best to implement it: to create a national register or to join a register which meets the ICTRP conditions, such as ClinicalTrials.gov. It is tending towards choosing a customized form of association which will request additional information as well as the registration information – in this case, the consent of the volunteer (HEALTH CANADA, 2006).

The importance of Brazilian participation in the global effort is clear, as it would help to encourage registration in the country, give greater visibility to trials carried out here and contribute to improvements in the quality of the data made available. It also reinforces the system of ethical and health review and the principles which guide them, as well as supporting health, science and technology policies, both national and institutional.

The discussions about the WHO proposal, initially restricted to the relevant authorities, such as the Department of Science and Technology (DECIT) of the Secretariat of Science, Technology and Strategic Inputs (SCTIE) of the Ministry of Health (which took on the proposal), the National Sanitary Surveillance Agency (ANVISA) and the National Council for Ethics in Research (CONEP), were broadened at the VIII National Congress and the XI International Congress on Public Health, which took place in Rio de Janeiro in August 2006.

The activities promoted by PAHO, DECIT and the Oswaldo Cruz Foundation (Fiocruz) were attended by representatives of government, publishers, the pharmaceutical industry and patients, as well as foreign (LATINREC and one from South Africa) and national registers of researchers (ICICT/Fiocruz), in other words quite a wide range of stakeholders, which culminated in the decision to create a national database.

We are now faced with the same questions as those facing the Canadians: what is the best way to implement the proposal? Is it worth setting up a National Register? Table 3 shows some statistics about trials registered on ClinicalTrials.gov in March 2007. According to the table, there were 511 trials registered in the database which listed Brazil as one of their sites – around 1.5% of the trials in the database. However, only 82 of these listed only Brazil. So, at least these trials would be registered in our database. However, this number is certain to rise, since the announcement at the last International Congress on Public Health of the decision by Latin American journals to begin only accepting registered trials for publication within a year, as mentioned above.

Would it be a better option – as Canada believes – to join a register which meets the ICTRP conditions? The interest of a register such as ClinicalTrials.gov, for example, in a partnership with Brazil would be the stimulus it would give to registration and the validation of its data about trials carried out in the country as well as the possibility of dissemination in Portuguese. Indeed, this is the aim of the WHO when it proposes a decentralized structure – the proximity of the register of trials makes these tasks easier. For Brazil, the advantage would lie in the establishment of a register at a reduced cost, because it would not need to fund the necessary technical infrastructure.

Table 3 – The top five countries in number of registrations globally and the top four in Latin America

Country	Total Studies	Single country	Multiple countries
EUA	23187	19995	3192
Canada	3299	1312	1987
Germany	2339	916	1423
France	2121	914	1207
UK	1867	632	1235
Brazil	511	82	429
Mexico	458	46	412
Argentina	425	19	406
Chile	209	12	197

Source: ClinicalTrials.gov, accessed on 08/03/2007.

A series of other decisions need to be taken for the implantation of a National Register, and one of them is the registration policy in the country. Registration may be considered voluntary, or be in some way made compulsory. This compulsory status must not drive away industry trials. For a middle way the Canadian discussion is once again relevant (HEALTH CANADA, 2006), as it suggests that the government could initially require only that the trials it funds be registered, but that it should make representations so that other Canadian institutions follow its example.

Final considerations

Whatever choice Brazil makes, the important thing is that the data which is registered is used, in particular by the Ministry of Health, the funder.

The main benefit will lie in discovering what is happening in Brazil in relation to clinical trials: What

are the projects underway? Who funds them? Who executes them? The more direct use of the data will be for assisting science and technology policy and policy to support innovation in the health industry complex, whether by encouraging research and development activities, where public health needs are not being addressed by industry, or by regulating the process, encouraging the generation of knowledge to assist the incorporation of new products and technologies in the health system.

But the benefits of the registration of clinical trials go beyond government actions in relation to innovation, contributing to the generation of new products: adding new knowledge to the stock used by pharmaceutical research and development and the majority of health inputs; signaling what is being studied and where there are gaps, where the chances for innovation are more favorable, due to less competition. At the same time, it represents a "shop window" for national researchers/ research centers, providing greater international interaction and insertion, as well as facilitating the access of companies to the resources they need; and a "shop window" for companies to attract partnerships and to support them in their search for partners.

We hope that this article has helped to share the discussion and encourage debate about registration of clinical trials, not just to assist government actions, but also to encourage the registration of trials carried out in Brazil.

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About the authors

José da Rocha Carvalheiro

José da Rocha Carvalheiro has a medical degree by the School of Medicine of the *Universidade de São Paulo* (USP), he has been a teacher at the USP School of Medicine in Ribeirão Preto since 1963, where he accomplished the titles of Doctor in Parasitology, Teacher, Associate Professor and Senior Professor in the Social Medicine Department. Currently retired from USP, he is the Vice President of Research and Technological Development at *Fundação Oswaldo Cruz*, where he coordinates the *Projeto Inovação em Saúde* [Innovation in Health Project]. He is a member and President of the *Associação Brasileira de Pós Graduação em Saúde Coletiva* [Brazilian Association of Collective Health] (Abrasco), Scientific Editor of the *Revista Brasileira de Epidemiologia* journal, Member of the *Centro Brasileiro de Estudos de Saúde* [Brazilian Center of Health Studies] (Cebes) and of the Editorial Board of the *Revista Brasileira de Vigilância Sanitária* journal. He has been working in the area of Public Health with emphasis on Epidemiology, working mainly with the following themes: epidemiology; Aids; science, technology and innovation in health; vaccine and immunobiologics development policy.

Cristiane Quental

Cristiane Quental is an economist, graduated at the School of Economy and Administration of *Universidade Federal do Rio de Janeiro*, with master's and doctor's degree in Administration by the Post-Graduation in Administration Institute (COPPEAD) of *Universidade Federal do Rio de Janeiro*. She has a post-doctorate at the Scientific and Technological Politics Department of Geosciences Institute of the *Universidade Estadual de Campinas*. She is a researcher at the Escola Nacional de Saúde Pública (Ensp) of *Fundação Oswaldo Cruz* in the following themes: Science Politics and Management, Technology and Innovation in Health; National System of Innovation in Health; Research and Development in Health; Management of Public Research Institutions and Health Industrial Complex. She coordinates the Professional Master in Science and Technology Management in Health offered by Ensp to managers of federal science and health technology organizations and is an adviser for the *Projeto Inovação em Saúde* [Innovation in Health Project] of Fiocruz's Presidency, an institution involved in the process of implementation of a Clinical Trials Registration in Brazil.