JOURNAL OF EVIDENCE-BASED MEDICINE

Journal of Evidence-Based Medicine ISSN 1756-5391

Brazilian Clinical Trials Registry and the challenges for clinical research governance

Josué Laguardia[1], Alessandro Luís Piolli[2], Margareth Prevot[1], Luciano Ramalho[3], Ricardo Gamarski[4] and Claudio Nishizawa[5]

[1]Instituto de Comunicação e Informação Científica e Tecnológica em Saúde – ICICT, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil
[2]Instituto de Geociências, Universidade Estadual de Campinas, Campinas, Brazil
[3]Centro Latino-Americano de Informação em Ciências da Saúde – Bireme, Organização Pan-Americana da Saúde, São Paulo, Brazil
[4]Secretaria de Ciência, Tecnologia e Insumos Estratégicos – SCTIE, Ministério da Saúde, Brasília, Brazil
[5]Gerência Geral de Medicamentos, Agência Nacional de Vigilância Sanitária – Anvisa, Brasília, Brazil

Keywords
ReBEC; clinical trials; governance; Latin America; Brazil

Correspondence
Dr. Josué Laguardia, Instituto de Comunicação e Informação Científica e Tecnológica em Saúde da Fundação Oswaldo Cruz (Icict/Fiocruz). Av. Brasil, 4365 Pavilhão Haity Moussatché sala 214, Manguinhos. CEP 21045–900 – Rio de Janeiro, RJ – Brazil.
Tel: +55–21-3568–3258
Email: jlaguardia@cict.fiocruz.br

Received 15 July 2011; revised 20 July 2011; accepted for publication 22 July 2011.

doi: 10.1111/j.1756-5391.2011.01145.x

Abstract

Over the past five years, efforts to set up a Brazilian clinical trials registry have progressed from early discussions in academic forums through to the establishment of the registry as a web-based computer platform. This article describes the process of developing and introducing the Brazilian Clinical Trials Registry (ReBEC), and its relationship with the authorities that regulate clinical research in Brazil. The Brazilian Clinical Trials Registry and the multilingual, free and open source, internet-based software developed to manage it are outcomes of partnerships among Brazilian federal and international health agencies. Information for describing the technical and operational dimensions of Rebec was drawn from technical documents and the records of the OpenTrials software development team and the ReBEC executive and advisory committees, which are available in free-access repositories. The Brazilian Clinical Trials Registry was launched in December 2010, and approved as a primary registry of the WHO ICTRP network in April 2011. ReBEC's arrival on-line and its acceptance as an ICTRP primary registry is a significant step in consolidating a policy of free access to information on clinical research in Brazil.

Introduction

Experimental studies are a valuable source of evidence on the efficacy and safety of health interventions and when recorded in public databases, all interested parties can access relevant information on the products or procedures under investigation. In this light, making information on the studies freely available heightens research transparency and enhances the ethical and scientific value of such studies. In addition, by providing patients, doctors, researchers, ethics committees, sponsors and other interested parties with free access to information about ongoing and completed clinical trials, it reduces unnecessary duplication of research efforts, because those planning new studies will be aware of all existing trials. Clinical trial participant recruitment rates are increased, especially for rare diseases or high-risk conditions, in turn improving the likelihood of successful outcomes for some clinical trials.

Registration of clinical trials also adds value to research results by providing a reliable source of information for evidence-based systematic reviews, meta-analyses and guidelines, helping to refine the evidence available to orient health practices. As a regional registry integrated with the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) (1), the Brazilian Clinical Trials Registry (ReBEC) opens up new possibilities for access to local studies – which are of increasing international interest, especially in BRICS member countries (Brazil, Russia, India, China and South Africa) – such as bioequivalence testing of generic and similar drugs, in which Brazil has acknowledged expertise. Another dimension implicit in the introduction of a clinical trials registry is its importance as an instrument of clinical research governance, in that it permits greater access to information by people interested in how clinical research is conducted and the outcomes that it leads to.

A primary registry for Latin America

In Latin America, the Pan American Health Organization (PAHO), jointly with the Latin American and Caribbean Center on Health Sciences Information (Bireme/PAHO/WHO), has supported the creation of a Latin America and Caribbean region clinical trials registry platform. The proposal to set up such a platform was presented during the 8th Brazilian Collective Health Congress, in Rio de Janeiro, in 2006, and discussed with representatives of Argentina, Chile, Cuba, Colombia and Brazil during the 15th Cochrane Colloquium, in São Paulo, in October 2007 (2). Discussion of how to go about setting up the ReBEC had its beginnings at both events. Over the following two years, various proposals were discussed, including forming a regional network of national registries, partnering with an international registry or setting up a primary registry integrated with the ICTRP/WHO network of primary registries. This latter option prevailed.

Recognizing the importance of the initiatives by the WHO and the International Committee of Medical Journal Editors (ICMJE) in orienting scientific journals to require that clinical trials must be registered before their results are published, Bireme issued a recommendation to the editors of scientific journals indexed in the Scientific Electronic Library Online (SciELO) and the *Literatura Latino-americana e do Caribe de Informação em Ciências da Saúde* (LILACS) on 15 May 2007 (http://espacio.bvsalud.org/files/5/1/051111052007/recomend_edit_rev_2007%20port.pdf). Accordingly, specific fields were introduced in LILACS and SciELO for the registration numbers of clinical trials in articles published by journals in the health field. Bireme expected all LILACS and SciELO scientific journals that publish articles on clinical trials to comply with this policy by the end of 2007. Compliance then became a prior requisite for journals to be included in, and continue to be indexed by, these information sources.

In 2008, two Brazilian government ministerial orders, MS/GM No. 1345 and 2448, provided for a commission to prepare the implementation project for a Brazilian primary registry with a flexible, open-source web platform for Latin America and the Caribbean (3). In 2009, the ReBEC Technical and Advisory Committees were established and tasked with defining rules for governance, review of operating procedures, and web system specification to be developed for the review and publication of clinical trial registries. The participants in these committees included the Science and Technology Department of the Science, Technology and Strategic Resources Secretariat of Brazil's Ministry of Health (Decit/SCTIE/MS), Bireme, the Pan American Health Organization, the Health Science and Technology Communication and Information Institute of the Oswaldo Cruz Foundation (ICICT/Fiocruz) and the National Health Surveillance Agency (Anvisa), whose functions are analogous to those of the European Medicines Agency (EMEA) and the United States Food and Drug Administration (FDA). PAHO, Brazil's Ministry of Health and the Oswaldo Cruz Foundation (Fiocruz) financed the development of the web platform, and management of ReBEC was assigned to ICICT/Fiocruz. The Brazilian Clinical Trials Registry is the product of this partnership among these three institutions, and joins with international endeavors in scientific reporting of clinical research.

The Brazilian Clinical Trials Registry (ReBEC) was launched on 16 December 2010, and is accessible at http://www.ensaiosclinicos.gov.br. Since 29 April 2011, it has been a primary registry of the WHO ICTRP network (1). The inclusion of ReBEC in the network of WHO primary registries should make an important contribution to biomedical sciences and clinical, ethical and political decisions all over the world, by affording free access to information on local and regional studies, as well as those that are part of multicentre trials. Jointly with the Cuban Public Clinical Trials Registry, ReBEC performs the role of primary registry across Latin America and the Caribbean, and trials can be registered in Portuguese, Spanish and English. In addition, ReBEC's open-source computational platform will contribute to the creation and establishment of other primary clinical trials databases. As of July 2011, 32 studies are registered at ReBEC, most of which are clinical trials.

The Brazilian Clinical Trials Registry

ReBEC's goals are to establish a wide-ranging, current record of ongoing or completed experimental and observational studies in Portuguese-speaking countries; to offer interested stakeholders access, free of charge, to reliable data from such studies for reviews, meta-analyses, guidelines and related policy making; to heighten research transparency, enhancing the ethical and scientific value of the studies; to make it easier to discover and control bias in design and publication, and to reduce language bias, by providing information in Portuguese on Brazilian studies that were previously recorded in international registries; to enter into ethical and regulatory processes; and to meet national and regional information needs. Information in Portuguese on completed or ongoing studies in Brazil is of the utmost importance in view of the constraints on obtaining data on such studies from sponsor institutions, requiring that such searches be performed in international, English-language registries.

Studies accepted for publication on ReBEC meet criteria defined by ICTRP and ICMJE. Accordingly, "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes", as well as non-experimental studies, are eligible for submission to ReBEC.

Registration data are provided by the sponsor, a representative clinical research organization, the lead investigator or another legal representative, as stipulated by Anvisa resolution RDC 39 (4). Brazilian and international multicentre studies should be registered once only by the sponsor or legal representative, including details of the lead investigator at each study site, according to CNS resolution No. 346–01/13/05 (5). Trials may be registered on ReBEC only after gaining approval from the ethics committee of the institution hosting the study and/or by the National Research Ethics Commission (*Comissão Nacional de Ética em Pesquisa*, CONEP), and before the first participant is recruited. Registration fields must be completed in Portuguese and English and possibly in Spanish, when there are recruitment sites in Spanish-speaking countries. Registration is free of charge and access is unrestricted.

At the application stage, it is compulsory for trial applicants to provide all 20 data items of the ICTRP trial registration dataset. Additional data relating to study type are also collected, along with descriptors for the interventions and health conditions or problems under study. The trial identifying number comprises a set prefix (RBR, standing for Brazilian Registry, in Portuguese) followed by a hyphen and a randomly-generated identifier whose first character is always a digit from 2–9 and the remaining 5 characters are drawn from the set "23456789bcdfghjkmnpqrstvwxyz". The registration date establishes when the study was published on ReBEC. The fields Scientific and Public Titles, Scientific and Public Acronyms and respective Expansions, Universal Trial Number (UTN), Secondary Identifying Numbers with Issuing Authority Name and Identifying Number, Primary Sponsor (Institution Name, Postal Address, Country, Type), Secondary Sponsor and Sources of Monetary or Material Support follow the ICTRP recommendations. The field "Health condition(s) or problem(s) studied" is subdivided into a free text field and two other fields where the registrant selects general and specific health condition descriptor terms and the respective codes using the ICD-10 and DeCs/MeSH vocabularies, through a webservice. Similarly, the "Intervention" field is sub-divided into a free text field and two fields for intervention code and description, using ICD-10 and DeCS/MESH web services. Registrants may include several conditions for study and intervention. Study Status defines the stage the study has reached – whether or not it is Recruiting, Suspended, Terminated, Withdrawn, Data Analysis Completed or Other. The Recruitment Countries list is based on ISO 3166. Dates of first and last enrollment are entered with the planned dates, and are subsequently updated with the dates that recruitment actually started and ended.

The fields Study Design, Target Sample Size, Key Inclusion and Exclusion Criteria, and Primary and Secondary Outcomes follow ICTRP definitions. The following fields have been added: Minimum and Maximum Age; Sex of Study Participants (male, female, both); whether the study includes an Expanded Access Program – Yes, No; Study Type – Interventional or Observational; Study Purpose – Diagnostic, Etiological, Prognostic, Prevention, Treatment, Other; Intervention Assignment – Single Group, Parallel, Crossover, Factorial; Number of Arms; Masking Type – Open, Single, Double, Triple Blind; Allocation Type – Non-Randomized, Randomized Controlled; Study Phase; Study Design – Cohort, Case-Control, Case Study, Crossover, Ecologic or Community Studies, Family Based, Other; and Time Perspective – Prospective, Retrospective, Retrospective and Prospective, Cross-Sectional, Other. These fields use the same categories as defined for the *Plataforma Brasil* computer platform (see below). Contact information is separated by contact type – Contact for Scientific Queries, For Public Queries, and Research Site. Registrants may append study protocols, addenda, description of results or links to reports, communications and/or published articles via the Attachments form. Registrants are asked to attach a copy of the institutional ethics committee letter of approval as proof of authenticity, as well as the institutional ethics committee process identifying number or national research ethics information system (*Sistema Nacional de Informação sobre Ética em Pesquisa*, SISNEP) registration number in the Secondary Identifying Numbers field. Studies which have not yet started recruiting are accepted (prospective registration), as are those for which recruitment started after 1 January 2010 (retrospective registration).

After submission, the record is reviewed by ReBEC technical staff, and observations are made to guide the registrant as to any mistakes or inconsistencies. When these have been corrected, the registrant re-submits the record to be checked again by the ReBEC team or reviewers and, if no further corrections are needed, the record is published on the ReBEC website. Registration data can be updated by registrants but the original information is not eliminated. It is linked to the updated record, maintaining an audit trail.

The computer platform used to manage ReBEC is OpenTrials, which is multilingual, free and open source software (FOSS), designed and implemented in collaboration among Bireme, Brazil's Ministry of Health, Fiocruz, PAHO and Anvisa. The Brazilian registry is the first instance using OpenTrials. National and regional instances of this platform are being considered in Latin America and the Caribbean under PAHO/WHO supervision, following the distributed model proven by the Virtual Health Library (VHL) network. OpenTrials is being developed openly and transparently on the portal of the Virtual Health Library Developers Network (*Red de Desarrolladores da Biblioteca Virtual em Saúde*) at http://reddes.bvsalud.org/projects/clinical-trials/wiki/OpenTrials, where the project's documentation and products are publicly accessible.

In addition to the functionality inherent to the record submission, review and publication process, the OpenTrials platform permits data to be imported from the operating system used by the ethics committee network of CONEP. Data are imported by Opentrials in XML format, based on a Document Type Definition (DTD), which supports multilingual trial records and is able to serialize a trial as a format with all its information, to be recovered and/or imported by other databases. It can be updated to the current model, and avoids namespaces to keep it as simple as possible and independent from a standard ICTRP format. The DTD enables all instances to be interoperable, and facilitates data exchange to WHO standards. Users can apply a python script (validate.py), available from http://reddes.bvsalud.org/projects/clinical-trials/browser/trunk/opentrials/repository/xml, to validate their clinical trial XML file against a predefined vocabulary described in two DTD files – one with a DTD description of the fields of the Opentrials data template (opentrials.dtd), and another with the definition of the controlled vocabularies (opentrials-vocabularies.mod) of some fields of the data template. Users can download the python script file and, after including their study information in a xml file based on the two DTD files, can validate it using the command "python validate.py your-file-name.xml". Before validation, the lxml package, available at the python web site, must be installed and running. After the xml file is validated, it can be uploaded to ReBEC. In addition to this import function, Opentrials also supports data export in ICTRP format. The DTD used for import differs from the export DTD, because the ICTRP does not provide for the multilingual records supported by Opentrials.

Integration of ReBEC with Brazil's health governance system

The process of institutionalizing the Brazilian health care system in its present form can be traced back to the reformulation of the National Health Council (*Conselho Nacional de Saúde*, CNS) in 1990. In that year, Decree No. 99.438 redefined new attributions for the CNS and participating organizations and bodies. After a series of debates on the role of the CNS, publication of Presidential Decree No. 5.839/2006 established a new structure in 2006. Following the deliberations of the 11th and 12th National Health Conferences, the CNS came to choose its members via an electoral process and to comprise 48 councilors, who represent users (fifty percent of seats), health personnel, managers and providers (6).

The National Research Ethics Commission (CONEP) was set up by CNS Resolution No. 196/96 for the purpose of implementing standards and guidelines to regulate research involving human subjects. It is a collegiate and advisory body designed to formulate guidelines and strategies in the CNS sphere of interest. CONEP acts jointly with a network of ethics committees distributed and organized in public and private teaching and research institutions. Researchers, health personnel and user representatives participate in both CONEP and the ethics committees. The ethics committees review all protocols for research involving human participants, and the primary responsibility is with decisions on the ethics of research to be performed at their institution. Ethics committees also have an advisory, educational and oversight role, of receiving complaints and requiring these be investigated. The role of CONEP is to examine the ethical aspects of studies (referred to it by institutions' ethics committees) involving human participants in special thematic areas, including studies in genetics and human reproduction; indigenous populations; projects involving biosafety considerations; research coordinated from abroad or with foreign participation; research involving the transfer of biological material abroad; and projects that in the, duly justified, opinion of the institution's ethics committee should be examined by CONEP.

Ethics committees selected previously by CONEP are interconnected via Internet in a National Research Ethics Information System (SISNEP). This system facilitates registration of studies involving human participants, guides the progress of each project before it actually begins, fosters the formation of a national database, and makes it easier for researchers to monitor the status of their projects. SISNEP will be replaced by the *Plataforma Brasil*, which is currently being developed and will have a database in five modules: public, researcher, ethics committees, CONEP, and Anvisa. The *Plataforma Brasil* will be an important primary, Portuguese-language source for research in Brazil and will serve as a tool for sharing Anvisa decisions, and as an information source on adverse events and research reports, in addition to expediting access to updated versions of research projects, and review of related alterations.

The ReBEC system will integrate with the *Plataforma Brasil* by way of the Opentrials XML format import functionality, enabling studies to be pre-registered on ReBEC, with the registrant's agreement, thus reducing duplication of effort in the submission process. However, it will be the responsibility of the registrant to translate the content of ReBEC registration fields (Study Title, Description of the Intervention, Study Design, Inclusion/Exclusion Criteria, and Study Outcomes) from Portuguese into English and, sometimes, Spanish. This procedure is necessary, because one aim of this project is to give international visibility to the records through the WHO ICTRP.

As regards regulation of clinical research in Brazil, the requirement that clinical trials be registered is regulated by RDC 39/08 (4), which sets out the rules governing clinical research in Brazil. The requirement applies only to phase

III therapeutic confirmatory studies that request registration (that is, innovative product, new therapeutic application or registration changes) or revalidation of registration with Anvisa. These must be registered in the clinical research registration database of ICTRP or another registry recognized by ICMJE. Proposed changes for reformulation of RDC 39/08 include compulsory registration on ReBEC. Just like *Plataforma Brasil*, ReBEC will serve as an instrument to support Anvisa's management of clinical research. Activities developed by Anvisa in the regulation of clinical research sites, including good clinical practices inspections for update or correction needs, can improve the quality of data registries.

Challenges

New features to be implemented in future versions of the platform and, consequently, integrated into ReBEC's work processes include file import in XML format from other primary registries, improved usability of study submission and review processes, and inclusion of ontologies for more refined searches of published studies. Among the challenges, quality control of reviews of studies in two or three languages requires using standardized fields and, as a result, adopting taxonomies that meet registrants' needs and enable information to be recovered quickly and accurately, thus ensuring the studies contribute effectively to science, to clinical, ethical and political decisions, and to clinical research governance.

Support from scientific journals, research institutions, and financing organizations and agencies – by requiring that studies, particularly clinical trials, are registered – is fundamental to guaranteeing ReBEC's political sustainability. Another important aspect is the project's financial sustainability: at present it is financed from Brazil's National Health Fund (*Fundo Nacional de Saúde*) under Process No. 25000.087889/2010–32, for health research and evaluation of new technologies for the national health service (SUS). Inclusion of ReBEC as a strategic project of Brazil's Ministry of Health is designed to ensure the project makes the transition from its initial stage to becoming established as a government program. ReBEC's entry into operation and its joining the network of primary ICTRP registries represent significant steps towards its becoming established as a policy of free access to information on clinical research, transparency and accountability in Brazil.

References

1. Ghersi D, Pang T. From Mexico to Mali: four years in the history of clinical trial registration. J Evid Based Med 2009; 2(1):1–7.
2. Castro, RCF. Registros de ensaios clínicos e as consequências para as publicações científicas. *Medicina (Ribeirão Preto)* 2009; 42(1): 31–5.
3. Brasil. Ministério da Saúde. Departamento de Ciência e Tecnologia, Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Registro Brasileiro de Ensaios Clínicos (Rebrac): fortalecimento da gestão de pesquisa clínica no Brasil. *Rev. Saúde Pública* 2009; 43: 387–388.
4. Brasil. Resolução – RDC MS/Anvisa No. 39, 5 June 2008 – approves the rules for the conduct of clinical research among other provisions. Available from http://www.anvisa.gov.br/medicamentos/pesquisa/legis/rdc39_08.pdf (Accessed 16 July 2010).
5. Brasil. Resolução 346, 13 January 2005 – establishes rules for consideration of multicenter research projects in the Research Ethics Committees System (CONEP). Available from http://conselho.saude.gov.br/resolucoes/reso_05.htm (Accessed 16 July 2010).
6. Conselho Nacional de Saúde. História do CNS. 2011. Available from http://conselho.saude.gov.br/apresentacao/historia.htm (Accessed 23 January 2011).