

# Current clinical research environment. Focus on Psychiatry

## Cenário atual da pesquisa clínica. Foco em Psiquiatria

Sonia Mansoldo Dainesi,<sup>1</sup> Helio Elkis<sup>2</sup>

### Abstract

The introduction of international guidelines on Good Clinical Practices (GCP) in 1996, immediately followed by the publication of Resolution CNS 196/96 in Brazil, created a great opportunity for Brazilian research centers to participate in international trials. Such studies must be strictly monitored in order to assure compliance with the regulations, as well as with the standards of patient safety. Clear agreement among the investigator, the sponsor and the institution carrying out the study must be previously defined in order to avoid any conflicts of interest during or after the study. Operational aspects, such as the time needed to gain regulatory approval of the study design, strategies for patient recruitment/retention and appropriate logistics, are also important. In 2005, the Brazilian National Clinical Research Network was established, bringing together a number of research centers in teaching hospitals. The objective was to subsidize public clinical research with state-of-the-art practices and appropriate technical/scientific training programs. The development of research protocols that prioritize public health care needs in Brazil is other fundamental goal of this network. This article addresses general aspects of clinical research, as well as some specific issues in psychiatry. Improving the health and quality of life of the global population is certainly the major objective of all of the work done in this area.

**Descriptors:** Clinical research; Regulatory approval; Conflict of interest; Placebo; Clinical trial registration

### Resumo

A introdução de diretrizes internacionais de Boas Práticas Clínicas, em 1996, imediatamente seguida pela publicação da Resolução do Conselho Nacional de Saúde 196/96, abriu uma grande oportunidade para a participação de centros de pesquisa brasileiros em estudos internacionais. Tais estudos devem ser estritamente monitorados, a fim de assegurar a adesão às legislações, assim como garantir a segurança dos pacientes envolvidos. A fim de evitar possíveis conflitos de interesse durante e após o estudo, todos os aspectos relacionados devem ser claramente definidos previamente entre o pesquisador, o patrocinador e a instituição. Aspectos operacionais, tais como tempo para aprovação regulatória do estudo, métodos de recrutamento e retenção de pacientes e a logística em geral, também são importantes. Em 2005, a Rede Nacional de Pesquisa Clínica foi criada no Brasil, somando a experiência de vários centros de pesquisa ligados a hospitais de ensino. Seu objetivo é reforçar a atividade de pesquisa clínica no país, com práticas atualizadas e adequado treinamento técnico-científico. O desenvolvimento de protocolos de pesquisa que foquem as prioridades de saúde do país é outro objetivo fundamental da Rede. Aspectos gerais da pesquisa clínica e algumas particularidades em Psiquiatria são discutidos no artigo. O objetivo final de todo o trabalho nesta área de pesquisa é, sem dúvida, a busca de melhores condições de saúde e qualidade de vida da população.

**Descritores:** Pesquisa clínica; Avaliação regulatória; Conflito de interesses; Placebo; Registro de estudos clínicos

<sup>1</sup> Núcleo de Apoio à Pesquisa Clínica (NAPesq, Clinical Research Support Center), Hospital das Clínicas, Medical School, Universidade de São Paulo (USP), São Paulo (SP), Brazil

<sup>2</sup> Department and Institute of Psychiatry, Medical School, Universidade de São Paulo (USP), São Paulo (SP), Brazil

Financing: None

Conflict of interests: Sonia M. Dainesi has previously worked at Rhodia Farma, Sandoz and, more recently (until March 2005), as the Medical Director of Aventis Pharma. She is also a member and former President (2004-2005) of the Sociedade Brasileira de Medicina Farmaceutica (SBMF, Brazilian Society of Pharmaceutical Medicine). Helio Elkis was Principal Investigator in clinical trials developed at the Instituto de Psiquiatria-HC-FMUSP and has also acted as a consultant, received travel support, been a member of the speaker's bureau or received research grants from: Eli Lilly, Janssen, Pfizer, Sanofi-Synthelabo, Astra-Zeneca, Biossintética, Bristol Myers Squibb, Acadia, Lundbeck, Novartis and FAPESP

Submitted: August 6, 2006

Accepted: January 4, 2007

### Correspondence

Sonia Mansoldo Dainesi

NAPesq – Núcleo de Apoio à Pesquisa Clínica - Diretoria Clínica - HCFMUSP

Rua Ovidio Pires de Campos, 225 – 5º andar

05403-010 São Paulo, SP, Brazil

Phone: (55 11) 3069-7531 Fax: (55 11) 3069-6971

E-mail: sonia.dainesi@hcnet.usp.br

## Introduction

Some months ago, in the United Kingdom (UK), the first human testing of TGN1412, a new monoclonal antibody, was initiated. In a completely unexpected way, the volunteers taking part in this trial experienced serious adverse events that did not reflect the results obtained in initial laboratory studies, which had enabled the sponsor to progress to investigations in human volunteers. The clinical trial had been approved by the local ethics committee, as well as by the Medicines and Healthcare Products Regulatory Agency (MHRA), the UK regulatory authority responsible for clinical trial approval. According to the information available, the study design was in total compliance with standard clinical research guidelines. Nevertheless, the question remains: how did this tragic episode occur, if everything was running according to the rules? Good question; difficult answer.<sup>1</sup> In addition, after this episode, how can public and professional confidence in the MHRA be restored, vis a vis its role in regulating trials? Similar concerns with the United States Food and Drug Administration (FDA) emerged in 2004 after the voluntary worldwide market withdrawal of rofecoxib by Merck & Co.<sup>2</sup> Furthermore, while this kind of event will probably change forever the face of clinical drug development, it gives us the opportunity to learn many valuable lessons.

## Safety first

Years of animal and laboratory testing precede the clinical phases of drug development, which is classically conducted in four phases<sup>3</sup> (Table 1) and based on the International Conference on Harmonization - Good Clinical Practice (ICH-GCP) principles.<sup>4</sup> Considerable efforts are made to identify various types of toxicity in vitro and in vivo (through animal studies). Nevertheless, a relative lack of severe toxicity in animal models should never be taken as a guarantee of safety in humans, as recently evidenced by the story of TGN1412.

Even after having conducted large, well-designed, randomized controlled trials to test the efficacy and safety of new medicines, the risks can continue to frighten us after their introduction into the market. This is because some clinical situations will never be reproducible in the clinical trial setting, and some questions can only be answered through real-world testing.<sup>5</sup>

The completeness of safety reporting in randomized trials must also deserve a close look. An article published in 2001 evaluated the quality and quantity of drug safety reporting in 192 randomized drug trials in 7 different areas of drug therapy.<sup>6</sup> Severity of adverse clinical events was adequately defined in only 75 (39%) of the trials, and laboratory-determined toxicity was adequately reported in only 56 (29%). Only 88 (46%) of those trials presented the specific reasons for discontinuation

of study treatment due to toxicity. The conclusion of the authors was that, although the quality and quantity of safety reporting varied across medical areas, study designs and settings, they were largely inadequate. Therefore, the standards for safety reporting in randomized trials should be revised to address this deficiency – and so they were. A set of parameters to evaluate safety reporting, in order to offer a standardized assessment tool, was suggested and developed. These parameters included specifying the number of patients withdrawn from the study due to adverse events, per study arm and per type of adverse event. These parameters were later included in the Consolidated Standards of Reporting Trials (CONSORT) statement, first made public in 1996 and periodically updated.<sup>7-8</sup>

It is important to note that all clinical trials, from phase I to IV, should be carried out according to basic ethical principles, principally those defined in the Nuremberg Code and Declaration of Helsinki.<sup>9-10</sup> Such studies should be closely monitored using modern methods to ensure compliance with appropriate regulations and patient safety standards. In addition, the ICH Harmonized Tripartite Guideline, established in 1996, should always be followed in terms of the responsibility that investigators and sponsors have concerning safety and efficacy reporting.<sup>4</sup>

As demand for patients to participate in clinical trials increases and development times decrease, speed in patient accrual becomes crucial. In addition, it has been recently asked that pharmaceutical companies conduct trials that reflect real-life situations, involving patients who, for example, have underlying diseases or are taking concomitant medications. Even following well-defined and recognized methodology, the artificial world created by the clinical trial design is sometimes criticized and some additional 'real-world' studies should try to cover the various aspects not well described in the development phase. In view of this, together with the fact that longevity is increasing, with more people living into their eighties and probably requiring additional, longer-term concomitant treatments, the repercussions are obvious: more people will need more drugs, opening the door to more trials and, hence, more patients enrolled in such studies.<sup>11</sup>

## An opportunity to grow, learn and refine research skills

The pressure for patient enrollment, as well as the ongoing improvement in the quality of research techniques, has been responsible for the increasing participation of Western Europe and Latin America, including Brazil, in international multicenter trials, since the availability of and access to treatment-naïve patients is great in these countries. In addition, most therapeutic areas are represented in such countries, and the incidence/prevalence of most diseases, especially in the major cities, is similar to that seen in the traditional markets.<sup>12</sup>

Based on the number of registered centers in the major countries, the average annual growth rate of clinical trials being conducted in Latin America is approaching 20-30%. In addition, Latin America has played a significant role in many pivotal trials, and Brazil, for example, has appeared as the main enroller in the world in some of these trials.

Despite this impressive performance, it must be borne in mind that just becoming larger is not sufficient when talking about research: compliance and quality have to follow this growth trend very closely. Therefore, in order to successfully participate in international studies, some related clinical

**Table 1 - Clinical research: the four phases**

Clinical phases of research			
Phase	Number of Patients	Duration	Objective
Phase I	Tens (healthy subjects)	Several months	Safety
Phase II	Hundreds	Several months to 2-3 years	Short-term safety and efficacy
Phase III	Hundreds to thousands	1 to 4 years	Safety and comparative efficacy
Phase IV	Thousands to millions	Several years	Post-approval pharmacovigilance

research aspects must be reinforced: time needed to gain regulatory approval, appropriate strategies for patient recruitment/retention, GCP training, fair costs and logistics (appropriate and available). Let us address these aspects one by one:

1) Time needed to gain regulatory approval: Most sites have an institutional review board or ethics committee, which typically comprises a multidisciplinary group of health professionals, together with some representatives of the laity. The role of such bodies is to evaluate the study protocol in order to ensure that patient rights are protected, and that the study does not expose the patient to any unnecessary risk. In addition, health ministry approval is sometimes required. A drug import license must also be acquired, which can add some weeks to the process. These startup timelines are two to three months in the United States (US) and approximately four months in the European Union (EU). In Brazil, this process can take 6 to 7.5 months, although much effort has been put forth in order to accelerate this process. In this aspect, it is fundamental to have, on the ground, well-prepared staff who knows the local regulatory requirements thoroughly, since even a small error in regulatory submission can cause considerable delays in the planned timelines.<sup>12</sup>

2) Appropriate strategies for patient recruitment/retention: Patient recruitment and retention rates in Latin America are typically reported to be 3 to 6 times greater than those achieved in the USA and Western Europe for a similar protocol. These high patient recruitment rates routinely compensate for the slower regulatory approval process. Figures 1 and 2 show an example of recruitment in a multicenter clinical trial carried out in Latin America, including Brazil. It is also important to have referral systems to ensure that all potential patients are evaluated for inclusion. The motivation for patients to participate is similar across most developing countries: greater access to treatment for their disease, stronger doctor-patient relationships and altruism.<sup>13</sup> The fact that health care is more centralized in some cities, such as São Paulo, makes such cities more attractive as sites for clinical trials. Retention rates for clinical trials in Latin America are also

considerably higher than in US and EU, the drop-out rate being one-third to one-half of that seen in the US.<sup>12</sup>

3) GCP training: Concerns regarding quality are not a serious issue in Latin America to date. Based on a review of the FDA inspection database, the quality of trials conducted in Latin America is similar to that of those conducted in the US. Again, the key factors are training, careful monitoring and a proactive quality assurance system.<sup>14</sup>

4) Fair costs: In recent trials, the cost per patient in Latin America has ranged from 50% of to slightly more than the cost per patient in the US. There are several potential explanations for these variations: study size (large sites are more cost-effective than are small sites); site and contract research organization personnel costs, which are often significantly (10-40%) less than in the US; need for additional therapies that must be supplied by the sponsor for an add-on trial; and shipping costs, which can increase study costs considerably.<sup>12</sup>

5) Logistics: Laboratories offer services ranging from simply collecting samples to shipping the samples directly to a central lab in another country. Certainly, the sponsor can ease and speed up the shipping and logistics process by working with local experienced staff early on to ensure that commercial invoices and packing lists meet country-specific requirements. Regarding drug importation and storage, the drug label texts are needed in the local language. Local regulations also require that all pertinent documents (protocol, investigator brochure, informed consent form, patient diaries and quality of life questionnaires) be presented for regulatory review in the local language.

Currently, there is much more public awareness of the potential risks associated with drug development. Complete disclosure of potential conflicts is, therefore, in the best interest of the faculty, staff, investigators and patients, all

### Regional trial, coordinated by Brazil

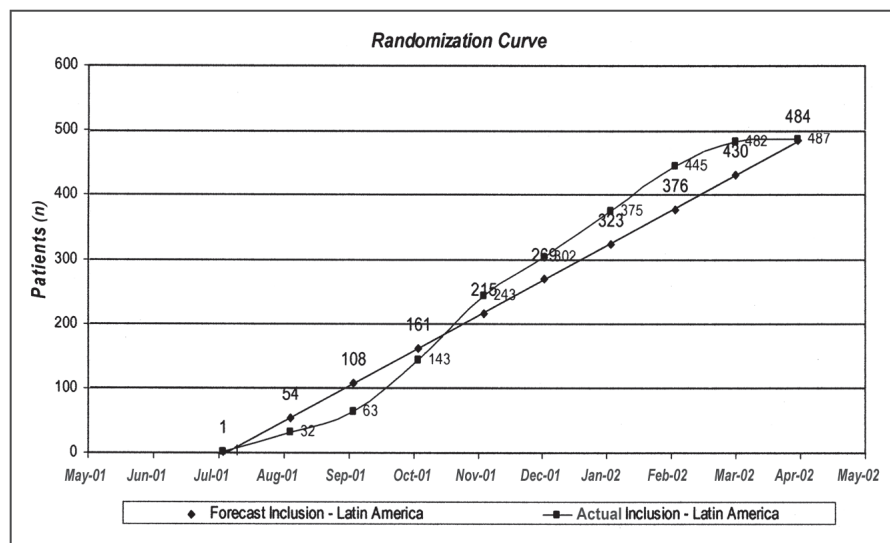
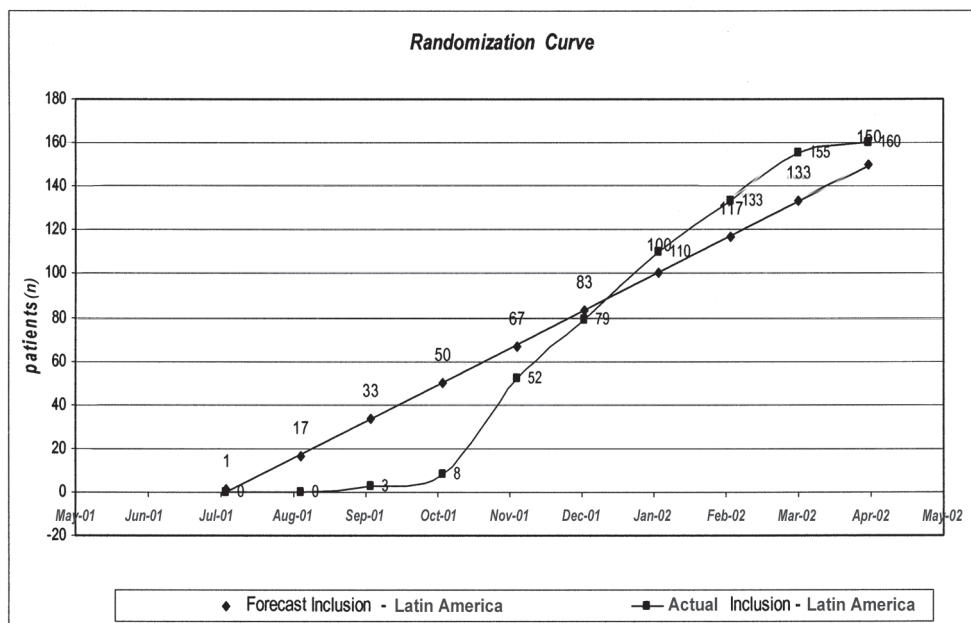


Figure 1 - Patient enrollment in a clinical trial conducted in Latin America and coordinated by a Brazilian center

### Regional trial: Brazilian enrollment



**Figure 2 - Cumulative patient inclusion in Brazil: delay in the regulatory phase and subsequent recuperation, achieving the predicted number of patients**

of which should recognize that disclosure of personal financial interests is vital to continued public credibility.<sup>15</sup> It is quite clear that all parties would benefit from greater transparency in the management of conflicts of interest. However, even in well-recognized journals, there is sometimes no mention to past or current positions of the authors that might significantly affect their opinions and might be relevant to readers who want to understand the position and tone assumed by these authors.<sup>16</sup> Disclosing a conflict does not imply that someone is behaving improperly, and most conflicts can be managed if clearly disclosed. In March of 2002, the *Annals of Internal Medicine* published some guidelines for individual physicians and institutions, strongly recommending that the latter establish their own internal policies.<sup>17</sup>

#### The experience of National Networks

It is worthwhile to observe how research networks are being established to help promote clinical research activity around the world. In 2001, in the UK, the National Cancer Research Network (NCRN) was created to improve the National Health System (NHS) capacity to facilitate clinical cancer research. At that time, it was recognized that research had to become more closely integrated with cancer care to improve recruitment to randomized controlled trials and other trials. One of the NCRN tasks was to develop the infrastructure to support research within the NHS and establish local cancer research networks.<sup>18-19</sup>

The NCRN proved to be highly effective and, by 2004, had succeeded in more than doubling the rate at which cancer patients were accrued for clinical research trials. However, the advance observed in cancer research was not representative of the clinical research environment as a whole. As a consequence, in March of 2004, the UK government

announced the provision of an additional organ to improve the clinical research environment, the United Kingdom Clinical Research Network (UKCRN). One of the UKCRN priorities was to strengthen the UK research infrastructure in order to formally support clinical research sponsored by different organizations. In the first year, the focus was establishing coordinating centers and their teams, who worked to facilitate high-quality studies aligned with public research priorities. The criteria used to select the centers were aimed at ensuring maximum geographical coverage across the entire UK. A program of activities supported by the UKCRN includes: involvement in advisory group/committee meetings and clinical study groups across the networks; identifying/assisting with research priorities; advising authors regarding the design of a study; monitoring study progress; disseminating study information and results; identifying relevant research outcomes; assisting with systematic reviews; and producing research information. The result was a world-class infrastructure ensuring high-quality research, funded by both commercial and non-commercial institutions, with the aim of improving the health and quality of life of the UK population.<sup>18-19</sup>

This ability to respond flexibly to more specific national needs justifies the growing importance that is being given to the establishment of clinical research networks. The idea was also implemented in Brazil in 2005, when the Brazilian government established certain rules pertaining to the selection of research centers linked to teaching hospitals in order to build the National Clinical Research Network. The *Hospital das Clínicas* of Medical School of Universidade de São Paulo (HCFMUSP) was one of the sites chosen through this process.<sup>20</sup> Task forces are being set up to provide a supportive learning environment that will foster high-quality, safe and effective research in the country.

These groups will focus on developing research protocols that prioritize Brazilian public health needs, as well as integrating standard operating procedures.

Like all other commercial companies around the world, pharmaceutical companies are results-driven. In this context, some so-called neglected diseases, such as malaria, tuberculosis, leishmaniasis, etc., cannot always meet the prerequisites to attract their investments. Similarly, such companies rarely pursue the development of medicines after the patent protection period has expired. As a result, in these cases, as recently defined by the Drugs for Neglected Diseases Initiative (DNDi), studies have to be conducted driven not by return on investment but by need.<sup>21-22</sup> Projects must be carefully selected to fill the gaps in the drug development pipeline, in order to improve the quality of life and the health of people by using an alternative model to develop drugs for these diseases. This is another lacuna that could be filled by the National Clinical Research Network as well as by individual professional societies.

In this not-for-profit model, driven by the public sector, a variety of players would collaborate to raise awareness of the need to research and develop drugs for those neglected diseases that fall outside the scope of market-driven research and development. More important, they would also build public responsibility and leadership in addressing the needs of patients suffering from such diseases. Certainly these goals can be achieved by strong participation of the professional societies and government through research protocol development for these neglected diseases ("old drugs for old diseases"), for non-drug-related procedures (surgical techniques, psychiatric/psychological treatments, alternative medicines/methods, etc.), for drugs out of patent, etc. It is certainly a business to be explored, which could have a significant impact on the lives of thousands of people through a package of effective, sustainable, rapid and cost-effective treatment interventions.

#### Particular aspects on conducting clinical research in psychiatry

Early great discoveries in psychiatric treatment were never subjected to clinical trial. Inducing malaria to cure neurosyphilis (in 1917) and pre-frontal leucotomy as a treatment for psychosis (in 1935) - which actually contributed to Jauregg and Egas Moniz, respectively, being awarded Nobel Prizes - as well as electroconvulsive therapy, developed by Cerletti and Bini in 1938, were not tested against placebos.<sup>23</sup>

The discovery of antipsychotics and antidepressants in the 1950s, the basis for the second biological psychiatry revolution according to Shorter, was the result of "a mixture of scientific preparation and dumb luck",<sup>24</sup> since they were administered to patients during uncontrolled observational trials. However, during that same era, pioneering scientists performed the earliest controlled trials in psychiatry, comparing treatment versus placebo, either using chlorpromazine<sup>25</sup> for schizophrenia or lithium for bipolar disorder.<sup>26</sup>

Randomized controlled trials as we know them today began to be performed only in the 1980s. Such trials tested selective serotonin reuptake inhibitors, new generation antidepressants, mood stabilizers and second-generation antipsychotics. In terms of the 'safety first' issue, it is of note that the reintroduction of clozapine, the prototypical 'atypical' antipsychotic, with almost no extrapyramidal side effects but with great efficacy in refractory schizophrenia, was only possible when it was

compared to chlorpromazine in a multicenter randomized controlled trial in 1988.<sup>27</sup> The obstacle was the fact that, in the early 1970s, clozapine had caused 18 (8 of which were fatal) cases of agranulocytosis in Finland, and was therefore nearly banned from the psychiatric armamentarium.<sup>28</sup> With adequate blood count monitoring, clozapine became a safe drug, is still the treatment of choice for refractory schizophrenia and paved the way for the development of second-generation antipsychotics, which are the mainstays of the contemporary treatment of schizophrenia.

Like all other medical specialties, psychiatry is experiencing a cultural shift towards evidence-based practice and randomized controlled trials are ranked as the highest level of evidence, whereas uncontrolled studies, case series or expert opinions are ranked as lower levels.<sup>29-30</sup>

Randomized controlled trials in psychiatry are performed in the same way as are their counterparts in other medical specialties. However some issues have been raised regarding the specificity of clinical trials in psychiatry in terms of the complexity of patients (especially in terms of comorbidities), the complexity of the interventions and whether results of controlled trials can be generalized to clinical practice. Therefore, observational studies, as well as simpler large clinical trials, have been proposed.<sup>23</sup>

Another specific issue is related to the execution of preclinical trials in psychiatry. What are the appropriate models? Are they reproducible in human beings? How can non-drug therapeutic approaches be compared utilizing the randomized clinical trial methodology? Additional difficulties with double-blind design and placebo-controlled studies should be mentioned as well. The use of placebos is indeed another point of controversy. There is still considerable debate regarding the ethical issues of placebo use in psychiatry. When no effective treatment exists, the usual comparator is a placebo - but if there is a proven treatment? May we utilize placebo as a comparator in a disease for which there is a well-known treatment? When using an active drug as a comparator, it is usually necessary to have a large patient sample in order to identify statistically significant differences between arms. Therefore, more patients must be submitted to investigational drugs and to their potential side effects, which could be at least partially avoided by utilizing placebo-controlled trials (fewer patients needed). This is just one of the issues remaining in the open debate on the methodological and pragmatic aspects versus ethical aspects of using placebos and, therefore, leaving patients without treatment for a period.<sup>31-33</sup>

Recently, the concept of 'practical clinical trials' (also known as 'pragmatic trials' or 'large, simple trials') have emerged and are defined as large studies (i.e., with enough power to detect small to medium effect sizes) that "compare[s] clinically important interventions, a diverse population of study participants representative of clinical practice, inclusion of a range of heterogeneous practice and measurements of a broad range of clinically relevant health outcomes".<sup>34</sup>

Such practical clinical trials are developed in networks in productive partnerships involving federal, community and academic centers.<sup>34</sup> A recent example is the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), which was organized and sponsored by the US National Institute of Mental Health, with the participation of various academic centers across the US, and compared the effectiveness of new generation antipsychotics in 1480 patients with schizophrenia.<sup>35</sup>

Indeed this new modality of clinical trials represent a shift from the traditional perspective of randomized controlled trials in psychiatry, which focused primarily on efficacy, as evaluated through outcome measures such as a reduction in symptom severity, by using psychopathological scales, such as the Hamilton, Beck or Positive and Negative Syndrome Scale (PANSS), and appropriate side effects scales (e.g., Simpson-Angus for extra-pyramidal symptoms).

Practical clinical trials, however, evaluate effectiveness, which is measured by other parameters such as compliance, cost effectiveness and quality of life. In the case of the CATIE study, the primary outcome measure was discontinuation for any reason. As an example, all of the drugs studied (risperidone, olanzapine, quetiapine, ziprasidone and perphenazine) proved efficacious, as measured by the PANSS, but more than 60% of the patients discontinued the drugs for a variety of reasons (lack of efficacy or intolerable side effects).<sup>35</sup>

#### The Clinical Trial Registry: where are we?

An editorial written by the International Committee of Medical Journal Editors (ICMJE) and published simultaneously on September 8, 2004 in several journals supported the need for a comprehensive trial registry. The clinical trial registry would provide patients and health practitioners with relevant information about ongoing studies around the world.<sup>36</sup>

Despite great interest in this idea, there is a wide gap between theoretical ideas on trial registration and their implementation. This gap may be due to the lack of universal criteria for registration and to differing interests. The various registries are also at different stages of development.<sup>37</sup> In addition to the US registry, sponsored by the US National Library of Medicine and the European registry, available at <http://www.clinicaltrials.gov> and <http://www.controlled-trials.com>, respectively, some other initiatives have been developed, such as the Ottawa Statement, in 2004 (<http://ottawagroup.ohri.ca>) and The Australian Clinical Trial Registry (<http://www.actr.org.au>).

The International Clinical Trials Registry Platform (ICTRP), organized by the World Health Organization (WHO) and validated by the ICMJE as well as by the International Federation of Pharmaceutical Manufacturers and Associations is also under development (<http://www.who.int/ictpr/en>). In order to maximize the portal utility, the WHO recommends that a unique number should be defined for each study, the universal trial reference number, which will make the connection between the primary registry in which the study was included and the WHO database registry.<sup>38</sup> The WHO also suggests that, prior to the first patient recruitment, trial sponsors or researchers record in a certified and publicly accessible registry a minimum of 20 key details related to the clinical trial.

The Iberoamerican Cochrane Network has been working on the Latin American Ongoing Clinical Trial Register in order to collect information on clinical trials undertaken in Latin American countries (<http://www.latinrec.org>). It will be a freely available registry, with information including the basic data required by the ICTRP and will receive the WHO-assigned unique identification number. Protocols can be completed in the native language of the trialist (Portuguese, Spanish or English), but information will be translated to English to apply for a unique identifier. This registry will comply with the Ottawa Statement criteria and the WHO ICTRP.<sup>37</sup>

Since July of 2005, the ICMJE has refused to publish the results of any clinical trials not included in an authorized

registry. The benefits of such a global initiative are, in addition to the previously mentioned updating of information on ongoing studies, a larger potential for recruitment of clinical trial participants, the promotion of equitable distribution of resources for clinical trials truly devoted to real health care needs and better monitoring of ethical conduct. Another goal of this project is to avoid the duplication of studies, since this is an important confounding factor and an example of 'publication bias', which refers to the bias introduced by the selective publication of research results. Other examples of such bias include not publishing a trial result and citation bias.<sup>38</sup> The impact of excluding difficult to locate studies (unpublished trials and trials published in languages other than English or in journals not indexed in the MEDLINE database) and trials of lower quality (non-double-blind trials, for example) from meta-analyses has been well described. The consequences range from substantial overestimation of treatment effects (indicating less benefit of the intervention) to substantial underestimation of treatment effects (indicating more benefit).<sup>39-40</sup> The distortion of medical evidence caused by this kind of publication bias, in addition to being unethical, can actually harm patients. Another problem observed is the exclusion of research published in languages other than English. This is a particular form of bias known as 'language bias', in which randomized controlled trials with positive effects or greater estimates of effect size tend to be published in English-language journals rather than in the original native language of the author(s).

The importance of trials that are difficult to locate seems to vary across medical specialties: unpublished trials are particularly prevalent in oncology, whereas trials published in languages other than English and trials published in sources not indexed in MEDLINE are important in psychiatry, rheumatology and orthopedics.<sup>39</sup> The registration of clinical trials is, therefore, a decisive and important step toward reducing such bias.

#### Conclusion

In order to avoid tragedies like the one that occurred with TGN 1412 and, at the same time, to promote better research outcomes, how should the process of stimulating clinical trial development be altered? First, the dramatic TGN 1412 case already provided some new insights into drug development, as described in the document recently released by the UK taskforce created to study the case and the existing regulatory guidelines for biopharmaceuticals. It was clear that there were no major safety-related issues not addressed in the available guidelines, as demonstrated by the fact that there have been thousands of previous trials without any major incidents.<sup>41</sup> However, specific points could be clarified and perhaps merit greater emphasis, primarily in relation to the first administration of a new drug in humans. The interim report is available for public consultation, and the final report is scheduled to be released by the end of November 2006.<sup>42</sup>

Second, we always want to understand the rationale behind specific decisions; therefore, some principles of fairness, such as engagement, explanation and clarity of expectations, must be examined when introducing new concepts and methodologies.<sup>43</sup> A fair process builds trust and commitment, trust and commitment produce voluntary cooperation, and voluntary cooperation drives performance, leading people to go above and beyond the call of duty by sharing their knowledge and applying their creativity.

The health care system has faced various issues and crises in recent years: the progressive increases in the cost of health care have become a nightmare for administrators. The health care area is naturally more prone to these crises due to the simple fact it operates in a sector in which every variation can have a great impact on our health and, hence, on our core values. Only a correct and careful handling of the related issues, of which clinical research is only one, can ensure the ongoing improvements we need to guarantee the health of the global population in this new century.

## References

- [No authors listed]. As investigators seek answers and victims of UK drug-trial disaster recover, all clinical testing may suffer a setback. [cited 2006 March 28]. Available from: <http://www.clinicaldiscovery.com/readNews.aspx?newsId=19>.
- Topol EJ. Failing the public health – rofecoxib, Merck and the FDA. *NEJM*. 2004;351(17):1707-9.
- Dainesi SM. Seeking harmonization and quality in clinical trials. *Clinics*. 2005;61(1):3-8.
- [No authors listed]. International Conference on Harmonization (ICH) Guidelines. Good Clinical Practices (E6). [cited 2006 July 30] Available from: <http://www.fda.gov/cder/guidance/959fnl.pdf>.
- Dainesi SM. Pharmacovigilance: more than ever, an overall responsibility. *Clinics*. 2005;60(4):267-70.
- Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA*. 2001;285(4):437-43.
- Moher D, Schulz KF, Altman D. CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA*. 2001;285(15):1987-91.
- Moher D, Schulz KF, Altman DG. Revised recommendations for improving the quality of reports of parallel group randomized trials 2001. CONSORT Group. The CONSORT Statement. [cited 2006 July 30]. Available from: <http://www.consort-statement.org/Statement/revisedstatement.htm>
- [No authors listed]. World Medical Association - Declaration of Helsinki. Ethical principles for medical research involving human subjects. [cited 2006 July 30]. Available from: <http://www.wma.net/e/policy/b3.htm>
- [No authors listed]. Directives for human experimentation. Nuremberg Code. [cited 2006 July 30]. Available from: <http://ohsr.od.nih.gov/guidelines/nuremberg.html>
- Peachey J. Putting safety first. *Scrip Magazine*. 2003;17-8.
- Hurley D. Leveraging Latin America assets in clinical trials. GCPJ, March 2006, p.16-19. Also available from: [http://www.kendle.com/media/recent\\_editorials/Kendle\\_Latin\\_March\\_06.pdf](http://www.kendle.com/media/recent_editorials/Kendle_Latin_March_06.pdf)
- Getz KA. A swift predominance of ex-US sites. *Appl Clin Trials*. 2005;14(12):21-2. Also available from: [www.actamagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=261633](http://www.actamagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=261633).
- [No authors listed]. Investigational human drugs: clinical investigator inspection list. [cited 2006 July 24]. Available from: URL: <http://www.fda.gov/cder/regulatory/investigators/default.htm>
- Goldim JR. Conflicts of interests and their repercussions on science. *Rev Bras Psiquiatr*. 2006;28(1):3-4.
- Goodyear M. Learning from the TGN1412 trial. *BMJ*. 2006;332(7543):677-8.
- Coyle SL; Ethics and Human Rights Committee; American College of Physicians – American Society of Internal Medicine. Physician–Industry Relations. Part 1: individual physicians. Part 2: organizational issues. *Ann Int Med*. 2002; 136(5):396-406.
- [No authors listed]. The UK clinical research network. [cited 2006 June 14]. Available from: URL: [www.clinicaldiscovery.com/readArticle.aspx?articleId=23](http://www.clinicaldiscovery.com/readArticle.aspx?articleId=23).
- [No authors listed]. Building a first class research environment in the UK. [cited 2006 July 10]. Available from: URL: <http://www.clinicaldiscovery.com/readArticle.aspx?articleId=13>.
- [No authors listed]. Chamada Pública MCT/MS/FINEP – Ação Transversal – Implantação de Unidades de Pesquisa Clínica em Hospitais de Ensino – 04/2005 – Projetos Aprovados. [cited 2006 July]. Available from: [http://www.finep.gov.br/fundos\\_setoriais/acao\\_transversal/resultados/Resultado\\_Pesquisa\\_Clinica\\_04\\_2005.PDF](http://www.finep.gov.br/fundos_setoriais/acao_transversal/resultados/Resultado_Pesquisa_Clinica_04_2005.PDF).
- Depoortere E, Legros D, Torreële E. Developing a needs-based and rational approach to identify neglected diseases and select R&D projects that could maximally impact treatment options. Working Group. Nov 2001. [cited 2006 July 22]. Available from: <http://www.accessmed.msf.org/upload/ReportsandPublications/23920021528595/1-5.pdf>.
- [No authors listed]. DNDi project pipeline 2005. [cited 2006 July 22]. Available from: <http://www.dndi.org/newsletters/10/portfolio.htm>.
- Everitt B, Wessely S. Clinical trials in Psychiatry. Oxford: Oxford University Press; 2003.
- Shorter E. A History of Psychiatry - From the era of the Asylum to the age of Prozac. New York: John Wiley & Sons, Inc; 1977.
- Elkes J, Elkes C. Effect of chlorpromazine on the behaviour of chronically overactive psychotic patients. *Br Med J*. 1954;2(4887):560-5.
- Schou M, Juel-Nielsen N, Stromgren E, Voldby H. The treatment of manic psychosis by the administration of lithium salts. *J Neurol Psychiatry*. 1954;17(4):250-60.
- Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45(9):789-96.
- Ban T. Academic psychiatry and the pharmaceutical industry. *Prog Psychopharmacol Biol Psychiatry*. 2006;30:429-41.
- Strauss SE, Richardson WS, Rosenberg W, Haynes RB, Sackett DL. Evidence Based Medicine: How to practice and teach EBM. 2nd ed. London, UK: Churchill Livingstone; 2000.
- [No authors listed]. Levels of Evidence and Grades of Recommendation. Oxford Center for evidence-based medicine. [cite 2006 Nov 15] Available from: [http://www.cebm.net/levels\\_of\\_evidence.asp](http://www.cebm.net/levels_of_evidence.asp).
- Fineberg NA, Gale TM, Hawley CJ. Is there place for placebo controlled trials in the treatment of affective disorders? *Rev Bras Psiquiatr*. 2006;28(2):89-90.
- Elkis H, Gattaz WF. Algumas recomendações para estudos com placebo. *Rev Bras Psiquiatr*. 2000;22(4):153-4.
- Cho HJ. Revivendo o antigo sermão da medicina com o efeito placebo. *Rev Bras Psiquiatr*. 2005;27(4):336-40.
- March JS, Silva SG, Compton S, Shapiro M, Callif R, Krishnan R. The case for practical clinical trials in psychiatry. *Am J Psychiatry*. 2005;162(5):836-46.
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209-23.
- De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke AJ, Schroeder TV, Sox HC, Van Der Weyden MB; International Committee of Medical Journals Editors. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N Engl J Med*. 2004;351(12):1250-1.
- Revez L, Delgado MB, Urrutia G, Ortiz Z, Garcia Dieguez M, Marti-Carvajal A, Calgua E, Vieyra A, Ciapponi A, Hidalgo R, Pantoja T, Sanchez LM, Martinez Pecino F, Tristan M. The Latin American Ongoing Clinical Trial Register (LATINREC). *Rev Panam Salud Publica*. 2006;19(6):417-22.
- Cuervo LG, Valdes A, Clark ML. El registro internacional de ensayos clinicos. *Rev Panam Salud Publica*. 2006;19(6):365-70.
- Egger M, Juni P, Bartlett C, Hohenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technol Assess*. 2003;7(1):1-76.
- Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ*. 1997;315(7121):1533-7.

41. [No authors listed]. The Association of the British Pharmaceutical Industry. TGN1412: Joint industry taskforce produces guidelines to improve conduct of early stage clinical trials. [cited 2006 July 29]. Available from: [http://www.abpi.org.uk/press/press\\_releases\\_06/060724.asp](http://www.abpi.org.uk/press/press_releases_06/060724.asp).
42. [No authors listed]. The Expert Scientific Group (ESG), Department of Health (UK), Government News Network. Interim report on phase 1 clinical trials published.[cited 2006 July 29]. Available from: <http://www.gnn.gov.uk/environmentfullDetail.asp?ReleaseID=216727&NewsAreaID=2&NavigatedFromDepartment=False>.
43. Kim WC, Mauborgne R. Fair process: managing in the Knowledge Economy. *Harvard Business Review*. 1997;65-75.