Cuba's National Clinical Trials Coordinating Center: Emergence, Evolution, and Main Results

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ABSTRACT

The rapid development of Cuba's pharmaceutical industry in the 1990s created a need for structures to ensure clinical evaluation of products before their introduction into medical practice and subsequent marketing. One of the centers founded for this purpose was the National Clinical Trials Coordinating Center. This paper summarizes the factors that motivated the creation of the Center and presents a brief history of its organizational development over the last 17 years. It also describes the main components of the system for designing and conducting clinical trials, and the most significant contributions of each toward achieving the Center's objectives.

KEYWORDS Contract research organization, clinical evaluation, drug industry, clinical trial, Cuba

INTRODUCTION

One of the most important phenomena for medicine and clinical research occurred in the 1950s: the emergence of the controlled clinical trial as a methodology to assess different treatments and provide evidence needed for medical decision-making. The development of this new methodology was a landmark whose implications have transcended the academic plane, to set standards in the regulatory environment with the ultimate aim of protecting the public's health.[1]

The clinical trial is commonly considered the "gold standard", the ideal method for evaluating a treatment or intervention in humans,[2] and constitutes a paradigm for medical technology assessment in general.

Currently, one of the greatest challenges the medical-pharmaceutical and biotechnology industry faces after the preclinical research phase is precisely that of clinical evaluation.[3]

Introduction of a drug into medical practice requires previous development and evaluation, first in animals (preclinical evaluation) and then in human subjects (clinical evaluation). The preclinical phase includes chemical-pharmaceutical, pharmacology, and animal toxicology studies that contribute sufficient evidence of quality, safety and efficacy to justify moving on to clinical research.

Clinical research includes all studies involving patients, whether focused on etiological, diagnostic, therapeutic or prognostic aspects. Clinical studies that evaluate the usefulness and safety of agents for disease treatment or diagnosis are known as therapeutic clinical trials or diagnostic clinical trials, respectively. They are prospective studies in human subjects, comparing the effect and value of a new intervention with a control intervention.[4]

The clinical trial is an experiment designed in strict adherence to ethical standards in which subjects are randomly assigned to different interventions that are carried out and supervised simultaneously. This research enables evaluation of the efficacy and safety of a drug or product for humans and is based on: comparisons with standard treatments or diagnostic technologies; randomized, blind comparative study of at least two concurrent patient groups; and a specific sampling design and subsequent statistical data analysis.[5]

Clinical evaluation, the stage prior to approval, includes several phases:[6]

- Phase I. Safety and tolerance. Pharmacokinetics and pharmacodynamics.
- Phase II. Efficacy, safety, tolerance and other pharmacological aspects.
- Phase III. Efficacy [confirmation], safety and tolerance.

Once the product being tested is approved, a fourth phase generally follows:

- Phase IV. Post-marketing studies and surveillance.

Over the last 20 years, the growing and ever more competitive development of the medical-pharmaceutical and biotechnology industry, coupled with an increasingly demanding regulatory environment, have prompted the search for solutions yielding higher quality and more efficient results. A type of institution has emerged, typically in developed countries, specializing in conducting such studies. Known as Contract Research Organizations (CROs), these have certain advantages in terms of cost, quality, and speed of clinical evaluation—a process requiring more resources and effort.[7]

Research undertaken by this type of organization is known as contractual research and includes the planning, organization, and conducting of clinical trials, as well as a range of organizational procedures that contribute to trial implementation.

Clinical trials also facilitate monitoring of a medical product post-marketing; introduction of modifications to treatments in medical practice; and education of doctors to promote a critical approach and accurate evaluation of the use of drugs, other medical treatments and diagnostic methods. Clinical trials also help improve quality of medical services through application of the most advanced methods in diagnosis, treatment and evaluation of the diseases under study.

The development of Cuba's biotechnology and medical-pharmaceutical products since the 1980s is well known.[8] These products have required clinical trials prior to approval and marketing both in Cuba and abroad.

Traditionally, each production center took responsibility for both preclinical evaluation and clinical evaluation of its products, work-

ing directly with hospitals. Some clinical trials were successfully completed with due rigor in design and execution, providing valid results. But most faced major scientific and organizational difficulties; they took too long and in the end did not provide the results required by regulatory agencies, although the products had shown real potential for approval and marketing.

Ever more stringent requirements for approval of drugs and biotechnology products, particularly in developed countries, led Cuba to design a strategy that would contribute to approval and marketing, and achieve products' timely introduction into medical practice and international markets.

One of the strategy's objectives is to organize and develop the country's regulatory activity, an ever more demanding and rigorous process, over time bringing it more closely in line with international scientific standards. As the regulatory framework was being restructured, an infrastructure was also created for evaluation of medical-pharmaceutical and biotechnology products prioritized for development: chemical-pharmaceutical, preclinical toxicological and pharmacological.

Within this infrastructure, an institution was needed to enable clinical evaluation of new products whose priority required prompt approval in the country and abroad. At the end of 1991, an organization was established to design and conduct clinical trials, comprising a national center and coordination network: the National Clinical Trials Coordinating Center (CENCEC, its Spanish acronym): http://www.cencec.sld.cu

This paper, based on analysis of institutional documents and unpublished technical reports, provides an overview of CENCEC's evolution from its founding, and touches on its main results over the last 17 years (1991–2008).

EMERGENCE OF CENCEC

As part of the restructuring process, the Priority Products Central Commission conducted a survey in all research centers on drugs with potential to qualify for approval, with the following results:

- For many products, clinical trials had been designed, initiated and coordinated by the producers themselves, and were either under way or completed, pending processing and statistical data analysis or preparation of a final report, with delays at each stage.
- In some cases, the clinical trial began before completing the preclinical or chemical-pharmaceutical phases.
- Most studies were in single centers with long patient recruitment periods.
- Difficulties with scientific and methodological rigor were found in design and implementation.
- Studies were identified in which good clinical practices were not applied and quality assurance was lacking.

CENCEC, conceived as a national scientific-technical unit and part of a coordinated national network from the outset, was established by Ministerial Resolution No. 10 of 1992 (based on Council of Ministers Resolution No. 627 of November 30, 1991). Its purpose was to design and organize implementation of clinical trials to evaluate products for registration and marketing, including drugs, reagents, biologics, instruments, and therapeutic devices and procedures; as well as to conduct comparative epidemiological studies, all with rigorous adherence to good clinical practices and at reasonable cost.[i,ii]

Within the Ministry of Public Health (MINSAP, its Spanish acronym), CENCEC was conceived of as a budgeted high-level scientific unit with separate legal status, implementing MINSAP's policy to promote clinical trials of priority products. With the development and progressive refinement of its structure and functions, CENCEC has gradually achieved greater organization and better results, meriting its designation in other categories, [e.g. as a national research center.—Eds].[iii,iv]

CENCEC OBJECTIVES AND FUNCTIONS

CENCEC arose with the objective of ensuring clinical assessment of priority medical-pharmaceutical and biotechnology products with full ethical, scientific and methodological rigor in compliance with international standards and with the required efficiency to obtain product approval for marketing in Cuba and abroad.[1]

To fulfill this objective, CENCEC carries out and contributes to the design, ethical aspects, organization, coordination, implementation, overall quality assurance, data management, statistical analysis and preparation of final reports on products under consideration. Also part of the center's purview are studies to assess new health technologies, and support for clinical research needed to resolve major health problems faced by the health system (epidemics, other emergencyies or needs).

From the beginning, one important aim was to establish a multicenter trials network involving a range of specialized institutions where studies could be carried out. This network enables implementation of multicenter clinical trials across the country in order to increase efficiency and expedite results in compliance with required quality standards. This was facilitated by the existence of a single health system with sufficient infrastructure and trained personnel in all provinces.[9]

CENCEC's main scientific-technical services include:

1. Guidance on clinical product evaluation strategies.
2. Guidance on regulatory issues (review of preclinical information, advice on preparation of clinical reports for submission to the Drug Regulatory Agency).
3. A range of services for design and implementation of therapeutic and diagnostic clinical trials:
   - Design and preparation of protocols or review of protocols prepared by producer (including data collection log).
   - Selection of researchers and clinical sites.
   - Convening and incorporating expert opinion in review and ethics committees.
   - Planning, acquisition and distribution of material resources.
   - Statistical, statistical analysis and sampling design.
   - Implementation supervision (tracking recruitment progress and updating the sponsor).

i Resolución 10 Ministerio Salud Pública 1992
ii Resolución 627 Consejo de Ministros 1991
iii Resolución 72/2000 Ministerio de Ciencia y Tecnología y Medio Ambiente: "Unidad de investigación desarrollo"
iv Resolución 25/2004 Ministerio de Ciencia y Tecnología y Medio Ambiente. Inscripción del centro y red de coordinación nacional en el Registro de "Entidades de Ciencia e Innovación Tecnológica"

- Internal quality assurance activities (site visits for initial evaluation, launching, quality control and final trial reporting).
- External quality assurance activities in all phases of the study (auditing).
- Data management, including database programming; data entry, correction and cleaning; and database quality control before statistical processing.
- Statistical processing with appropriate software programs.
- Preparation of final report with producer and principal clinical investigator.
- Workshops to standardize criteria and discuss final report with all participating researchers.

EVOLUTION AND MAIN RESULTS OF CENCEC AND THE NATIONAL NETWORK

Design and methodology of clinical trials conducted by CENCEC have adhered to the gold standard required for these studies. Scientifically, most have been conceived as control studies, passing through each phase until final confirmation of efficacy. Subsequently, post-marketing studies have been designed.[v]

In the early years, however, there were some problems with the design and planning of clinical studies. These included excessive delays in the planning phase as well as rejection of some product technical reports by the Drug Regulatory Agency, since once the protocol was finished, commencement of the study was not authorized due to incomplete preclinical or chemical-pharmaceutical information.

To address this weakness, CENCEC undertook its first important change: establishment of a regulatory affairs group in charge of evaluating available preclinical information in the application documentation and recommending whether or not to start preparing the clinical trial protocol.

Various strategies were also developed to improve study design, chief among them:

- Formulation of clinical trial protocol guidelines, in particular for Phase III.
- Collective debate on protocol proposals received and/or prepared.
- Training and professional development for all personnel involved.
- Joint efforts with sponsoring centers and clinical investigators to review and refine designs and protocols.
- Interaction with product registries (for both drugs and medical devices) to improve each phase.
- Establishment of a Quality Committee to evaluate protocol designs and first drafts, as well as to recommend whether or not to continue each study.

Organizationally, the National Clinical Trials Coordinating Network, conceptualized from the beginning as part of the Center, has played a key role. Conducting clinical trials takes major organizational effort and dedication, and the Center's national-level status means its organizational activities go beyond the institution itself. Activities such as coordination, implementation and quality assurance, among others, are carried out through the network.

Multicenter trials apply a single protocol at various clinical sites in a country, region or the world.[1,8] They require specialized coordination, uniform criteria and centralized monitoring and data collection. Their basic objectives are to enroll patients more quickly in order to obtain results and to ensure that efficacy is as close as possible to effectiveness.[5]

The Network has functional units in the country's medical universities, with more than 30 professionals who divide their time between academic responsibilities and leadership of clinical trials.

These clinical studies are conducted in the services of teaching hospitals attached to the medical universities in each territory. To enhance the Network's effectiveness, subcenters have been set up three provinces and coordinating groups in nine provinces, all methodologically subordinated to CENCEC. Each is responsible for coordination, quality assurance and training of clinical research personnel in its jurisdiction.

CENCEC also utilizes the National Clinical Trial Sites Network, composed of hospitals throughout the country, to promote development of multicenter trials, fulfill producers' demand for clinical trials, and speed patient recruitment. In doing so, it expedites product development and subsequent approval.[9] The Sites Network also contributes to researchers' knowledge and skills in conducting clinical trials.

Some specialties have created their own clinical site networks. For example, oncology, with over ten years' experience and a large number of clinical sites, functions in coordination with the National Oncology Specialty Group and MINSAP's National Cancer Control Unit to conduct clinical trials. The psychiatry network, with participation from the National Psychiatry Specialty Group and MINSAP's Mental Health Division, has fewer clinical sites, although two are internationally recognized for good clinical practices.[vi]

To ensure quality and compliance with good clinical practice guidelines (GCP), a project was initiated to accredit clinical sites fulfilling these norms. The process consists of two parts: preparation by CENCEC of clinical trial sites for accreditation, and, once declared ready by CENCEC, site accreditation by the government's National Drugs Quality Control Center (CECMED, its Spanish acronym). To date, preparations have begun in 10 units in various provinces, two of which have already received accreditation: the National Toxicology Center and the Medical-Surgical Research Center.[vii]

Other organizational results include:

- Review and adaptation of the Center and Coordinating Network organizational structure to international CRO standards and our national experience. To this end:
  - New working groups were established for design, analysis and data processing, quality assurance, organization and international cooperation.
  - New professional profiles were created and their responsibilities in conducting clinical trials defined in accordance

v Estado actual de la Investigación Clínica para evaluación de agentes terapéuticos y diagnósticos: Cumplimiento de Normas Internacionales y situación en Cuba. Trabajo presentado en la Reunión de Directivos del Polo Científico del Oeste, 1999.

vi Proyecto Ramal: Formación de recursos humanos en ensayos clínicos con drogas psicofarmacológicas (CENCEC).

vii Proyecto Ramal: Certificación de sitios clínicos para la realización de ensayos clínicos en servicios hospitalarios y unidades asistenciales del SNS (CENCEC).

with the state of the art in applied clinical trials and the principles of comprehensive project management.
  - Specialized professional job categories were established, such as project manager, clinical research assistant (monitoring), data management technician, statistical analysis expert, quality auditor, organizational manager and research manager, etc.
- Implementation of a master plan, with timetable and periodic trial monitoring through monthly inspections and reports to the producer.
- Introduction of an automated system for monitoring implementation of clinical trials throughout the Network.
- Work to integrate approaches with several production centers such as the Molecular Immunology Center and the Genetic Engineering and Biotechnology Center, in close collaboration with CECMED, to conduct clinical trials in compliance with commonly established criteria and procedures.
- Organization of national workshops to standardize criteria for trials, prior to initiating multicenter clinical trials.
- Establishing relationships with suppliers to develop quality improvement procedures in material resource planning, supply assurance and distribution.

Other important structural, organizational and functional changes have been made at the Center itself, improving several essential components, including:

- Planning and distribution of supplies from CENCEC to the entire national network. CENCEC projects availability and demand for medical resources and supplies at each clinical site. These are acquired centrally by the Center and distributed through the certified clinical trial supply distribution service of FARMACUBA's national distribution channels.

- Data management and statistical processing, conceived from the trial planning stage and including everything from creation of data collection logs to design and validation of databases, data entry and statistical procedures.

- Quality assurance, implementation of GCP guides defined by CECMED in 1992; establishment of the Independent Quality Assurance Unit (1995); and later, implementation of a Quality Management System (2006), the latter ISO 9001-certified in 2008 by the National Standards Office and the international body AENOR (Spanish Association for Standardization and Certification).

- Ethical aspects of clinical trials, with the updating and harmonization of GCP guides and supervision of compliance with these; notably, CENCEC has participated since 2001 in the Working Group on Good Clinical Practices in the Americas.[10]

- Human resource development in the Center, the Network and the national health system, beginning with seminars, conferences and workshops, eventually establishing the Academic Development Unit and designing a "curricular strategy for development and ongoing training of human resources in clinical trials"[viii]—skills development in the short, medium and long term. Worth mentioning are four editions of a national clinical trials diploma course through 2007, and the current process under way for accreditation of a master's degree in clinical trials.

- International cooperation, directed above all toward training in clinical trials for personnel in the Center, Network and health system; sharing of experiences between Cuba and other countries; and increasing the Center's visibility and international credibility.

- Creation of a public clinical trials registry (available at: http://registroclinico.sld.cu), in compliance with international requirements for public registration of all clinical trials prior to implementation, to ensure transparency of findings.

RESULTS OF CLINICAL EVALUATION: CLINICAL TRIALS 1992–2008

A summary of the most important results of the Center's main mission—clinical evaluation of medical-pharmaceutical and biotechnology products—is presented in Table 1, including organization, sponsoring centers, products evaluated and their categories, sites and clinical investigators involved, as well as patients recruited. During the analysis period, 103 clinical trials were completed, assessing a total of 51 products from 24 sponsoring centers. The total number of clinical trial sites was 816, with 2035 investigators participating. More than 14,000 patients were recruited for these trials.

Table 1: Summary of clinical trials 1992–2008

Parameters	Number
Completed clinical trials	103
Sponsoring centers	24
Products	51
Clinical trial sites	816
Average sites per clinical trial	7.2
Clinical trial investigators	2035
Average investigators per clinical trial	19.7
Patients recruited	14,386

Three sponsors—the Genetic Engineering and Biotechnology Center, Molecular Immunology Center and National Scientific Research Center—account for 65% of total trials completed (Table 2). Products from these centers account for 50% while the remaining 50% are divided among other centers of Havana's Scientific Pole and other institutions.

Table 2: Clinical trials and products assessed by sponsor

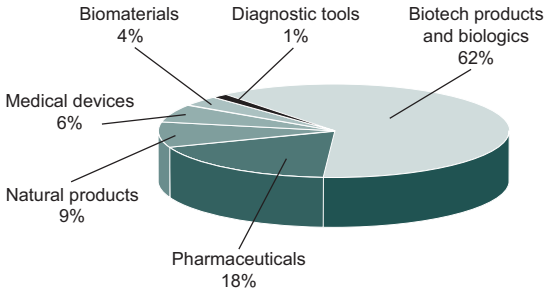
Sponsoring centers	Clinical trials	%	Products evaluated	%
Genetic Engineering and Biotechnology Center	33	32.0	7	13.7
Molecular Immunology Center	25	24.3	13	25.5
National Scientific Research Center	9	8.7	5	9.8
Other centers in Havana's Scientific Pole	15	14.5	11	21.5
Centers in other provinces	6	5.8	3	5.8
Other institutions	9	8.7	8	15.6
International studies	6	5.8	4	7.8
Total	103	100	51	100

viii Proyecto Ramal: Estrategia curricular para el desarrollo y actualización de los recursos humanos en Ensayos Clínicos (CENCEC).

CENCEC's participation in international clinical trials accounts for a little more than 7% of the total number of studies completed. This is due to the basic mission for which the Center and Network were created: evaluation of Cuban biotechnology and medical-pharmaceutical products prioritized for development, for which the demand has remained steady and even increased during recent years.

Most studies completed are of biotechnology products (62%), followed by trials of pharmaceutical products (18%). This is explained by the tendency of the biotechnology industry to develop ever greater numbers of novel molecules requiring clinical trials for approval and marketing (Figure 1).

Figure 1: Completed clinical trials by product type



CENCEC's work has contributed to approval of medical products in Cuba for one or more indications, and in some cases to international approval, increasing potential for product export revenues contributing to the country's development.

Table 3 presents the results of Drug Regulatory Agency evaluation: 26 products were successfully approved, six of these for extended clinical use throughout the country [Refers to health authorities encouraging broader use in Phase IV trials.—Ed.]. Another 11 already-registered products were approved for extended clinical use.

Table 3: Results of Drug Regulatory Agency evaluation

Results	Number
Product approval	20
Approval and extension of clinical use	6
Extension of clinical use	11
Exploration or proof of concept	6
Academic or public health research [non-commercial]	4
Not approved	4
Total	51

CENCEC activities have also benefited the national health system, leading to:

- Improvements in health indicators, modified as a result of introducing new products or products approved for new indications.

- Changes in health care standards for the disease for which a product was evaluated, since for a clinical trial protocol to be accepted, it must meet the highest diagnostic, evaluative and treatment standards for the disease; and the introduction of new diagnostic methods, new evaluation technologies and new treatments associated with the product under study, such as concomitant treatments or active treatments applied in control groups.

- Input to MINSAP decision-making on serious health issues (such as epidemics, substitution of imports and evaluation of new technologies).

- Training and professional development of personnel participating in a given study, whether those in medical specialties or in areas specific to the clinical trial, since participation requires study of the most current knowledge of the disease or entity under evaluation. Personnel also gain from capacity-building in other aspects of research such as GCP, ethical aspects and principles of evidence-based medicine, contributing to greater scientific rigor, and thus, better patient care.

FINAL CONSIDERATIONS

CENCEC was created in the 1990s to ensure design and execution of trials of Cuban products requiring evaluation before entering national and international markets. This objective has been met and expectations surpassed. The Center has positively evolved in line with international trends and the increasing needs of Cuba's biotechnology and medical-pharmaceutical industry, and the clinical research needs of the national health system.

One vital factor in strengthening the Center was the implementation of the National Clinical Trials Coordinating Network throughout the health system, ensuring greater efficiency and promptness in conducting clinical trials.

CENCEC and its Network constitute a comprehensive organization across the country, differentiated from other similar institutions in the world (CROs). Some of CENCEC's distinguishing characteristics include its national scope, its combination of scientific services with academic and health research, and continued human resource development.

Continual review and adaptation to international trends in contractual clinical trial research have helped the Cuban organization stay current. From the Center's creation, it was designed to offer a complete range of services, usually only available from large global or multinational contract research centers. These functions have been consolidated, prompting structural and organizational changes in line with global trends and domestic conditions.

Proof of the Center's achievement of its original objectives lies in the total number of completed clinical trials leading to registration of a range of important biotechnology and pharmaceutical products; the active participation of the health care system in the clinical trials program; modification of health indicators and health care standards; and improving performance among a critical mass of health care personnel.

CENCEC's challenge is to maintain and surpass the quality achieved in its structure and purview in order to ensure a clinical evaluation process that meets international standards. Growing demands on the part of industry and the need to conduct more research with a public health focus challenge the organization to seek efficient solutions to reach goals unimagined 18 years ago.

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