A PROPOSAL FOR THE DEVELOPMENT OF A REGIONAL CAPACITY IN THE COUNTRIES OF LATIN AMERICA FOR CLINICAL TRIALS IN TUBERCULOSIS

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CLINICAL TRIALS FOR TUBERCULOSIS
AN ASSESSMENT OF FACILITIES, RESOURCES AND NEEDS

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1. INTRODUCTION

Clinical as well as public health practice needs to be based on scientific evidence. Evidence is created through scientific research.

Randomised controlled clinical trials have long been recognised as the definitive method for assessing the efficacy of a particular medical intervention. Such trials provide information that is superior in quality to the findings arising from non-randomised interventions, since they are designed to minimize bias, which may confound the results of any investigation. Clinical trials have played a pivotal role in identifying chemotherapy regimens for the treatment of tuberculosis, which have achieved high rates of cure with low levels of toxicity and reasonable duration of chemotherapy.

While the development of effective chemotherapy has had an important impact in industrialized countries, rapidly reducing morbidity and mortality caused by tuberculosis, the disease remains a major health burden in low-income countries. The cost of standard short-course chemotherapy, with efficacy rates of almost 100%, is less than US$ 10 per patient. However, even this low cost is proving a challenge for the provision of treatment, especially in the 22 listed poorest countries of the world, four of which (Bolivia, Honduras, Guyana and Nicaragua) are in the Latin American Region.

Clinical trials have to meet two essential conditions in order for the results to be reliable. Firstly, they have to meet international standards of Good Clinical Practice (GCP) and, secondly, sufficient numbers of patients be enrolled so that the trial has statistical power.

In order to achieve statistical power, large scale multicentre trials may need to be carried out allowing the recruitment of large numbers of patients within a short space of time, and yielding reliable results which may then be used by international organisations, such as the WHO, to make evidence-based recommendations to National Tuberculosis Programmes (NTPs).

There is, thus, a need to develop an international network of centres capable of carrying out trials of the chemotherapy of tuberculosis as well as of surrogate markers of relapse.

The rising rates in the incidence of tuberculosis in the Latin American Region are of concern the regional NTPs. It is, thus, reasonable to plan the development of a regional coordinating centre and the inclusion of at least some of the most affected countries in such a network with a view to developing research capacity in the area and enable these nations to respond adequately to their own health needs. Experience in international studies has shown the convenience of establishing regional coordinating centres for these trials.

The Centro Internacional de Entrenamiento e Investigaciones Médicas (CIDEIM), is a non-governmental, non-profit organization in Cali, Colombia, dedicated to research on infectious diseases and to the training of researchers. CIDEIM has developed the capacity to offer scientific and technological assistance both to other organizations and to the community. It is, therefore, ideally placed to be the coordinating centre for international multicentre trials in tuberculosis in the Latin American Region.
2. THE SITUATION IN LATIN AMERICA

The Latin American Region comprises all the countries of the Central and South American Continent with a population that exceeds 500 million. Seventy five percent of the population lives in urban areas. According to Pan American Health Organization (PAHO) data, 251,613 new cases of tuberculosis were reported in the Americas in 1998. Over the last 10 years, the figure has remained relatively stable in the Region. In addition PAHO estimates that tuberculosis (TB) killed more than 75,000 persons in Latin America and the Caribbean in 1995. The majority of cases are among persons in their most productive adult years, 25 to 54 years old (see table of notification rates by age and country for the year 2002 below). More than half of the estimated cases occur in Brazil, Peru and Mexico. The majority of nations in the Region still face serious rates of 25/100,000 or more. Nine countries (Bolivia, Dominican Republic, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Paraguay and Peru) face severe rates of more than 70/100,000: Recently published data from WHO database 2004 report 394,219 smear positive new TB cases for 11 Latin American countries including: Bolivia, Chile, Colombia, Costa Rica, Republica Dominicana, Ecuador, El Salvador, Guatemala, Haiti, Honduras, Nicaragua, Panama, Paraguay, Perú, Uruguay and Venezuela. These 11 countries have a total population of 196,277,000 and face an increase of 25/100,00 new smear positive cases in 2000 to 31/100,000 in 2002 which indicates a 25% increased rate over that period.

TB cases may be increasing in the region due to various factors including: (a) the breakdown of public health infrastructure and the weakening of TB control programs specifically; (b) economic crises and growth of marginalized urban and rural populations with living conditions conducive to spread of the disease; (c) the expansion of the Human Immunodeficiency Virus (HIV) epidemic; and, (d) increased travel and migration. Several countries with previously steady declines in case rates, including Argentina, Brazil and Cuba, have experienced recent rebounds in reported incidence.
Latino American Region, Tuberculosis smear positive notification rates by age, 2002 (Rates by 100000)

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The spread of tuberculosis creates new challenges for TB control in the Region because HIV infected individuals are 30 times more likely to develop tuberculosis. PAHO estimates that more than 250,000 persons are co-infected with TB bacteria and HIV. Approximately 5% of the tuberculosis cases in the region were associated with HIV co-infection, but this proportion likely varies widely from country to country, with HIV infection levels.
3. THE RÔLE OF CIDEIM

CIDEIM is a non-profit, non-governmental organization dedicated to biomedical research in infectious diseases and the development of research capability. Its mission is to propitiate development and well being through generation of biomedical knowledge. The research conducted by CIDEIM is largely the result of clinical and epidemiological observations of transmissible diseases. CIDEIM was constituted as an autonomous Colombian institution in 1990. Its institutional heritage dates from 1961 with the establishment of a Technical Assistance Mission by presidential decree through which Tulane University and the then newly established School of Medicine of the Universidad del Valle in Cali conducted a broad program of cooperation in human health research. This program evolved over the following three decades from a bilateral program of international cooperation to a national program with international recognition and in which COLCIENCIAS (Colombian government organism established in 1973 to promote the development of science and technology) became a permanent advocate.

In 1989, at the initiative of COLCIENCIAS, a Provisional Board of Directors was designated to define the future of CIDEIM. This group of renowned local and national academic and civic leaders determined the constitution of CIDEIM as an autonomous organization. This decision was a definitive step in the process of national appropriation of the research and training mission of CIDEIM. In 1994 COLCIENCIAS officially became a founding member of CIDEIM, and in this capacity donated the building in which CIDEIM has functioned since 1975.

The research and training activities conducted since 1990 have involved the collaboration of colleagues in 29 Colombian and over 35 international institutions in 15 countries. In recognition of CIDEIM’s interdisciplinary competence in the investigation and management of human leishmaniasis and its capacity to impact regionally, the institution was designated a WHO Collaborating Centre in Leishmaniasis in 1992. This designation has subsequently been extended to January 2007.

National and international graduate and undergraduate students undertake apprenticeship, training or develop their thesis research projects at CIDEIM. Students have been supported by COLCIENCIAS, WHO/TDR training grants, Fulbright Fellowships, Yale University Down’s Fellowship, Ministère de l’Enseignement Supérieur et de la Recherche Francaise, The Fogarty NIAID Minority International Training Program, Colombia’s ICETEX (Colombian Institute for Technological & Post-graduate Education) and several research projects grants. The award of the WHO/TDR Regional Training Consortium Grant to CIDEIM, the Centers for Disease Control (CDC), the Instituto Oswaldo Cruz and the Universidade Federal de Rio de Janeiro created new training opportunities and paradigms that prevail today.

The Board of Directors of CIDEIM is constituted by national and local scientific and civic leaders. Specialized institutional committees ensure the compliance with national and international standards and regulations for biomedical research. Most of the members of the committees are independent external authorities i.e. they are not employees of CIDEIM. The committees include: Scientific Advisory Committee, Ethics and Prevention...
CIDEM has carried out several controlled clinical trials over the last few years, mainly in the evaluation of strategies to prevent the transmission of leishmaniasis and new treatment modalities for malaria and leishmaniasis. (1,2,3,4). At present the Clinical Unit is in the process of implementing a trial designed and financed by the International Union Against Tuberculosis and Lung Diseases (IUATLD) to investigate the efficacy of a new treatment delivery form in preventing the emergence of multiresistant tuberculosis.

With the establishment of a CRO, CIDEM intends to extend its recognized basic investigational know-how to advance its capacity to carry out controlled clinical trials. The CRO is headed by Dr. William Cárcenas, a clinical physician (internist) with a Master’s degree in Clinical Epidemiology and some experience in the design and conduct of clinical trials.

The biostatistics section of the Epidemiology Unit up to now has been adequate for basic research, however, strengthening of data management and analysis capacity is needed in order to adequately respond to the CRO development. Clinical Monitoring with Good Clinical Practices assurance (ICH-GCP) is another requirement for effective functioning of the CRO, and although a workshop for 12 CIDEM staff was conducted last year, this capacity needs to be developed anew in the context of the CRO.

Since 1992 CIDEM has been working on different aspects of Tuberculosis. Interaction with regional health authorities, international sponsors and research centers has made it possible to standardize methods for detection of the disease and the evaluation of TB activities. Several research projects, and laboratory advances have resulted in publications that support the claim of CIDEM’s expertise on TB. Particular research on mycobacterial resistance and susceptibility along with critical social aspects has formed the main thrust of CIDEM’s investigative effort on this disease.

The existing tuberculosis infrastructure and the persistent high incidence rates of TB in the region allows for adequate capacity to carry out large-scale chemotherapy trials in tuberculosis. As the Regional Coordinating Bureau, we would like to propose the Centro Internacional de Entrenamiento e Investigaciones Médicas in Cali, Colombia as the Coordinating Center for regional multicenter trials. The institutional profile presented above substantiates its ability to carry out the trials, the related staff training, trial monitoring, data management as well as the statistical analyses and follow through to the publication of the trial outcomes. The rationale for this proposal is the need of a regional coordinating site consistent with the language, ethnic, cultural and socio-political identity of the region, which facilitates direct communication and coordinating activities. Furthermore, reasonable distances for coordination and standardization meetings as well as training seminars and workshops would help in cost containment. Such a center would also give the region confidence for self determination of strategies and projects that promote TB control programmes. A regional coordinating site would give TB workers the opportunity to decrease epidemiological and public health impact of tuberculosis by working directly in high incidence areas.
4. INTERNATIONAL MULTICENTRE TRIALS

The most effective anti-tuberculosis drugs to be developed in the recent past have been the rifamycins and these became available some 30 years ago. Although, these drugs enabled the duration of chemotherapy to be reduced to 6 months from 18 months, it has become apparent that this reduction has not been sufficient to ensure that all patients are successfully treated.

Two strategies remain to those concerned with the elimination of tuberculosis.

**Strategy No.1: New drugs for the treatment of tuberculosis**

There is, therefore, a need for the identification of new and effective drugs for the treatment of tuberculosis, which could allow a further reduction in the period of chemotherapy. Within the foreseeable future, it is anticipated that new molecules of treatment will become available to be tested in clinical trials.

**Strategy No.2: Drugs currently available for the treatment of tuberculosis**

In the short term the testing of available drugs in different combinations, rhythms and shorter durations remains an important area of investigation.

This will necessitate large scale controlled clinical trials. Such large scale trials can only be carried out through international collaboration, with countries pooling their resources to provide suitable trial capacity and capability. The framework required for carrying out international collaborative clinical trials includes a network of sites at which the research is to be carried out as well as a system to support the network to ensure that the work is carried out at a high level of technical competence.

International multicentre trials can and should be carried out. Not only do they allow the recruitment of large numbers of patients within a short space of time, they yield reliable results which may then be used by international organisations, such the WHO, to make evidence-based recommendations to National Tuberculosis Programmes.

For a comprehensive evaluation of treatment efficacy through controlled clinical trials, the network of trials centre must represent a wide range of geographical diversity. The rationale for the geographical diversity also includes

1. variation in the prevalence of HIV infection,
2. genetic differences (illustrated by differences in rates if isoniazid acetylation) that may influence the response to treatment,
3. differences in behavioural/social patterns and
4. prevalence of multi-drug resistant tuberculosis in these countries.
5. PROGRAM OBJECTIVES

1. To develop an international network of clinical trials centres in Latin America. Participating centers must fulfill the following criteria:
   - They are in a country with an established National Tuberculosis Programme (NTP) that is implementing the recommended DOTS Strategy.
   - The NTP offers an uninterrupted supply of drugs and diagnostic materials, free of charge, for all patients.
   - An established recording and reporting system, following the IUATLD/WHO guidelines, providing all the information necessary for a cohort analysis.
   - They have access to a laboratory capable of microscopy, culture and susceptibility testing with a system of quality assurance.
   - They have personnel who can be trained in the conduct of clinical trials and who are capable of supervising treatment and monitoring progress. This should include a clear protocol for defaulter tracing.
   - An agreement from the Ministry of Health for participation in clinical trials.

2. To strengthen capacity of clinical trials centers in operations research through
   - Training in the conduct of controlled clinical trials
   - Data management
   - Quality assurance in laboratories
   - Develop and enlarge the local ethical principles guiding trials in human subjects.
   - Site visits
   - Attendance of participants at workshops and courses on tuberculosis

6. THE ADMINISTRATIVE FRAMEWORK

There should be a well constructed framework of administrative to supervise the collaboration.

The Central Co-ordinating Office (CCO) which is responsible for:

- Development of the protocol
- Recruitment of the participating centres
- Training of the local staff
- Despatch of the drugs and study forms to the participating centres
- Raising funds for each study
- Monitoring the conduct of the study
- Organising the meetings of the Steering Committee
- Organising the meetings of the Data and Safety Monitoring Committee

Participants meetings at regular intervals to review:

- The intake to the trial
- The criteria of eligibility are being met
- Treatment supervision is correct
- Specimen collection is regular
- Losses to follow up are not excessive
7. TRAINING NEEDS TO STRENGTHEN CAPACITY

The objective of capacity strengthening not only entails training in the conduct of controlled trials and of data management. It requires also quality assurance in laboratories and regular site visits.

Conduct of controlled clinical trials

We believe that participation in the trials will strengthen the capacity of the participating centres to perform internationally significant operations research. By following the protocol, in every detail, collaborating institutions in low income countries will develop their capacity, in terms of designing and carrying out studies relevant to their own situations. They will acquire knowledge as to how to conduct randomised clinical trials.

Each participating centre is visited before the trial begins. Detailed discussions take place with the head of that institutions and any staff members designated to be directly involved with trial.

At each centre, the staff members involved would consist of at least one doctor to oversee the good conduct of the trial, members of the nursing staff to ensure that treatment is taken under supervision and another paramedical person to visit the patients’ homes. These persons constitute the local management committee which meet, together with the laboratory staff, at regular intervals, to discuss the progress of the trial.

Data management

Where the capacity and capability exists for centres to carry out their own data management, this will be encouraged and strengthened. Where it does not exist, local staff members will be trained to do data entry.

Good Clinical Practice (GCP)

The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use has defined Good Clinical Practice (GCP) as an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical data are credible. Each centre will be encouraged to develop standards of GCP consistent with those defined by the ICH.

Good Laboratory Practice (GLP)

In order to have consistently reliable results a system of quality assurance, carried out by microbiologists, will be set up. This will consist of, in the first place, the completion of a questionnaire by each laboratory so that the present situation may be evaluated. Regular visits to the participating laboratories by microbiologists who would evaluate the laboratory methods, equipment and recording in order to ensure that the results are reliable would be envisaged.
8. RESOURCES TO MEET THE TRAINING NEEDS AND TECHNICAL SUPPORT REQUIREMENTS

Workshops and Seminars

The process of training in operations research, and of capacity strengthening to do such research, will require a sustained effort over a period of, at least, five years. Activities will consist of repeated workshops on research issues, especially statistical procedures and protection of human subjects. The training will, therefore, have to be a continuous process. Staff changes at participating centers will also mandate a continuous training scheme in order to strengthen the performance of new and old participants as well as the NTPs.

These meetings would be attended by investigators from the participating centers as well as other personnel of National Tuberculosis Programmes. Since we consider that, one of the most important things a programme can do is evaluate the efficacy of its interventions or of proposed new interventions, the participants will consist of staff already taking part in the clinical trials network and thus in settings that require the application of such skills.

Although this episodic training is extremely important, it should also be noted that participating centers receive continuous on site training through regular site visits by experts and through continuous monitoring and evaluation of performance by the Data and Safety Monitoring Committee. This helps the staff to deal with local situations and strengthens the performance of the NTPs.

In order to enhance enrolment capacity there is a need to extend this kind of training to centers not yet participating in a clinical trial.

Each workshop would address the following topics:

a. Framing the research question
b. Preparing a research protocol
c. Statistical matters: confidence, significance, power, sample size, sampling methods
d. Study procedures: randomisation, enrolment, treatment phase, follow-up phase
e. Drafting forms and questionnaires
f. Laboratory procedures relevant to the TB programme's studies
g. Human subjects protection and trial oversight
h. Data management
i. Analysis of the data: basic approaches, impact of confounding and losses, etc.
j. Critical issues in clinical trials:
   - when to stop?
   - outcome events?
   - critical data or specimens?
   - serious adverse events
k. Resources available
l. Reporting the results
m. Intellectual property rights
**Technical support and investment in laboratories**

It is proposed to develop a system of laboratory evaluations and provide training for operational and health and safety procedures where necessary.

Training needs may include:
- GLP and document control
- ‘Health and Safety’
- Equipment calibration, monitoring and maintenance
- Quality Control, Quality Assurance

And support needs include:
- Technical
- Problem solving
- Strategic planning for GLP
- Strategic planned replacement of equipment
- IT and the internet
- Purchasing of equipment and consumables
- National Reference Laboratories, to provide leadership for the laboratory network in their country
- Validation of methods and procedures
- Development of new methods and procedures which are appropriate for the conditions that prevail in these countries.

**9. EVALUATION PROCEDURES**

A system of regular evaluations will be established to review the performance of each trial centre. Attempts will be made to recruit new centres. Poorly performing centres will, if their performance cannot be improved, be dropped.

**Resources to evaluate training**

In order to evaluate the effectiveness of the training activities, regular analyses of the performance of each center will be carried out. In addition to the number of training sessions undertaken and the registration of each, overall performance will be assessed using the following criteria:
- Rate of intake, both the number of enrolled subjects and the percent of enrollees among all possible candidates, a rough measure that all potential subjects are being properly screened.
- Eligibility of patients, for example their residence within the catchment area are being properly screened.
- Quality of documentation, especially the number of discrepancies and incomplete tests.
- Quality of laboratory results, especially the number of discrepancies and incomplete tests.
- Rate of non-compliance and results of efforts to reduce it.
- Assessment of the informed consent procedure
- Rate of loss to follow up and result of efforts to trace defaulters.
10. PROVISIONAL AGENDA

Day One CHAIR Dr. Nancy Saravia Monday 7th March

08h00 Welcome Dr. Nancy Saravia

08h20 Overview of CIDEIM Dr. Francisco Miranda

08h40 Overview of INTERTB Dr. Amina Jindani

09h00 Why do we need RCTs? Dr. José Becerra

09h15 Essentials of the RCT Dr. José Becerra

09h30 COFFEE BREAK

10h00 Framing the research question Dr. Elsa Villarino

10h30 Preparing the protocol Dr. Elsa Villarino

11h00 Study procedures Dr. William Burman
  • randomisation
  • enrolment
  • treatment phase
  • follow up phase

12h00 LUNCH BREAK

13h00 Statistical considerations Dr. José Becerra
  • confidence
  • significance
  • power
  • sample size
  • sampling methods

14h00 Drafting forms and questionnaires Dr. Elsa Villarino

14h30 Data management Dr. José Becerra

15h00 COFFEE BREAK

15h30 Critical issues Dr. William Burman
  • serious adverse events
  • outcome events
  • critical data or specimens
  • when to stop Dr. José Becerra

16h30 DISCUSSION
Day two CHAIR Dr. William Burman Tuesday 8th March

08h00  Site requirements  Dr. Amina Jindani

08h30  Site monitoring  Dr. Amina Jindani

09h00  Trial oversight  Dr. Stefan Goldberg
  • Steering Committee;
  • Data & Safety Monitoring Committee

10h00  Analysis of data  Dr. José Becerra
  • Basic approaches
  • Impact of losses to follow up
  • Impact of confounding

11h00  COFFE BREAK

11h30  Publication of data  Dr. Stefan Goldberg

12h00  Laboratory procedures  Professor Ernesto Montoro

13h00  LUNCH

14h00  Laboratory procedures  Dr. Beatriz Ferro

15h00  TEA BREAK

15h30  Resources available
  • Enrolment capacity  Dr. Marcos Burgos
  • Follow up capacity  Dr. William Cardenas

16h30  DISCUSSION
Day Three CHAIR Dra. Maria Consuelo Miranda  Wednesday 10th March

08h00  Human subjects protection  Dra. Consuelo Miranda
  •  Responsibilities of investigators

09h00  Human subjects protection (continued)
  •  Considerations for MDR Trials  Dr. Bill Burman
  •  Intellectual property rights  Dr. Amina Jindani

10h00  COFFEE BREAK

10h30  Future clinical trials
  Trial of moxifloxacin  Dr Bill Burman
  High dose rifapentine trial  Dr. Amina Jindani
  Treatment trial of MDRTB  Dr. Carole Mitnick
  Prevention trial of MDRTB  Dr. Mercedes Becerra

11h30  Surrogate markers of relapse  Dr. Amina Jindani

12h00  LUNCH

13h00  FINAL DISCUSSIONS

13h30  CONCLUSIONS  Dr. José Garcia
  Acknowledgements  Dr. Hildegard Piñeros
  Thanks  Dr. Amina Jindani

14h00  Farewells  Dr. Francisco Miranda
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