The Tuberculosis Trials Consortium: A Model for Clinical Trials Collaborations

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THE TUBERCULOSIS TRIALS CONSORTIUM (TBTC) IS A COLLABORATION of North American tuberculosis clinics and investigators whose mission is to conduct programmatically relevant research concerning the diagnosis, clinical management, and prevention of tuberculosis infection and disease. The purposes of the TBTC are to conduct research that expands clinical and epidemiologic knowledge of TB and facilitates the diagnosis, clinical management, and prevention of TB infection and disease; to integrate research into the care of people infected with tuberculosis; to promote research within local TB control programs through collaboration on clinical research relevant to public health settings; and eventually to provide a forum for international collaborative research of importance to both domestic and international TB control.

The United States Public Health Service and the Department of Veterans Affairs have a distinguished history of conducting clinical trials to evaluate new drug regimens for both the treatment and prevention of tuberculosis.[1-4] In 1960, the Centers for Disease Control and Prevention (CDC) assumed a major role in these studies when the Tuberculosis Division of the Public Health Service was transferred to CDC. Subsequently, CDC coordinated a series of multi-center clinical trials that helped to establish rifampin-based, short-course therapy as the standard for treatment of tuberculosis. The Public Health Service also conducted studies to provide the scientific basis for preventive chemotherapy, which remains a major component of our tuberculosis elimination strategy.

Support for the infrastructure required for these studies gradually diminished until the last completed trial, USPHS Study 21, was nearly terminated several times during its course for lack of adequate funding. With the infusion of federal support for tuberculosis control in the early 1990s, and with renewed interest in the search for better TB therapies, CDC established a consortium of investigators to conduct clinical trials in tuberculosis. The consortium sites include public health departments, academic medical centers, and Veterans Affairs Medical Centers (VAMCs).

New drugs and regimens for both tuberculosis treatment and prevention, new diagnostic tests, and new vaccine candidates currently are being

developed. At the same time, the challenges posed by the goal of tuberculosis elimination increase as rates of drug resistance increase[5] and as the costs associated with assuring high rates of adherence rise.[6] The TBTC provides a unique resource for clinical studies and can play an important role in improving tuberculosis treatment and prevention.[7]

CREATION OF THE TBTC

In 1993, CDC announced an open competition in the US and Canada for clinical sites interested in participating in a TB clinical trials group. Seven 5-year contracts were awarded that year. Sites were selected based on demonstrated access to TB patient populations, experience in clinical trials, demonstrated scientific ability of the proposed clinical team, and presentation of a convincing plan for patient recruitment, management and follow-up. Because this group did not have the capacity to recruit the number of patients thought necessary for large-scale treatment trials, an additional competition was held in 1994 and five additional 5-year contracts were awarded; award criteria were similar. Awardees were academic medical centers or tuberculosis control programs in departments of public health.

Concurrently, discussions were underway with Dr. Fred Gordin at the Veterans Affairs Medical Center in Washington, DC. Dr. Gordin was chair of the Community Programs for Clinical Research on AIDS (CPCRA), a major AIDS clinical trials group funded by the National Institute of Allergy and Infectious Diseases. He proposed to organize a group of VAMC sites that could join with the CDC clinical sites. CDC responded by developing a 5-year Memorandum of Agreement with the Washington (DC) VA Medical Center, through which a group of 15 VA medical centers were funded. The Washington (DC) VAMC held an open competition for a research organization to serve as clinical site monitor for the VA sites; a 5-year contract was awarded to Westat, Inc., Rockville MD, in 1994.

The 12 CDC contract investigators and representatives of the VAMC group met several times in 1994 to design the first major treatment trial of the Tuberculosis Trials Consortium. The group chose to evaluate a once-weekly regimen based on rifapentine in its first major trial. The trial was named USPHS Study 22.[8]

Enrollment into the study began in April 1995 and continued through November 1998 (n = 1075). A Data and Safety Monitoring Board composed of recognized experts in clinical TB, in clinical trial statistics and management, and in HIV epidemiology, was recruited in 1995 to review interim analyses of the evolving trial data.[9] Close relationships with local tuberculosis control programs were essential for successful recruitment and man-

Figure 1. Map of current sites

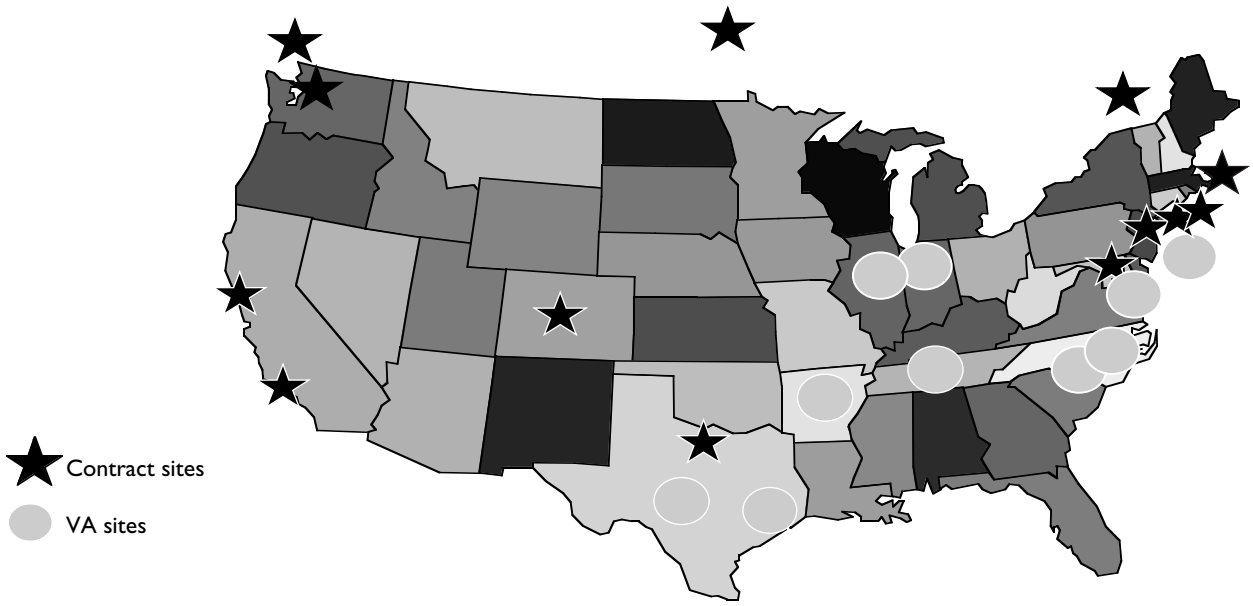
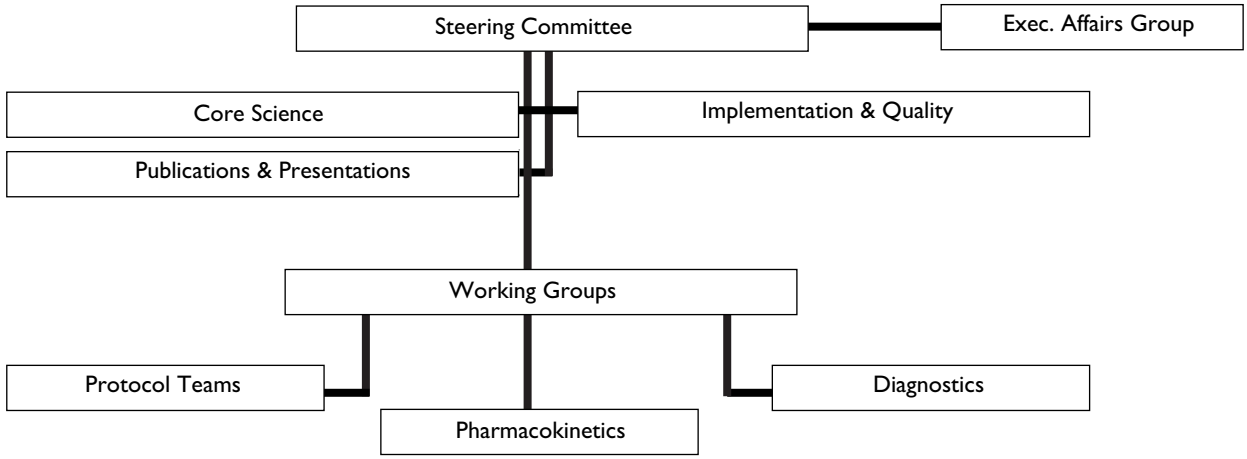


Figure 2. Committee structure of Tuberculosis Trials Consortium



agement, and such relationships were carefully fostered by successful sites.

Organizational restructuring. By 1997, it was clear that the Consortium had both opportunity and interest to examine other research issues, but that a different organizational structure could better engage the capacities of the study investigators. CDC staff met that summer with key investigators, including the chief of the VA side of the Consortium. The group developed a proposal for reorganization that was modeled on the organizational structures of the major AIDS clinical trials groups, the Community Programs for Clinical Research on AIDS, and the Adult AIDS Clinical Trials Group. The proposed structure allowed far greater independence to investigators in the selection and design of studies, as well as in trial implementation and monitoring; the CDC roles were to be more collaborative and less supervisory.

Consortium investigators adopted this proposal and approved by-laws in May 1998, establishing a steering committee made up of one representative from each clinical site and one from CDC as the governing body of the Consortium. Several working committees were established, composed of elected Consortium investigators and coordinators, in collaboration with CDC staff. In 1999, CDC conducted a formal external recompetition. New 10-year contracts were awarded to 13 (7 prior TBTC members and 6 new sites) of 26 applicants. The VA conducted a similar recompetition, and 10 VAMC sites were funded to continue for 5 years as members of the TBTC.

CURRENT INFRASTRUCTURE AND STUDIES

The infrastructure of the Tuberculosis Trials Consortium now includes:

- A network in the United States (20) and Canada (3) of 23 clinical sites whose principal investigators are recognized experts in tuberculosis (Figure 1)
- Experienced clinical coordinators and outreach workers at each site
- A formal committee structure to facilitate executive functions (Figure 2)
- A communications system that includes semi-annual meetings, conference calls, study newsletters and e-mail
- Collaborative relationships with local tuberculosis control programs to facilitate the recruitment and management of trial patients
- An expert Data and Safety Monitoring Board that reviews active protocols
- Coordination with the CDC Institutional Review Board (IRB) and local IRBs at the 23 sites
- A Data and Coordinating Center at CDC
- Cooperative relationships with key manufacturers of tuberculosis drugs and with key regulatory agencies, such as the Food and Drug Administration (FDA)
- Support for training, site monitoring and protocol development from Westat, Inc., an experienced contract research organization
- Laboratory support from CDC's Division of AIDS, STD and TB Laboratory Research, Tuberculosis/

Mycobacteriology Branch. (Available from URL: **http://www.cdc.gov/ncidod/dastlr/TB/**)

- A total budget (exclusive of CDC laboratory costs) exceeding $6.7 million per year; $5.4 million is dedicated to extramural support, $1.3 million to support project officers and staff for the TBTC Data and Coordinating Center at CDC
- Current and planned studies of the TBTC are shown in Table 1

Patient populations. Patients enrolled in TBTC trials have generally been representative of TB patients in the US and Canada. For example, Table 2 shows characteristics of patients who are HIV-negative and enrolled in TBTC Study 22, comparing them to characteristics of patients with TB reported in the US, 1997–98. Study 22 included many people with characteristics that impeded reliable follow-up (homelessness, unemployment, prior incarceration, and illicit drug use, for example). However, TBTC patient populations have under-represented people who cannot readily provide informed consent (such as those who are impaired or currently incarcerated, and children). The Consortium is working with the CDC and local institutional review boards to address the special human subjects issues of such groups as children and prisoners so they might participate, particularly in trials of

Table 1. Current and planned studies of the TB Trials Consortium, as of June 2001

Study number	*Description of study*	*Enrollment target*	*Start date*	*Current status*
I. *Efficacy and Safety Trials*				
22	Efficacy trial of once-weekly isoniazid and rifapentine in the continuation phase of therapy for pulmonary TB	1000	April 1995	Completed
23	Safety and efficacy trial of rifabutin-containing short-course therapy for HIV-TB.	200	March 1999	In progress
24	Efficacy of intermittent therapy for patients with INH-resistant TB or INH intolerance.	200	September 1999	In progress
25	Phase I-II dose escalation study using same design as Study 22, randomizing to 600, 900, or 1200 mg rifapentine.	150	July 1999	Completed
27	Treatment trial using a modified once-weekly rifapentine-based regimen, including patients at high risk of relapse	Not yet defined	To be determined	Planning
II. *Pharmacokinetic (PK) Studies*				
22PK	Evaluate isoniazid, rifampin, and rifapentine PK in Study 22	150	September 1997	Analysis
23A	Evaluate isoniazid and rifabutin PK in Study 23 (HIV-TB)	200	July 1999	In progress
23B	Evaluate rifabutin and nelfinavir interaction in HIV-TB	15	February 2000	In progress
23C	Evaluate rifabutin and efavirenz interaction in HIV-TB	15	December 1999	In progress
25PK	Evaluate PK of rifapentine at each of 3 doses in Study 25.	45	March 2000	Analysis
III. *Diagnostic Studies*				
Serum Bank	Collection of sera from patients with suspected or proven TB	150	May 1997	Completed
NAA	Use of several nucleic acid amplification (NAA) methodologies in the prediction of outcome of TB treatment	50–100	March 2000	In progress
IV. *Prevention Trials*				
26	Trial of treatment of latent TB infection comparing 3-month once-weekly isoniazid + rifapentine vs. 9-month isoniazid therapy	7700	May 2001	In progress

treatment of latent TB infection ("preventive therapy").

MANAGEMENT AND QUALITY ASSURANCE

The TBTC management approach has been one of Total Quality Management.[10] Investigators, coordinators, monitoring center staff, and CDC staff function on an equal footing. Decision-making is shared and democratic, as prescribed in the TBTC by-laws. All major issues (adoption of new protocols or new policies, for example) must be decided by the full Steering Committee. Decisions are based on >50% majority vote, except for votes to start or stop a study or to amend the bylaws, which require a 2/3 majority. Disputes are usually resolved within the committee structure, but occasionally have required Consortium-wide conference calls to reach full understanding and resolution.

Equally important as its role in decision-making, the TBTC membership has assumed the major role in development of the Consortium's quality assurance program. In the context of each study, the Implementation and Quality Committee develops quantitative quality assurance indicators related to performance of critical protocol-related functions. These are evaluated both as global and as site-specific measures. For example, Figure 3 shows the quality assurance indicators for Study 22. The Implementation and Quality Committee uses these indicators to identify sites experiencing performance difficulties; these sites receive progressive assistance designed to improve performance. CDC also periodically evaluates the cost performance (cost per patient enrolled or cost per patient completing study) of each site. Feedback with regard to ongoing per-

Table 2. Selected characteristics of patients in Tuberculosis Trials Consortium Study 22, compared with all patients reported with tuberculosis, United States, 1998

Characteristics	*Patients who are HIV negative in Study 22 (N = 1004)* Percent	*Patients reported with TB in the US in 1998 (N = 18,361)* Percent
Age (years):		
<15	0.0	5.9
15–24	8.6	8.4
25–44	46.1	34.7
>44	45.3	51.0
Male gender	74.9	62.2
Race/ethnicity:		
Non-Hispanic White	17.6	24.5
Non-Hispanic Black	39.7	31.8
Hispanic	25.1	22.3
Asian	13.8	19.7
Native American	3.7	1.4
Birth place:		
US	59.9	58.7
Canada	4.5	—
Mexico	13.6	9.5
Other foreign	22.0	31.8
Education:		
Less than high school graduate	55.5	NA
Homeless for more than 6 months	18.6 (in past 5 years)	6.3 (in past 12 months)
Unemployed for more than 1 year	43.2 (in past 5 years)	59.3 (in past 24 months)
Illicit drug use	20.8 (in past 5 years)	10.6 (in past 12 months)
Have diabetes	15.4	NA
More than 10% below ideal body weight	28.8	NA
Prior treatment for active TB	7.0	NA
TB Culture-positive at diagnosis	100.0	80.8
Resistant to Isoniazid (MIC >1.0 ug/ml)	Excluded	8.0
Resistant to Isoniazid and Rifampin	Excluded	1.1
Extrapulmonary disease only	0.0	19.3

NA = Not available

Figure 3. Lists of quality assurance indicators for Study 22

- Eligibility of enrolled patients
- Completion of study phase therapy
- Correct number of treatment doses
- Performance of required cultures & CXRs
- Completion of Follow-Up phase
- Potential losses to Follow-Up
- Retention for sample size

formance is a critical part of the TBTC self-management program.

As part of the effort to define clearly the capacity of the Consortium, the Implementation and Quality Committee is estimating the work demands (intensity) of each TBTC protocol, and the work capacity of each site based on its human resources. These intensity and capacity standards will assist the TBTC in assessing its ability to undertake and complete new studies.

Performance problems. Management of serious performance challenges has depended on the specific problem. When enrollment lagged at the beginning of Study 22, all sites with lower than projected enrollments were asked to submit a written plan to increase enrollment; this measure served to strengthen relationships with local TB control programs at several sites. When an early analysis revealed that several sites were not reliably obtaining required sputum samples, a review of quantitative findings with the entire Consortium led to improved performance at most sites. Finally, in several instances when both enrollment and quality of performance in data collection continued to falter despite multiple efforts, sites withdrew from the TBTC by mutual agreement between local investigators and CDC or VA administrators.

CDC's role in the Consortium. The Research and Evaluation Branch in the Division of TB Elimination at CDC plays a substantial role in the Tuberculosis Trials Consortium. Staff both in this branch and in the Computing and Statistics Branch serve as the Data and Coordinating Center (DCC) for the Consortium. The DCC includes approximately 12 full- or part-time staff members who have met weekly for the past six years and who function as a team. A medical epidemiologist serves as project officer for each TBTC study. The Data and Coordinating Center performs all data management, including design and printing of data entry forms, data entry and verification, data cleaning, and data analysis. DCC staff provide statistical support, oversee and track the human subjects protections activities of the Consortium, and coordinate communications for the TBTC.

CDC's Mycobacteriology Laboratory serves as reference lab by providing isolate storage and management, conducting confirmatory drug susceptibility testing and DNA fingerprinting of isolates as required, and participating substantially in selected protocols (such as the NAA study). CDC's HIV Immunogenetics Laboratory also provides support for NAT2 and cytochrome p450 2C19 genotyping.

The contract research organization. Through a competitive contract awarded by the Washington, DC, Veterans Administration Medical Center, the Consortium's contract research organization (CRO) (currently Westat, Inc.), has fulfilled many key functions for the TBTC. For example, the organization performs on-site monitoring activities, visiting each field site at least twice annually. The research organization handles regulatory compliance issues, assists in protocol development, and shares responsibility with the Implementation and Quality Committee for all Consortium education and training. The CRO staff also manages supplies and logistics for most protocols and provides assistance to facilitate the management of contracts with commercial firms. Because its multiple roles are integral to the success of the TBTC, the CRO is represented on all key executive committees.

TBTC oversight and prioritization. Both the Consortium investigators and CDC recognized the need to set formal priorities and to assure external oversight at several levels. The TBTC investigators and coordinators themselves provide the first level of review through their service on the Consortium's steering and executive committees. The entire Consortium meets twice yearly to discuss its program of research, adopt new protocols, and assign new priorities. The program of research proposed by the Consortium is then reviewed annually within the Division of TB Elimination by senior staff, referred to as the Scientific Advisory Group of Experts (SAGE). In addition, the Advisory Council on the Elimination of Tuberculosis, which provides external counsel on tuberculosis control to CDC and the Secretary of Health and Human Services, periodically reviews the Consortium's program of research. Finally, virtually all tuberculosis research funded by CDC now undergoes review by a cross-divisional group with expertise in tuberculosis-related issues, called TB Leads. Thus, TBTC both pro-

vides and benefits from multiple, inter-locking levels of internal and external review. These controls serve to assure that activities undertaken by TBTC meet both intramural and external standards for priority and quality.

RELATIONSHIPS WITH EXTERNAL AGENCIES

Largely through the Data and Coordinating Center at CDC, the Consortium has established cooperative relationships with other agencies involved in tuberculosis research and clinical trials. These include the US Food and Drug Administration, the Office of Human Research Protections (OHRP, formerly OPRR), and the National Institute of Allergy and Infectious Diseases (NIAID). The FDA's Center for Drug Evaluation and Research assists the Consortium in its use of investigational new drugs. OHRP granted the Consortium formal status as a Cooperative Protocol Research Program, under which Cooperative Project Assurances were obtained. Investigators in the TB Research Unit (funded by NIAID) are collaborating in the Consortium's NAA study.

Relationships with the commercial sector. Commercial development of new drugs for tuberculosis treatment and prevention has been impeded in recent years by serious obstacles.[11] The overall cost of developing a new drug from chemical laboratory to patient market, is estimated to be $300 million to $500 million. Although a significant portion of this cost is devoted to preclinical and clinical studies, the majority expense actually derives from the necessity to defray costs of prior failed development efforts. In addition to this high development cost, the industry has been further discouraged by strong pricing pressures from the public sector, by the lengthy development process required, by the risk that successful drugs will be reserved for treatment of tuberculosis only (thus diminishing their market potential by disallowing secondary, and often lucrative, uses for other diseases), by challenges to global patent protections, and by the risk that the long treatment periods required for tuberculosis may unmask chronic toxicities of a medication that could be used successfully for short-term conditions. The Global Alliance for TB Drug Development, a recently established initiative with initial support from the Rockefeller Foundation and the Bill and Melinda Gates Foundation, will function as a virtual pharmaceutical company and promote TB drug development through the establishment of partnerships with both private and public sector companies and agencies. The TBTC is eager to collaborate with the Global Alliance in clinical trials of new agents.

The Consortium initiated collaboration with the commercial sector in its Rifapentine Trial (TBTC Study 22, supported in part by the manufacturer, Aventis), by making evolving trial data available for timely regulatory review in the US and in Europe.

The Consortium has also begun to collaborate with other private firms. In Study 23, which aims to describe outcomes of therapy for HIV-TB, test kits for HIV viral load measurement have been provided by the manufacturer, Bayer. Several TBTC studies have obtained partial funding from private companies whose products are involved. For example, Study 23B assesses the pharmacokinetic interactions of rifabutin and nelfinavir (an HIV protease inhibitor manufactured by Agouron), Study 23C assesses the pharmacokinetic interactions of rifabutin and efavirenz (an HIV non-nucleoside reverse transcriptase inhibitor manufactured by DuPont Pharmaceuticals), and the NAA study assesses the ability of a commercially available NAA test (manufactured by Gen-Probe) to predict the outcome of tuberculosis therapy. The company funds defray such costs as those for measuring serum drug levels. Without such external funding, the TBTC could not undertake these small but useful additional studies. As the marginal cost is small, the group is not driven by this funding; however, it does allow the TBTC to accomplish more than it could otherwise. And because TB research has not been perceived as a profitable area commercially, it is unlikely that these studies would occur without the substantial involvement of a group such as the TBTC.

HUMAN SUBJECTS PROTECTIONS

The TBTC has an extensive system for protection of human subjects. Because CDC staff members are directly involved in the design, execution and analysis of these studies, all Consortium protocols must obtain approval from a CDC institutional review board, and must be reviewed by local IRBs at all participating field sites. Before a site may enroll patients in a specific study, the site's locally approved consent form must be re-reviewed and approved by the CDC IRB. The Data and Coordinating Center maintains a detailed tracking system to assure that required approvals are obtained. Approved protocols are re-approved both at CDC and at local sites on an annual basis. Documents related to human subjects protections (signed consent forms and IRB reports, for example) are reviewed as a part of each site monitoring visit. All on-going studies undergo periodic review by a three-person Data and Safety Monitor-

ing Board whose members are recognized experts in epidemiologic and laboratory science, clinical TB and HIV, and the conduct and analysis of clinical trials. Finally, because of the Consortium's relationships with commercial firms (and despite the general lack of commercial interest in TB clinical research), a formal policy on identification and management of potential conflicts of interest is also being developed.

ACTUAL AND EXPECTED EFFECTS

It is anticipated that the effects of the Consortium's work will be evident at multiple levels. First, TBTC research is expected to form the basis for future tuberculosis treatment and prevention recommendations. This is already the case with Study 22, which will influence the next joint tuberculosis treatment recommendations of CDC and the American Thoracic Society concerning both the use of new rifapentine-based regimens and the use of standard rifampin-based therapy. Study 23 will better define parameters for treatment of people with HIV-TB, as will Study 24 for patients whose tuberculosis is resistant to isoniazid or who cannot tolerate therapy with this agent. The Consortium's pharmacokinetic studies will help to define the role of therapeutic drug monitoring in treatment of tuberculosis, and the importance of interactions between anti-TB and anti-HIV medications. Future studies will define the appropriate role for short-course treatment of latent tuberculosis infection and the optimal use of rifapentine in TB therapy.

Second, the Consortium's studies indicate new means for strengthening routine TB program functions. For example, the experience of the TBTC in Study 22 has clarified the importance of counting doses of therapy, rather than relying on any estimation of the duration of therapy, in determining the adequacy of treatment. Involvement of local programs in the Consortium's program of research is expected to enhance performance at those sites. In addition, the Consortium has strengthened relationships between academic medical programs and tuberculosis control programs at many sites.

Third, the Consortium represents a tangible "public good" which has already been cited in meetings with pharmaceutical manufacturers as a means by which the public sector can help to diminish the discouragingly high costs of new drug development. A single Phase 3 clinical trial of a promising new anti-TB agent undertaken by the TBTC in support of a new drug application would represent a potential contribution of $15 million to $25 million to the development of that agent.[12] Such a contribution may help to encourage companies which have been reluctant so far to pursue development of new anti-TB medications. This potential will be needed: the alarming rates of multidrug-resistant tuberculosis being documented in numerous areas outside the US clearly signal a future requirement for such drugs. In this context, the Consortium illustrates the model for public, non-governmental, and commercial collaborations which will be needed to meet the needs of tuberculosis control in the coming decades.

Fourth, the Consortium intends also to contribute to the practice of clinical trials. For example, a new TBTC evaluation effort will describe the roles of central (CDC) and local institutional review boards in TBTC protocols. This effort defines a more efficient model for future conduct of trials both to strengthen human subjects protections and to improve the efficiency of the process by which new studies are approved and monitored.

CONCLUSION

The Tuberculosis Trials Consortium is a unique collaboration between the public and private sectors that draws upon the resources of academic medicine, organized public health at the federal and local levels, and the commercial sector. Although the TBTC is a CDC-funded extramural prevention research activity that is intended to be implemented in the private sector, its administration follows a model that allows for substantial CDC involvement as a partner in the work. This new type of public-private partnership is a cooperative model enlisting the best and most productive members of several disparate communities interested in tuberculosis control. Key elements of the collaboration include mutual respect, relative independence of the members, maintenance of a public health focus through continued CDC involvement, and a strong emphasis on continuous quantitative evaluation of performance and efficiency.

It is our hope that this type of collaboration can capitalize upon the strengths of both internal and external partners. While current tuberculosis therapies are efficacious, further research is needed not only to realize their full effectiveness and efficiency, but to develop new therapies that will be needed to address the growing challenge of multidrug-resistant TB.

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