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Assessment of global capacity to conduct tuberculosis drug development trials: do we have what it takes?

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SUMMARY

OBJECTIVE: To assess clinical trial sites and associated mycobacteriology laboratories for their capacity to conduct registration-standard tuberculosis (TB) drug trials and develop a database of assessed sites and laboratories.

SETTING: Assessments of clinical trial sites and associated mycobacteriology laboratories were conducted in 39 countries from 2006 to 2008.

DESIGN: Sites were interviewed using a set of questionnaires to assess the clinical site, pharmacy, data management, regulatory, ethics and importation requirements and mycobacteriology laboratory. Each site and laboratory was rated as able to conduct TB drug registration trials within 0–6 months, >6–12 months, >1–2 years and >2 years.

RESULTS: Eighty-four clinical trial sites and associated mycobacteriology laboratories in 39 countries were assessed. Of the clinical trial sites, 50% were judged capable of being ready within 6 months, 32.1% in 6–12 months and 14.3% in 1–2 years. Three sites would be ready in more than 2 years. Of the 72 mycobacteriology laboratories, 27.8% could be made ready within 6 months, 37.5% within 6–12 months and 27.8% within 1–2 years.

CONCLUSION: This survey indicates that developing adequate capacity to fully evaluate the compounds now in the clinical phases of development will require significant capacity-building efforts.

KEY WORDS: TB drug development; ICH GCP; GLP; mycobacteriology laboratory; registration standard

ALTHOUGH TUBERCULOSIS (TB) is a curable and preventable disease, it still kills approximately 1.7 million people every year, with an estimated 9.27 million new cases of active disease occurring annually.[1] The current first-line anti-tuberculosis regimens require a minimum of 6 months of therapy. Adherence to the long and complicated treatment course is challenging and is a major obstacle to the effective use of existing drugs.[2] As a result of inadequate treatment and poor adherence, drug resistance is becoming more common,[1,3] and fears of an epidemic with multidrug-resistant (MDR) or extensively drug-resistant (XDR) strains of TB are growing.[4]

There is a need for novel TB drugs and regimens that would shorten current treatment duration and/or allow more widely spaced intermittent treatment, improve the treatment of MDR- and XDR-TB and be safe for use in TB-HIV (human immunodeficiency virus) co-infected persons concurrently being treated for HIV infection.[5,6]

This decade has seen a revival of TB drug research and development, and there are now at least seven products in clinical development and the largest number of early-stage TB discovery projects in history.[6,7]

The drugs used today to treat TB were developed in the 1940s to 1960s, at a time when both the process and regulatory environment for developing new drugs differed significantly from today. One of the consequences of the expanding pipeline of TB drugs is a growing need for clinical trial sites capable of conducting TB drug trials to registration standards compliant with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) standards.[8,9] Given the dearth of TB drug development in recent decades, very few sites have direct experience with such trials.

To the best of our knowledge, no objective assessment of current clinical trial site capacity for the conduct of registration-standard GCP- and GLP-compliant TB drug trials has been performed. Such an assessment should help provide the necessary knowledge base and framework for building global clinical trial capacity, to the benefit of both clinical trial sites and sponsors of TB drug clinical trials. The TB Alliance commissioned an assessment of the capacity and readiness of clinical trial sites and their associated mycobacteriology and safety laboratories to

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conduct TB drug clinical studies in human subjects in accordance with the ICH GCP.[8,9]

METHODS

The services of three clinical research organizations (CROs) were contracted to conduct the assessments. Globally, 84 clinical trial sites and their associated mycobacteriology laboratories in 39 countries in Africa, Asia, Europe and the Americas were assessed.

The selection of clinical trial sites was based on sites having one or more of the following characteristics: expected to participate in the TB Alliance-Bayer global clinical development program for moxifloxacin, believed to have the potential to conduct early bactericidal activity (EBA) trials, known to have conducted past clinical studies in TB patients, and/or proposed to the TB Alliance by other interested stakeholders and having access to an adequate population of newly diagnosed, smear-positive TB patients.

Two internationally recognized microbiology experts with extensive *Mycobacterium tuberculosis* laboratory expertise were contracted as consultants to assist with the assessments of the mycobacteriology laboratories and to help ensure the quality of this key aspect of the assessments.*

The CROs collaborated with the TB Alliance to develop a set of clinical trial site evaluation questionnaires.† The questionnaires were based in part on a prototype previously developed by the European and Developing Countries Clinical Trials Partnership EU (EDCTP),‡ with input from the TB Alliance. The GLP laboratory assessors from the CROs, in collaboration with the two consultants, assisted with the development of the laboratory-specific questionnaire. These questionnaires were used during interviews with senior site and laboratory staff members. The topics covered in the questionnaires were:

1 the clinical trial site;
2 satellite clinical trial site (where relevant);
3 pharmacy facility;
4 data management infrastructure;
5 laboratory facilities;
6 regulatory authority, ethics committee and importation authority;
7 TB and HIV environment at the site.

The outcome of the assessments was documented and the information was used to rate each clinical trial site and laboratory as able to comply with GCP/GLP requirements for conducting TB drug registration trials, assuming a concerted capacity-building effort, in 0–6 months, >6–12 months, >1–2 years and >2 years.

The estimates for time to readiness are meant only as general guidelines to provide the TB Alliance, other sponsors, funders and interested parties, including the sites themselves, with a ballpark estimation for planning purposes. With the assistance of the senior and expert staff from the CROs, a model for rating the sites and laboratories in a consistent manner was developed. The ratings were estimated by the assessors evaluating the following considerations:

1 people: experience, training and number of staff on clinical trial site;
2 capacity: potential number of TB patients that the clinical trial site can accommodate;
3 patient population: adequacy of the patient population to meet the enrolment goals of TB trials.
4 process and procedures: presence and adequacy of standard operating procedures and processes.

The overall quality of the facilities and the equipment was also considered in the rating, including the availability of qualified health care professionals in the community and the time frame for recruiting new health professionals. The training of staff members was explored during the assessment. Qualified and experienced clinical research associates conducted the site assessments, while the laboratory assessments were conducted by GLP-laboratory auditors. Site and laboratory heads did a final review of all reports for factual correctness and accuracy from their perspectives of the readiness rating.

All data from these assessments are stored in a single database, designed to contain results from site assessments and supporting documents related to the various aspects evaluated. Access is provided via a user-friendly search engine and or country/category listing. The database can be accessed via the link (http://siteassessment.tballiance.org/). It is envisioned that users of the database will likely include investigators, potential sponsors of TB drug trials, potential donors exploring capacity-building opportunities, public health workers, academic institutions, TB advocates and activists.

RESULTS

The assessments were conducted at 84 clinical trial sites in 39 countries from five continents and in 23 different languages from May 2006 to December 2008. The geographical distribution of the 84 clinical trial sites by continent is as follows: Africa (n = 30) Asia (n = 22), South America (n = 13), North America (n = 7), Europe (n= 3) and Eastern Europe (n = 9).§

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†The full set of questionnaires is available at ftp://siteassessment.tballiance.org/questionnaires.

‡Personal communication, September 2007, M Makanga, EDCTP, Cape Town, South Africa.

§A list of the 84 sites is available from the authors.

Table 1 Clinical trial sites: number of assessed clinical sites by geographical region and expected time required to build capacity for participation in a Phase II and III TB drug registration trial

	Time required to build capacity			
Region	<6 months	6–12 months	1–2 years	>2 years
Africa (n = 30)	15	10	4	1
Asia (n = 22)	10	9	2	1
South America (n = 13)	4	5	3	1
North America (n = 7)	7	0	0	0
Europe (n = 3)	2	0	1	0
Eastern Europe (n = 9)	4	3	2	0
Total (n = 84)	42	27	12	3

Table 2 Mycobacteriology laboratories: number of assessed laboratories by geographical region and expected time required to build capacity for participation in a Phase II and III TB drug registration trial

	Time required to build capacity			
Region	<6 months	6–12 months	1–2 years	>2 years
Africa (n = 22)	6	7	6	3
Asia (n = 22)	7	10	4	1
South America (n = 11)	4	4	2	1
North America (n = 7)	1	6	0	0
Europe (n = 3)	2	0	1	0
Eastern Europe (n = 7)*	0	0	7	0
Total (n = 72)	20	27	20	5

* Two laboratories in Russia still to be assessed.

Although 84 clinical trial sites were assessed, only 72 associated mycobacteriology laboratories were evaluated, as a number of clinical sites shared the same mycobacteriology laboratory.

The results of the assessments according to the anticipated time needed to build adequate capacity at each site by global distribution are reported in Table 1 (clinical sites) and Table 2 (associated mycobacteriology laboratories).

DISCUSSION

The assessment questionnaires consisted of six subparts and approximately 80 pages. The same set of questions was used at all sites to help maximize the consistency and integrity of information gathered. The assessment reports reflect only the information within the scope of the evaluation questionnaires and report only information about the facilities and capacities of each clinical trial site and associated laboratory at the time each assessment was conducted. The reports also captured suggestions for capacity building and recommendations from the assessors based on the requirements for registration-standard GCP/GLP-compliant clinical trials. Suggestions for capacity building, and estimations of the expected timeframe given concerted effort and the required resources for fulfilling these recommendations were made. Each site and laboratory head did a final review of the readiness rating of their sites, and in all instances agreed with the rating of their site and laboratory, a result that supports the validity and robustness of these highly detailed evaluations.

The assessors rated each clinical trial site and mycobacteriology laboratory in terms of its overall readiness to participate in a registration-standard GCP/GLP-compliant, Phase II/III TB drug trial and not the readiness to conduct any specific protocol or clinical trial. These assessments do not replace the need for protocol-specific, pre-study assessments by sponsors considering the conduct of a specific clinical study.

The sites assessed included 15 of the 22 World Health Organization designated TB high-burden countries (no sites were assessed in Afghanistan, Bangladesh, Cambodia, Democratic Republic of the Congo, Myanmar, Pakistan and Zimbabwe). This study found that, overall, clinical trial sites are closer to being ready for participation in Phase II/III TB drug registration trials than their associated mycobacteriology laboratories. Of the 84 clinical trial sites, 42 (50%) were rated as having the potential to be ready within 6 months and another 27 (32.1%) in 6–12 months, given a focused and well-resourced effort to build the necessary capacity. Only 12 clinical trial sites were rated as requiring 1–2 years for capacity building, and three sites as requiring more than 2 years. Many of the sites (47/84) will require GCP training.

Of the 72 mycobacteriology laboratories assessed, 20 (27.8%) were rated to have the potential to be ready in 6 months, another 27 (37.5%) within 12 months, another 20 (27.8%) within 1–2 years and 5 more than 2 years given the appropriate, focused, capacity-enhancing efforts. Considering a clinical site and the associated mycobacteriology laboratory as a unit reveals that 51 (62.2%) of the trial sites have the potential to be ready in 12 months (Table 3). Only 31 (43.1%) of the mycobacteriology laboratories were accredited (Table 4); additional major deficiencies identified were the lack of quality assurance systems

Table 3 Number of assessed sites (clinical site and associated laboratory) by geographical region and estimated time required to be ready for participation in a Phase II and III TB drug registration trial

Region	<6 months	6–12 months	1–2 years	>2 years
Africa (n = 30)	6	11	9	4
Asia (n = 22)	7	10	4	1
South America (n = 13)	2	6	4	1
North America (n = 7)	1	6	0	0
Europe (n = 3)	2	0	1	0
Eastern Europe (n = 7)*	0	0	7	0
Total (n = 82)	18	33	25	6

* Two laboratories in Russia still to be assessed.

Table 4 Number of laboratories with accreditation and/or a quality assurance system and/or a quality manual in place, by geographical region

Region	Accreditation	Quality assurance system	Quality manual
Africa (n = 22)	4	7	7
Asia (n = 22)	13	17	15
South America (n = 11)	2	4	5
North America (n = 7)	7	7	7
Europe (n = 3)	2	2	2
Eastern Europe (n = 7)*	3	2	1
Total (n = 72)	31	39	37

*Two laboratories in Russia still to be assessed.

Table 7 Number of assessed laboratories with experience in supporting EBA studies and their capacity to perform quantitative sputum culture, by geographical region

Region	Experience with EBA	Quantitative sputum culture
Africa (n = 22)	3	3
Asia (n = 22)	4	4
South America (n = 11)	2	2
North America (n = 7)	0	0
Europe (n = 3)	1	1
Eastern Europe (n = 7)*	3	3
Total (n = 72)	13	13

*Two laboratories in Russia still to be assessed.
EBA = early bactericidal activity.

and/or quality assurance manuals at most sites. Furthermore, the lack of availability of standard operating procedures (SOPs) within many of the laboratories is a concern; 58/72 laboratories had at least some SOPs in place (Table 5), but these were not always comprehensive or regularly reviewed.

Most of the mycobacteriology laboratories (58/72) performed TB drug susceptibility testing on *M. tuberculosis* cultures, and just more than half of the laboratories could perform TB strain typing (Table 6). EBA studies measuring the EBA of a new agent over the first 2 days of treatment, or over a more extended duration of monotherapy, are an accepted method for investigating the bacterial killing effect of a new TB drug.[10] Only 13 of the evaluated mycobacteriology laboratories were determined to potentially have the capacity and experience to conduct EBA studies (Table 7). Two of these are located in South Africa, one in Uganda, one in Spain, two in Moldova, one in Russia, one in Brazil, one in Peru, one in Hong Kong, one in Thailand, one in Taiwan and one in India. EBA studies are likely to be an integral part of the development of new TB drugs, and there will be an increased need for clinical trial sites and associated laboratories capable of performing these specialised studies, including quantitative sputum culture, in coming years.

Table 5 Number of assessed laboratories with SOPs in place by geographical region and whether SOPs are determined to be comprehensive, are implemented and are regularly reviewed

Region	SOPs available	SOPs comprehensive	SOPs implemented	SOPs regularly reviewed
Africa (n = 22)	20	12	19	12
Asia (n = 22)	21	18	21	15
South America (n = 11)	5	3	7	5
North America (n = 7)	7	7	7	7
Europe (n = 3)	2	2	2	2
Eastern Europe (n = 7)*	3	2	1	2
Total (n = 72)	58	44	57	43

*Two laboratories in Russia still to be assessed.
SOP = standard operating procedure.

Table 6 Number of assessed laboratories capable of performing drug susceptibility testing and TB strain typing, by geographical region

Region	Drug susceptibility testing	TB strain typing
Africa (n = 22)	17	13
Asia (n = 22)	17	9
South America (n = 11)	8	6
North America (n = 7)	7	2
Europe (n = 3)	3	3
Eastern Europe (n = 7)*	7	5
Total (n = 72)	59	38

*Two laboratories in Russia still to be assessed.
TB = tuberculosis.

There are currently at least seven products in clinical development: two products in Phase I, three products in Phase II and two products in Phase III trials.[6,7] In addition, various groups are either already investigating or planning in the near future to investigate high-dose rifamycins for their potential to shorten TB treatment. Given the high attrition rate for compounds during clinical drug development across the pharmaceutical industry, we have assumed that, of the five products in Phase I and II trials, only three will advance further, to later stage clinical trials, i.e., one product in Phase I will move to a proof of concept/dose-ranging study and then a 2-month intensive phase treatment study, and two products in Phase II will move to pivotal Phase III clinical trials. These studies can only be conducted efficiently at sites that have access to high numbers of sputum smear-positive patients and, for an indication of drug-susceptible TB, demonstrate a low percentage of multidrug-resistant strains. High-quality sites and laboratories with large patient numbers will be in great demand to meet the enrolment targets of even the current set of compounds in clinical development.[11] There will be simultaneous demand in the future for sites with access to patients with MDR- and XDR-TB, as parallel programs will likely be conducted to develop new drugs for treatment of drug-susceptible and MDR- and XDR-TB. The workload at a site and laboratory will be such that most sites will be unable to conduct more than one trial at a time, be it a Phase II or a Phase III trial.

It is foreseen that large in-country studies will be required by many countries for registration of a new regimen; others may require Phase IV studies specifically designed for the individual country's National TB Program to gain experience with the new regimen. The protocol and design of such studies should be of a high standard to ensure the integrity of the data generated and not jeopardise or discredit the data from the pivotal registration studies. These studies should have a scientifically sound protocol and Ethics Committee approval.

The need to build research and infrastructure capacity and the infrastructure needed to meet these demands was recently highlighted by Schluger et al.[11] The TB Trials Consortium (TBTC), Centers for Disease Control and Prevention,[12,13] and the International Union Against Tuberculosis and Lung Disease have been active in developing clinical trial sites in Africa, the Americas, Asia and Europe. The EDCTP has recently pledged €600 million over 5 years to establish the capacity for and conduct of high-quality clinical trials throughout Africa.[14] These capacity-building initiatives and the development of resources are important steps forward, but are unlikely to be adequate to meet the need in coming years for clinical trial sites capable of conducting TB drug registration trials compliant with ICH GCP and GLP standards.[11] The cost associated with establishing the necessary resources and infrastructure is estimated to be US$1–2 million per site per year, and the cost of conducting late-stage Phase II and III TB drug registration trials is US$4000–12 000 per trial patient, depending primarily on location and trial design.[11]

CONCLUSION

In the foreseeable future, the development of new and novel TB drugs and regimens could be impeded by a lack of adequate clinical trial capacity, unless concerted, appropriately resourced efforts are made to build the capacity to meet the expected need. This survey indicates that developing adequate capacity to fully evaluate even those compounds now in the clinical phases of development will require significant capacity building efforts over the next few years at a number of clinical trial sites and mycobacteriology laboratories throughout the world, particularly in high-burden countries.

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RÉSUMÉ

OBJECTIF : Evaluer la capacité des sites d'essais cliniques et des laboratoires de mycobactériologie associés de mener des essais de médicaments pour la tuberculose (TB) avec enregistrement standard, et développer une base de données des sites et des laboratoires.

CONTEXTE : Au cours des années 2006–2008, on a mené

dans 39 pays des évaluations de sites d'essais cliniques et des laboratoires de mycobactériologie associés.
SCHÉMA : On a mené des entretiens dans les sites au moyen d'un ensemble de questionnaires pour évaluer le site clinique, la pharmacie, le traitement des données, les exigences réglementaires éthiques et d'importation, ainsi que le laboratoire de mycobactériologie. On a coté chaque site et laboratoire comme apte à mener des essais d'enregistrement des médicaments TB dans les 0 à 6 mois, >6 à 12 mois, >1 à 2 ans et >2 ans.
RÉSULTATS : On a évalué 84 sites d'essais cliniques et des laboratoires de mycobactériologie associés dans 39 pays. Parmi les sites d'essais cliniques, 50% ont été considérés comme aptes à être prêts dans les 6 mois, 32,1% dans les 6 à 12 mois et 14,3% d'ici 1 à 2 ans ; trois sites ne seraient prêts que dans plus de 2 ans. Sur les 72 laboratoires de mycobactériologie, 27,8% pourraient être prêts dans les 6 mois, 37,5% dans les 6 à 12 mois et 27,8% d'ici 1 à 2 ans.
CONCLUSION : Cette enquête indique que des efforts significatifs de développement des compétences sont nécessaires pour arriver à une capacité adéquate d'évaluation complète des produits actuellement dans les phases cliniques de développement.

RESUMEN

MARCO DE REFERENCIA : Evaluación entre el 2006 y el 2008 de los centros de ensayos clínicos y los laboratorios asociados de micobacteriología en 39 países.
OBJETIVO : Evaluar la capacidad de los centros de ensayos clínicos y los laboratorios asociados de micobacteriología de realizar ensayos farmacológicos de registro con los medicamentos antituberculosos y construir una base de datos con la información de los centros y laboratorios evaluados.
MÉTODOS : Se realizaron entrevistas en los centros con una serie de cuestionarios a fin de evaluar el centro clínico, la farmacia, el manejo de los datos, las regulaciones reglamentarias en materia de ética y de importación y el laboratorio de micobacteriología. Se calificó cada centro y cada laboratorio según el lapso en el cual alcanzaría la capacidad de realizar ensayos de registro de los medicamentos antituberculosos en : de 0 a 6 meses, entre 6 meses y 12 meses, entre 1 año y 2 años y más de 2 años.
RESULTADOS : Se evaluaron 84 centros de ensayos clínicos y laboratorios asociados de micobacteriología en 39 países. De los centros de ensayos clínicos se juzgó que el 50% estaría preparado en 6 meses, el 32,1% entre 6 y 12 meses y el 14,3% entre 1 y 2 años. Tres centros necesitarían más de 2 años. De los 72 laboratorios de micobacteriología, el 27,8% podría estar operativo en 6 meses, el 37,5% entre 6 y 12 meses y el 27,8% entre 1 y 2 años.
CONCLUSIÓN : Los resultados de la encuesta ponen de manifiesto los esfuerzos considerables que se precisan en materia de creación de la capacidad suficiente para la evaluación completa de los compuestos antituberculosos que se encuentran actualmente en fase clínica de desarrollo.