Preface

The Global Plan to Stop TB 2006-2015 [1]—and its companion piece, the Global MDR-TB and XDR-TB Response Plan 2007-2008 [2]—calls for integration into existing tuberculosis control efforts and massive scale-up of programmatic management of drug-resistant tuberculosis in resource-limited settings. In light of major gaps in the evidence regarding how best to execute this campaign, the MDR-TB Working Group of the Stop TB Partnership endorsed in 2007 an updated *research agenda* [3] that called for, among other efforts, multi-center clinical trials to improve the treatment of (multi)drug-resistant tuberculosis.

This goal overlapped with that of several other groups (including the New Drugs Working Group of the Stop TB Partnership and the Tuberculosis Trials Consortium). To unite these efforts and advance the clinical-trials agenda, a brainstorming session was organized by the Research Subgroup of the MDR-TB Working Group and the IUATLD Clinical Trial Division in Cape Town, S. Africa in November 2007. The Objectives were (i) to identify mechanisms for coordination of, and funding for, such clinical trials, (ii) to identify needs of network to pursue trials and (iii) to develop plan for pursuing mechanisms and meeting needs. This session included approximately 75 key players in MDR research and treatment, drug development, advocacy and funding. Attendees highlighted the urgent need to optimize treatment for drug-resistant tuberculosis through the development of appropriate randomized-controlled clinical trials and recommended further action to delineate the strategy and funding required to advance this effort.

Collectively, a decision was made to: 1) hold an international workshop in mid-2008 to refine ideas for a detailed, prioritized and budgeted plan for clinical trials of DR-TB treatment; and 2) to produce a document—dubbed alternatively a white paper, blueprint, or green paper—that reviews the obstacles to development of clinical trials for drug-resistant TB and develops an initial plan for overcoming these obstacles. As the idea for this document arose in a meeting held in South Africa, the Rainbow Nation, it was ultimately named the **"**Rainbow Document,**"** and is presented below.

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Glossary of Abbreviations

BMRC	British Medical Research Council
DOT	directly observed therapy
DMID	Division of Microbiology and Infectious Diseases
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
GCP	Good Clinical Practice
GLC	Green Light Committee for Access to Second-Line Anti-Tuberculosis Drugs
IND	investigational new drug
INH	isoniazid
IT	information technology
ITR	individualized treatment regimen
IUATLD	International Union Against Tuberculosis and Lung Disease
LTBI	latent tuberculosis infection
MDR-TB	multidrug-resistant tuberculosis
NIAID	National Institute of Allergy and Infectious Diseases
NTP	national tuberculosis control programs
OBR	optimized background regimen
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic(s)
RESIST-TB	Research Excellence to Stop TB Resistance
RMP	rifampicin
SOP	standard operating procedure
SSCC	serial sputum colony counting
STR	standardized treatment regimen
TBTC	Tuberculosis Trials Consortium
TDR	Special Programme for Research and Training in Tropical Diseases
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Summary

Nearly half a million new cases and an additional 1–1.5 million prevalent cases of drug-resistant tuberculosis (DR-TB) occurred globally in 2006. The disease is transmissible and deadly, and represents a public health emergency. However, there are substantial gaps in our understanding of how to best treat and prevent DR-TB. To address this problem, concerned patients, physicians, research scientists and other stakeholders met in Cambridge, Massachusetts in June 2008 and formed an organization dedicated to combating this epidemic. The Mission of the *Research Excellence to Stop TB Resistance (RESIST-TB) Movement* is to promote and conduct research to cure and prevent DR-TB throughout the world.

Section I of this document outlines the scope of the DR-TB problem, reviews the need for clinical trials to develop new tools to combat DR-TB, identifies the highest priority research needs, and outlines the obstacles to performing such trials.

Section II discusses specific site requirements for DR-TB clinical trials, including subject availability, laboratory support, access to drugs, Good Clinical Practice (GCP) skills, and specimen handling and data management capacity. In addition, priority research questions are examined in detail, including treatment duration, intensity, and monitoring schedules. The need to demonstrate effective strategies for special populations, such as children, HIV-infected persons, and pregnant women, is emphasized.

Section III summarizes the progress of RESIST-TB to date: the publication of the Cambridge Declaration, establishment of the Organization, and the ongoing development of its strategic plan, which represents a roadmap for the organization going forward. An administrative structure has been established to support these efforts and initial financial support has been procured; a website has been established (http://ghdonline.org/drtb-trials/) and committees of dedicated volunteers have begun to work towards improved DR-TB treatment and prevention. We invite you to join us in this effort.

I. Introduction

I.A. Overview

Drug-resistant tuberculosis (DR-TB), especially multidrug-resistant TB (MDR-TB; i.e., resistance to at least rifampicin [RMP] and isoniazid [INH]) has become an increasing threat to tuberculosis control in the world today: nearly half a million new cases and an additional 1–1.5 million prevalent cases of MDR-TB were estimated to have occurred globally in 2006. [4] In addition, extensively drug-resistant TB (XDR-TB) has been reported in 49 countries, most notably in high-HIV prevalence settings, raising the specter of TB epidemics with severely restricted treatment options that could jeopardize the progress made in global TB control. This has led to a revived interest in strategies to control DR-TB, especially in settings of high HIV prevalence. Over the last decade, MDR-TB treatment programs have expanded dramatically: 40 programs in resource-limited settings are managing treatment for nearly 30,000 patients. These programs receive quality-assured second-line drugs through a pooled-procurement mechanism supported by the Green Light Committee for Access to Second-Line Anti-Tuberculosis Drugs (GLC; see http://www.who.int/tb/dots/dotsplus/management_old/en/index.html) with support from the Global Fund to fight AIDS, Tuberculosis and Malaria and UNITAID. The requirements for approval by the GLC have markedly raised standards for MDR-TB treatment in resource-constrained settings. Some of these treatment programs have been operating for nearly 10 years and have developed sophisticated means of delivering supervised ambulatory treatment, guided by drug susceptibility testing (DST)—or drug resistance surveys—and other patient-specific characteristics. Although few of these sites have participated in clinical trials, their current standard of care could be raised to that certifiable as "good clinical practice" (GCP) with limited additional investment.

As a sign of redoubled interest, a clinical trial design has recently been developed that allows individualization of regimens while evaluating rigorously the safety and activity of a new drug. According to this design, implemented in trials of treatment of drug-resistant HIV infection and now in trials of DR-TB treatment, patients receive regimens tailored to DST results and individual characteristics. Patients are randomized to receive either the new drug in addition to the optimized background regimen (OBR), or the OBR alone. As long as randomization is successful in distributing key potential confounding factors equally between study arms, this methodology allows inclusion of patients heterogeneous in many characteristics: prior drug exposure, drug resistance profile, geography, ethnicity, and disease stage. A similar comparative trial design has been used successfully for the pivotal trials showing superiority of the last four antiretroviral drugs approved in the United States (enfuvirtide, tipranavir, darunavir, and maraviroc). [5]

There are several classes of anti-tuberculosis drugs in early clinical trials and more in preclinical development. [6] Several agents, already on market for other indications, have been used off-label for highly drug-resistant TB in countries with established market economies, and could be used for MDR-TB treatment in resource-constrained settings as well. In addition, new drugs with novel mechanisms of action are presently in development. [7] Some also have a narrow spectrum of activity, specific only to *M. tuberculosis*. Therefore, their activity is not limited by the presence

of resistance to currently available drugs and resistance is unlikely to develop through use for non-TB indications, which makes them good candidates for the treatment of DR-TB.

I.B. Why do we need to undertake clinical trials for MDR-TB?

DR-TB is a growing global public health problem. Drug-resistant isolates have been identified in nearly all countries surveyed since 1994 and nearly 500,000 cases of MDR-TB are estimated to emerge yearly worldwide. XDR-TB has been found in every region of the world and detected in 10% of MDR-TB isolates collected through a survey of the supranational laboratory network. [8] The MDR-TB epidemic is burgeoning in some settings such as the former Soviet Union and certain provinces in China and India. In addition, evidence of overlapping of the HIV and MDR-TB epidemics in some populations threatens control of these two epidemics.

MDR-TB treatment programs have rapidly expanded in recent years. Since 2000, the GLC has approved treatment of MDR-TB in more than 30,000 patients in 67 projects in 52 countries. It is estimated that approximately three times that number, or 90,000 patients, are receiving MDR-TB treatment outside the GLC mechanism. In 2006 alone, more than 20,000 patients with MDR-TB were reported to the World Health Organization (WHO) by more than 60 countries. The increasing number of MDR-TB treatment sites provides a setting in which trials could be implemented. The MDR-TB Working Group of the Stop TB Partnership established the goal of treating nearly 1.6 million MDR-TB patients by 2015, an ambitious target that can be achieved only with shorter and simpler treatment regimens.

I.B.1. Treating MDR-TB is presently difficult, expensive, time-consuming and requires an appropriate infrastructure. According to WHO recommendations, treatment of MDR-TB should include at least 4 drugs with almost certain effectiveness, and be based on DST and/or patient drug history. [9] An injectable agent (aminoglycoside or capreomycin) must be included among these drugs, for a minimum duration of 6 months. In some cases, more than 4 drugs should be started, i.e., when the susceptibility pattern is unknown, if an agent's effectiveness is questionable, or in clinically serious cases such as those with extensive, bilateral pulmonary disease. The drugs should be administered 6 days a week using directly observed therapy (DOT) throughout treatment, that should last at least 18 months beyond culture conversion, making it a very long undertaking (usually 24 months).

In the absence of any controlled trial comparing different regimens, the number and type of drugs required to treat a patient with MDR-TB is a matter of a controversy, even though specialists agree on basic principles, such as the minimum number of drugs to use and the inclusion of injectable agents. In contrast with evidence-based recommendations for treatment of drug-sensitive TB, however, recommendations for MDR-TB treatment are mainly based on expert opinion and observational studies: personal experience has largely become the basis for case management. Experts may differ in their approach to patient management according to their own experiences, which is not exempt from bias related to specific circumstances. As a result, treatment regimens vary substantially, from standardized 4-5-drug regimens given for less than 18 months, to individualized 24-month regimens utilizing more than 5 drugs. The efficacy of recommended MDR-TB treatment regimens may vary according to background sensitivity patterns and the drugs included in the combination. Drug interactions have been poorly documented to date. In addition, most of the drugs have substantial toxicity and potential for a

number of adverse events, contributing to early interruption of treatment. This can lead to further failure or relapse, with serious consequences both at the individual and the community levels, in terms of patient survival and the spread and amplification of resistance.

Treatment outcomes of patients with MDR-TB remain suboptimal. The long duration and toxicity of drugs lead to relatively high default rates (around 15% in a cohort of patients from 9 GLC-approved sites from 2000-2003). [10] Treatment success is slightly above 60% in GLC-approved sites. A review of earlier cohorts, largely HIV-uninfected, reported failure rates between 0% and 32% (crude weighted mean: 9.48%) and relapse rates between 0% and 17% (crude weighted mean: 2.43%). [11] Mortality rates are even higher in people living with HIV, varying from 5% to 20%. In addition to efforts aimed at improving the delivery of care, it is imperative to improve outcomes of MDR-TB treatment, either through the optimized use of currently available drugs or the introduction of new drugs.

I.B.2. Laboratory capacity is limited. It is generally agreed that DST should be used to guide therapy. This requires, however, the availability of suitable microbiology laboratories capable of performing sputum cultures and DST under full quality-controlled conditions. In fact, especially in low-income countries, such suitable microbiological laboratories for programmatic management of MDR-TB are usually sparse and limited to a few high-quality care centers, such as university teaching hospitals or research centers. Conventional DST on solid media has proven highly reliable for the detection of resistance to INH and RMP, but is hampered by the long delay in obtaining results (usually more than 2 months). In addition, it has poor reliability for the detection of resistance to some first- and second-line drugs. Alternative methods are increasingly used, based on liquid media or nucleic amplification, but these require sophisticated and expensive equipment demanding extensive maintenance efforts. These methods are very promising, as demonstrated in a recent study in South Africa in which a commercially available molecular line-probe assay gave interpretable results within 1-2 days in 97% of 536 consecutive smear-positive specimens. [12] Efforts to enhance operational feasibility of sending samples for testing through these novel methods in reference labs are also underway.

I.B.3. The parameters for effective use of standardized MDR-TB treatment are not well-defined. The present GLC recommendations for treatment of MDR-TB rely on two different strategies: (1) the individualized treatment regimen (ITR), which requires DST to be performed for each patient to be treated, and (2) the standardized treatment regimen (STR), which is an empiric alternative based on local resistance patterns determined from well-performed population-based anti-tuberculosis drug resistance surveillance. The ITR strategy allows systematic monitoring of patients' response to treatment and permits adjustments of time/duration of treatment according to patients' own DST results. It is usually presented as the *standard of care* for the treatment of MDR-TB, and is particularly recommended in areas with wide heterogeneity of drug-resistance patterns and extensive use of second-line drugs. However, this strategy is highly demanding in terms of resources and requires the availability of quality-assured laboratories capable of undertaking DST, as well as the presence of specialist physicians to prescribe regimens. It should be noted, however, that while DST for most first-line drugs is highly reliable, there are still no acceptable standards for the use of DST for several second-line drugs. Conversely, STR is usually based on the most common DST profile of the prevalent MDR-TB strains in a given region or country, and is recommended in areas with homogeneous drug resistance patterns and limited or no use of second-line drugs. As this strategy is much less

demanding in terms of tests and monitoring, it simplifies patient management and is less dependent on highly technical laboratories. It also allows simplified drug ordering and, through reduced costs, permits treatment of a greater number of patients. However, STR does not adapt to individual patients' response to treatment. This may decrease its effectiveness in particular conditions, and may contribute to additional acquisition of resistance. In many places, hybrid approaches are used in which DST is performed for a subset of drugs (e.g., first-line) and regimens are adjusted accordingly, while the use of other drugs is uniform, or is dependent on treatment history.

In the absence of controlled trials to validate specific recommendations for the treatment of MDR-TB, individual experts' experience and opinions prevail, and differ significantly. In any case, no prospective comparison of different strategies has been conducted in any setting. Therefore, we conclude that improvements are needed that will result in MDR-TB treatments that have improved effectiveness, less toxicity, shorter duration, lower cost, and more simplified delivery.

I.C. Priorities for randomized controlled trials

It is therefore urgent to undertake clinical studies aimed at identifying optimal regimens of existing or new drugs for the treatment of MDR-TB. These studies need to determine the best combinations of drugs and clarify the role of new drugs within the armamentarium for MDR-TB. Importantly, these studies need to be conducted in a range of populations showing various background resistance patterns, and should consider taking into account variables such as age, extent of disease, cavitation, and concomitant disease. The possible association of HIV with MDR-TB [4] and XDR-TB indicates the importance of taking HIV infection into account when conducting such trials and considering the potential interactions between the various MDR-TB drugs and antiretrovirals.

Numerous clinical trials are needed to assess the effectiveness of standardized or individualized MDR-TB regimens, as well as to evaluate the efficacy of new candidate drugs. The critical areas of investigation are the optimal duration and composition of the "intensive" phase, shortening treatment duration, decreasing the toxicity of drugs, drug-drug interactions, and reducing secondary spread of DR-TB. On a programmatic scale, it is essential to determine how to effectively deliver care and improve patient adherence to treatment. [13] Strategies developed to improve patient adherence to treatment of pan-susceptible TB or HIV might be suitably adapted to the case of MDR-TB.

I.D. Obstacles to implementing MDR-TB clinical trials

The lack of large-scale trials of MDR-TB treatment is the legacy of both outdated perceptions and very real and significant study design challenges. Historically, MDR-TB was perceived to be of little epidemiologic significance, an epiphenomenon of TB that could be avoided by better treatment. However, the dramatic increases in MDR-TB notification and the recent emergence of XDR-TB have clearly established the importance of MDR-TB and made clear that more needs to be done than simply improve management of drug-susceptible TB disease.

The heterogeneity of MDR-TB disease has also been regarded as an obstacle to clinical trials. There are considerable variations in resistance patterns of mycobacterial isolates, prior exposures to anti-tuberculosis drugs, and clinical manifestations of the disease both between and within different clinical settings. Thus, the definition of the target population for study and determination of eligibility criteria have been regarded as highly problematic, impeding the enrollment of adequate numbers of sufficiently homogeneous patients to achieve adequately powered studies. As noted above, the OBR methodology provides a means of conducting trials in spite of this heterogeneity. Moreover, allowing heterogeneity in trials provides significant advantages for the enrollment of participants and the generalizability of results.

The difficulty of identifying eligible patients in areas where certified GCP- and GLC-compliant infrastructures exist has also been considered a barrier to conducting MDR-TB trials. In general, TB trial capacity decreased after the long and productive era of British Medical Research Council (BMRC) trials, and relatively few TB trials have been conducted in the subsequent decades. Only recently has TB clinical research revived, with trials of shorter treatment of TB and the expansion of trial consortia conducting multicenter studies for the improvement of TB treatment (see Part III). Moreover, the emergence of dozens of programs meeting GLC criteria for delivering treatment for MDR-TB has expanded potential trial site capacity.

A major barrier to DR-TB clinical trials has been the complexity of MDR-TB interventions to study. There is large variability in the number and type of drugs utilized and in the duration of therapy. Thus, designing studies in which it would be possible to conclude that a particular intervention had succeeded has been perceived as very difficult. Consequently, multiple studies will be required. Through this effort, we have identified the three top-priority studies that could have immediate implications for program policy and inform future research.

Lastly, the argument that the effort to evaluate new drugs for MDR-TB would divert scarce resources from the development of shorter regimens for drug-susceptible tuberculosis has been invoked. However, clinical trials of new drugs for DR-TB treatment can enhance and accelerate drug development efforts. In fact, it is important that new compounds be evaluated in parallel for pan-susceptible as well as for drug-resistant TB to ensure their optimal use in treatment for both types of disease. As with HIV, clinical trials in patients with drug-resistant disease may even provide a quicker and less expensive path to licensure than trials for treatment of drug-susceptible disease.

II. What do we need to know to conduct clinical trials for MDR-TB?

II.A. Basic site requirements for an MDR-TB clinical trial

II.A.1. Subject availability. Regardless of study design, there are certain minimal requirements for a site to be able to participate in clinical trials that would advance our understanding of MDR-TB treatment. First, of course, is the existence of substantial numbers of patients with MDR-TB. Since eligible patients are only a part of total patient volume in a site, and those who consent to participate are an even smaller number, there has to be a substantial volume. Sites that can enroll only small numbers of subjects in a one-year period would be difficult to include in a network, because it would not be possible to control for site-specific factors in the analysis of the results. As a general rule of thumb, the eligible patient population should be at least twice the target enrollment number, since general experience shows that clinical trials rarely enroll as many as 50% of eligible subjects.

Although site recruitment capacity could be increased by extending enrollment, it would be preferable to recruit patients over a shorter period to avoid unnecessary delay in reaching trial conclusions. This is particularly important since TB trials with surrogate endpoints are not currently feasible, so clinical endpoints will need to be used, necessitating longer follow-up. It is important to make all efforts to ensure prompt completion of enrollment in MDR-TB studies, so that answers to these critical questions can be obtained as soon as possible.

Another factor in clinical trial selection is the ability to provide proper and complete patient follow-up. Sites that are referral centers for MDR-TB from dispersed catchment areas will need more resources than sites enrolling from local residents in order to complete clinical follow-up, which is essential for ensuring the validity of study results.

II.A.2. Laboratory support. In order to participate in clinical trials, laboratories at study sites must be able to identify MDR-TB in a timely manner and with reliable accuracy. This is also important since shipping MDR-TB isolates presents technical and administrative challenges. Thus, sites need to be able to perform culture and susceptibility testing using standard methods. While it is possible that all sites would not need to use the same methodology, failure to do so will increase variability and therefore sample size and trial cost, so uniformity in lab methods across sites is preferred. Study site laboratories must also participate in internal and external quality control programs on an ongoing basis to ensure that culture and susceptibility testing results are reliable. Availability of rapid diagnostic tests for MDR-TB (e.g., polymerase chain reaction (PCR)-based methods for rifamycin resistance) will greatly facilitate identification of eligible study subjects.

II.A.3. Second-line drugs. Since anticipated trial designs include the use of OBRs in at least one trial arm, sites must ensure the availability of the drugs indicated by *in vitro* DST, particularly second-line drugs. Even studies that assess the value of individualized regimens would require such capacity at all sites. In practice, most sites wishing to participate in clinical trials of MDR-TB will need GLC approval to guarantee access to quality-assured second line drugs.

II.A.4. Good Clinical Practice skills. Conformity with international clinical trial standards is required. This includes: human subjects training and review, use of investigational agents (including research pharmacy skills), source documentation, record keeping, data quality assurance, and patient follow-up. This capability is usually demonstrated by experience in previous clinical trials with satisfactory performance on real-time trial audits by independent outside monitors. For sites that do not have this experience, special GCP training is available for physician, nursing, data management and pharmacy staff. Such training can enable these sites to become eligible to participate in clinical trials.

In addition, sites that already have demonstrable trials capacity should also be supported before and during trials to maintain this capacity through training (e.g., refresher GCP training) and ongoing monitoring of performance.

II.A.5. Specimen handling expertise. Clinical trials require obtaining clinical specimens for analysis, either at local or central laboratories. Such specimens can be expected to include at a minimum isolates of *M. tuberculosis* and samples of patient serum and urine. Special care must be exercised in obtaining, storing and shipping such specimens. Careful labeling of specimens is essential, as is refrigerated storage. Thus, the site needs to have clinical personnel that have been specially trained in collecting, labeling, and aliquoting specimens. Laboratories must be able to document that they have properly processed and stored trial samples; refrigeration must be maintained and continuous refrigeration documented with an appropriate uninterrupted (and backup) power supply system in place. Staff need to be trained in the requirements for packaging and shipping clinical specimens. Such training will require knowledge of both hazardous materials regulations and local laws regarding the shipping of patient specimens. Moreover, the host country must permit shipment of live *M. tuberculosis* isolates.

II.A.6. Data management capability. Several methods are available for transmission of study data to a study data management and analysis center, but there are several features that all systems have in common. First, data must be independently verifiable by outside auditors. Second, data transmission, by mail, fax, or the internet, must be secure and reliable, with backup systems to ensure that data are not lost due to technical failures of transmission. The most desirable system is to use electronic data entry via the internet, with local backup, immediate response to data queries, and Information Technology (IT) support that can be accomplished in real time via the internet ("Active-X"). Thus, reliable internet access and local personnel with training to operate such systems is indispensable.

II.B. Questions to study in clinical trials of MDR-TB

The critical issues regarding MDR-TB relate to currently available drugs, as well as to drugs in development and how they may be used to provide more effective and shorter treatment. Two new drugs, TMC-207 and OPC-67683, are currently in Phase IIB trials and are expected to enter Phase III trials soon. Therefore, we propose that a strategy be developed that retains the ability to incorporate new drugs into future trials if and when they become available. This will entail designing studies focusing on currently available drugs, being prepared for the potential advent of new drugs in 3-4 years. When such drugs become available, they could presumably be added to

the OBR for all subjects in the trial, so that the OBR design could be maintained. Specific questions to study include:

II.B.1. Duration of treatment with injectable agents. Most MDR-TB treatment regimens currently include at least one injectable agent. However, delivery of these agents is painful, requires clinical encounters, and is associated with substantial toxicity. Variable duration of injectable use (from 6 to 15 months), without evidence of association with improved outcomes, suggests that shorter durations of administration of these agents may be adequate. Thus, a trial comparing shorter to longer courses with an injectable agent would likely achieve clinical equipoise. Alternative delivery systems (e.g., inhalation) of aminoglycosides and capreomycin could also be examined to simplify (or improve) treatment. The results of such trials, if outcome equivalency were demonstrated, would allow substantial conservation of program resources, minimize patient discomfort and toxicity, and potentially decrease dropout rates. Data from observational databases would be useful in identifying the norms of current practice and in determining the effects of either longer or shorter duration of injectables on treatment.

II.B.2. Composition of the intensive phase. Most treatment programs adjust the intensive regimen once susceptibility results are available by eliminating drugs to which the isolate is clearly resistant. However, the optimal target number and combination for this refinement are not clear. Clinicians variably believe that the patient should receive 3, 4, or 5 drugs to which the isolate is susceptible in vitro, with composition guided by an algorithm. [11] Since toxicity increases with the number of drugs, it is important to know whether fewer drugs can achieve equivalent cure rates. Moreover, enhanced evidence about the independent contribution made by each drug, or any synergies among drugs, will help to guide the choice of drugs. This question will likely require multiple, short, iterative trials of different combinations and numbers of drugs, relying on a bacteriologic endpoint to evaluate results. The absence of reliable or interpretable DST for some of these agents, however, presents a challenge for this line of questioning. Randomization should at least result in equal distribution of drugs for which there is no agreement on the interpretation of susceptibility testing. And, results on the *in vivo* contribution (net of activity and toxicity) will help determine which drugs should be prioritized for improving DST methodology.

II.B.3. Duration of continuation phase regimen. Current treatment guidelines are based on clinical experience and recommend that treatment for MDR-TB be continued for 18-24 months after sputum culture conversion is achieved. This results in costly prolonged courses of treatment that increase the risk of drug toxicity and the time devoted by program staff to each individual patient. Many clinicians believe that equivalent results could be achieved with shorter duration of the continuation phase of treatment, especially with regimens containing the later-generation fluoroquinolones. However, there are limited clinical and no animal model data to assist in choosing a shorter duration to study. The conservative approach would be to compare the longest duration to a shorter one; if this were equivalent in failure and relapse results, then an even shorter regimen could be studied. Examination of observational MDR-TB treatment databases is needed to determine what the usual "longest" duration is and what amount of shortening would be compatible with clinical equipoise. Demonstration that shorter regimens could be successfully used would greatly expand the ability of programs to treat MDR-TB patients with existing resources.

II.B.4. Can equivalent treatment outcomes be obtained with less frequent monitoring? Most programs monitor patients with monthly sputum smears and cultures, at least until culture conversion is achieved. For the duration of the continuation phase, various degrees of intensity are applied, from monthly cultures for the duration, to every three months. It is not clear whether the more intensive monitoring regimens contribute to improved patient outcomes, or are only associated with increased cost. These costs are substantial, both for laboratory tests and clinical staff time. However, more intensive monitoring may provide benefit, both in earlier detection of success and/or failure, and in improved adherence. Thus, investigation of the effects of less versus more intensive patient monitoring protocols could lead to more efficient use of program resources. In relation to this, it should be noted that the standardized definitions for MDR-TB treatment outcome proposed based on consensus statements [14] have not been prospectively validated.

II.B.5. Preventing DR-TB in close contacts of patients with DR-TB. In many settings, outbreaks of DR-TB occur among families and hospital workers living or working in close proximity to patients with DR-TB. Even when treatment is provided, the frequency of mortality and treatment failure among patients is disturbingly high. Moreover, the lengthy delays that often precede treatment for DR-TB provide ample opportunity for additional transmission of drug-resistant *M. tuberculosis*. Consequently, prevention of new cases of DR-TB, especially among individuals infected with HIV, is a high priority. Identifying agents, existing or experimental, that can be used safely for chemoprophylaxis in adults and children, regardless of HIV-infection status, will reduce substantially the morbidity and mortality from DR-TB. Trials of these regimens, however, will likely be large and of long duration in light of the relative infrequency with which active TB occurs among contacts. Other challenges will be presented by establishing optimal dose and duration, as well as management of the control arm. Placebo-control trials may be acceptable in this situation since INH is not likely to have activity against MDR- or XDR-TB infections. Household or occupational contacts of DR-TB patients, however, may theoretically also harbor fully susceptible infecting isolates that could be eradicated through INH prophylaxis.

II.C. Issues to address once the research question has been selected

II.C.1. Endpoints and other design issues. Many endpoints are possible, and the specific design will depend upon the question being asked. Currently, a substantial number of patients fail or default, so that cure is the most practical endpoint. However, studies of the duration of the continuation phase would likely require follow-up for a year after completion of therapy to assess recurrence. This endpoint would require that sites demonstrate the ability to locate and evaluate study subjects for at least one year after completion of MDR-TB treatment. Other potential endpoints could include survival or microbiologic endpoints such as culture conversion.

Numerous other design issues will have to be considered on a study-by-study basis. Considerations include when to randomize participants: at failure of prior regimen, diagnosis of MDR-TB, or composition of "final" regimen; limiting criteria for stratification (possibilities include: HIV status, study site, baseline bacillary load, cavitation, etc.), while retaining ability to produce valid, meaningful results.

II.C.2. HIV infection. All regimens need to be evaluated in HIV-infected persons as well as in HIV-uninfected persons. However, these two groups are different enough that answering study questions probably requires independent sample size calculations for each group. Thus, there is limited value in trying to study them together. One strategy that has been employed to date is inclusion of HIV-infected subjects in trials powered to detect an endpoint in the HIV-uninfected arm. This effectively provides a pilot study in HIV-infected persons, allowing a decision to be made about whether to proceed with a full study in this population. This strategy could also be used in the converse way, powering for an endpoint in the HIV-infected arm but also enrolling HIV-uninfected subjects into a companion pilot study. Ideally, two concurrent studies could enroll into two arms, each fully powered to answer the study question in the respective subpopulation.

II.C.3. Special populations. Given that a large number of persons with TB are children, it is important to plan for the enrollment of children into clinical trials of MDR-TB. This is complicated if new agents are involved because it is necessary to first perform pharmacokinetic (PK) studies in children. Both Tibotec and Otsuka have identified such studies as a priority. Similarly, pregnant women and patients with other medical conditions (e.g., diabetes) should also be enrolled to the greatest extent possible to ensure that study results can be generalized. Although children and other special populations would not be enrolled before Phase II trials were completed in adults, planning for their enrollment as part of an overall drug development strategy is essential to ensuring that information about the optimal use of these regimens in children is available in a timely fashion. [15]

II.C.4. Pharmacokinetic studies. PK studies are highly desirable, if not essential, for interpreting clinical trial results. They are needed to determine optimal doses and dosing intervals of drugs, the tolerability and safety of combinations, and the study of specific drug-drug interactions. While some sites without capacity for inpatient monitoring and frequent blood sampling can be included in clinical trials of MDR-TB, each trial must have some sites that can perform intensive PK monitoring. Optimally, all sites should have or be working toward this capacity. Novel methods, such as performing PK analysis on dried blood spots, could simplify this process substantially and expand the number of sites able to participate in trials. Such advances would also facilitate conduct of trials in pediatric populations.

II.C.5. Biomarker development. An important element in tuberculosis clinical trials research is the development of biomarkers that can serve as surrogate markers for relapse or cure, whether for drug-resistant or pan-sensitive TB. Studies in MDR-TB patients would likely offer the opportunity to develop such biomarkers with smaller sample sizes, since relapses occur more frequently than with pan-sensitive disease. Candidate biomarkers from sputum, blood, urine, or mycobacteriology specimens would subsequently require further qualification or validation in larger trials.

III. Establishment of "Research Excellence to Stop TB Resistance" (RESIST-TB)

III.A. Cambridge Conference and Declaration

A workshop was organized in Cambridge, MA, USA, in June 2008 to address issues related to the development and conduct of clinical trials for DR-TB and to advance the agenda for enhanced research and advocacy. Attendees of this workshop agreed to establish a formal organization to increase awareness of the DR-TB problem; to promote the design and implementation of clinical trials to provide the tools needed to control and eliminate DR-TB; and to ensure implementation of these tools in all areas of the world affected by DR-TB. This undertaking was unanimously supported by the 70 attendees, who decided that a declaration was needed to enunciate the magnitude and urgency of the DR-TB problem and call others to action. Thus, the "Cambridge Declaration" was drafted and circulated (see Annex 1), and a final version was approved in July 2008. This declaration has been posted on a website created for RESIST-TB at http://ghdonline.org/drtb-trials/ and numerous other individuals and organizations have subsequently co-signed.

III.B. Establishment of the Organization

The Cambridge Conference attendees proposed establishing an organization with a governance model which allows central coordination and careful planning of a prioritized agenda of clinical trials and related studies. This would be accomplished through active stimulation of collaborations between sites and research groups, without demanding exclusivity. This system would also allow funds to be absorbed from agencies that themselves have no mechanisms for inviting and selecting research proposals, such as governments. At the implementation level, it also allows inclusion of related research questions such as effectiveness and adverse effects in observational cohorts, and effectiveness of strategies for enhancing treatment adherence. Establishment of such an organization will require a legal status, a defined central decision-making structure, and a fiscal agent.

It was further determined that this organization would focus on work that complements that of existing institutions (e.g., the Global Alliance for TB Drug Development, the Stop TB Working Group for New Drug Development, FIND Diagnostics, etc.). Although RESIST-TB will incorporate newly developed drugs into regimens being tested for the treatment of DR-TB, RESIST-TB will initially focus on optimization of treatment of DR-TB with existing drugs. RESIST-TB will also consider involvement in Phase IV studies of new drugs or regimens, should new drugs become registered.

The conference attendees established several entities to execute the movement's work:

1) A Steering Committee with broad representation to oversee development of the Organization.

2) A Scientific Committee to evaluate specific trial designs and harmonize the development of individual clinical trial proposals.

3) Three topic-specific Clinical Trial Protocol Committees will report to the Scientific Committee (see section III.C.2).

4) A Site Capacity Development Committee will be created to assess current DR-TB clinical trial capacity at specific sites and outline a plan for enhancing this capacity. This Committee will report to the Steering Committee.

Attendees volunteered to join these Committees and the Steering Committee has appointed Chairs/co-Chairs.

III.C. Moving forward: Outline of a Strategic Plan

Multiple recent statements have called for increased research into treatment of MDR-TB. [2, 5, 16] The structure of a plan to improve and increase availability of treatment for DR-TB was addressed at the workshop and will be developed into a Strategic Plan for the organization. It represents a roadmap for achieving improved treatment of DR-TB and for translating the results of the research into programmatic interventions that can be widely implemented. The elements of this Strategic Plan will include: (1) Coordination with relevant entities involved in DR-TB drug development, testing, regulatory activities and treatment; (2) Scientific aspects; (3) Timeline; (4) Budget; (5) Advocacy and translational work; and (6) Fundraising. These are discussed in individual sections below.

III.C.1. Coordination with relevant entities involved in DR-TB drug development, testing, regulatory activities and treatment. Multiple clinical trials networks have been established in several regions throughout the world (summarized in Annex 2). Many of these networks are not currently prepared to enroll patients in trials of MDR-TB treatment, but a full program for trials of MDR-TB treatment would benefit substantially from the participation of these networks. Ideally, excess capacity—even if temporary—in bacteriology, pharmacology labs and data management, could be shared with a nascent MDR-TB trials network. With appropriate recognition for the substantial work already produced, existing networks could share instruments to accelerate the process and enhance prospects for standardization. The dozens of sites having received GLC approval and technical assistance for the management of MDR-TB could also work together to provide a network for trials of MDR-TB regimens. These sites are located mostly in settings of elevated MDR-TB prevalence, and some have substantial numbers of patients with HIV co-infection. Many of these programs are participating in the two industry-sponsored trials of MDR-TB treatment that are currently underway.

Collaboration between clinical researchers and experts engaged in complementary research is critical to the success of this clinical trials effort. TB animal researchers, pharmacologists, diagnostic researchers (including those with a focus on identifying surrogate markers), researchers working with special populations (pregnant women or children), and those conducting research in populations affected by HIV should all be included. This element of the plan will define collaborative processes to increase the efficiency of the research. As an example, coordination with researchers working on surrogate markers/endpoints is critical for the conduct of future DR-TB clinical trials, as it may decrease the burden of following-up patients for lengthy periods of time after treatment. Also, planning the investigation of new regimens or strategies to

include special populations will facilitate integration into national TB control programs (NTPs) of interventions found to be efficacious in trials. These collaborative activities are all consistent with targeted priorities identified in the NIAID (National Institute of Allergy and Infectious Diseases) research agenda.

A crucial point is to establish collaboration between this initiative and entities involved in development of TB drugs. Coordination will be necessary among trial networks, as well as with industry and public-private partnerships implementing TB trials. Such coordination will aim to optimize the number and quality of trials that can be run simultaneously and sequentially, respecting the confidentiality of proprietary information. Agreements that support the timely sharing of information among entities evaluating new and existing drugs are essential to the efficient execution of RESIST-TB's mission. These agreements will be forged acknowledging that motivations for moving forward may not be the same for RESIST-TB and industry members; there will also likely be additional sensitivities around shared information among industry partners. Industry trial results might have substantial implications for design of subsequent protocols, executed by different entities, both with respect to use of new compounds and, possibly, the use of surrogate trial endpoints. The flow of such information should be bidirectional, between industry and non-industry clinical trials networks with the view to accelerating achievement of the common goal of improving MDR-TB treatment.

Regulatory expertise should be sought from among members of the RESIST-TB to flesh out elements of a plan for approval for drugs and combinations. Each Protocol Committee will need to develop a detailed plan for gaining regulatory approval for the strategy being studied, were that strategy to be successful. They will need to identify the optimal path or mechanism to assure the most rapid approval possible (i.e., bridge, or new indication for existing drug). Such plans should include a list of elements/data necessary for submission of an approval package and the mechanism to be utilized (e.g., investigational new drug [IND], label extension, etc.).

The plan will also elaborate the necessary steps to move from the results of a Phase II or Phase III trial, resulting in approval of a drug or regimen, to integration of the findings into routine program practice (translation). Ideally, incorporation of suitable clinical trial results into policy and practice should be preceded by ample communication with appropriate entities, and be accompanied by operational research plans, in order to address further issues related to cost-effectiveness and feasibility.

In this respect, NTPs will also be important stakeholders in the development of trial sites and in the implementation of clinical trials. NTPs are responsible for identification of patients eligible for DR-TB treatment, are often involved in second-line treatment, and will be important end-users of the results of these trials. NTPs in countries where trial sites are selected or developed should therefore be made part of the process of planning and execution of these trials from the start. This should be reflected in the governance structure of RESIST-TB.

Another essential constituency is that of persons with or having recovered from DR-TB. The experience of these patients is critical to understanding how to best address shortcomings in DR-TB treatment and prevention. Their experiences will be considered in the design of all efforts of RESIST-TB to promote awareness of the DR-TB problem, in the design and implementation of

clinical trials to provide the tools needed to control and eliminate DR-TB, and in the implementation of these tools in all areas of the world affected by DR-TB.

III.C.2. Scientific aspects. The Scientific Committee will undertake the coordination and harmonization required for successful implementation of specific clinical trials. Examples include careful sequencing of the studies aimed at testing strategies for shortened treatment of DR-TB. Second, since trials using clinical endpoints take several years to complete, studies aiming to answer different questions should run concurrently. Finally, many sites have limited capacity for enrollment. In order to run multiple studies concurrently and cover highly heterogeneous populations, significant coordination among sites will be required.

A scientific plan for clinical trials to improve DR-TB treatment will be elaborated by the Scientific Committee**.** Initial priorities were identified at the Workshop. These will be elaborated and implemented in the first stage of the initiative. This will be accomplished by the establishment of three Scientific Protocol Committees: 1) *Drug Efficacy Protocol Committee*: to improve treatment for DR-TB through better understanding of the individual (or synergistic or antagonistic) contributions of each drug; 2) *Treatment Shortening Protocol Committee*: to shorten treatment for DR-TB, i.e., develop strategies that reduce the duration of the entire regimen to less than the current standard of 18-24 months; and 3) *Prophylaxis Protocol Committee*: to prevent DR-TB, i.e., promote chemoprophylaxis in close contacts of individuals with DR-TB. Each of these Committees will produce draft protocols for proposed trials. These will include the following elements: Study aims and objectives, Design, Sample size and composition (inclusion/exclusion criteria), Analysis plan, Timeline, Laboratory requirements, and Criteria for site participation. Future priorities will be identified by members of the Scientific Committee and collaborating entities, with final decisions resting with the Steering Committee. Special emphasis will be placed on adaptive designs that permit changes in background regimens, endpoints, or diagnostic tools as innovations become available.

Recruiting and preparing the requisite number of sites will be addressed by the Site Capacity Development Committee. This Committee will identify tools and opportunities required for developing DR-TB clinical trial sites, including the development of mechanisms for assessing needs, establishing budgets, coordinating training, and providing suitable GCP infrastructure, including data management systems. Timelines and curricula should be specified. Training should be both didactic and practical and would cover the following elements: GCP courses for clinical, laboratory, and data management staff; preparing, conducting, and documenting pilot studies according to GCP; development, execution, and evaluation of systems for patient follow-up during and after treatment; specimen storage and handling; data management and development of a data management system. Selected sites that aim to qualify as trial sites could conduct pilot cohort studies that would involve all aspects of the capacities and procedures needed for a clinical trial. Apprenticeships with sites successfully involved in ongoing trials will also be facilitated.

Recommendations for other sources of support will be elaborated in the strategic plan and should include evaluation of the possibility for collaboration with the NIAID/DMID (Division of Microbiology and Infectious Diseases)-sponsored International Clinical Science Support Network, the TB Alliance's site assessment initiative, and others. The Site Capacity Development Committee will, in consultation with these existing networks, develop a plan for coordinating and

advancing TB trials efforts. This will include maintenance of an up-to-date directory of site and network characteristics (see Annex 3).

III.C.3. Timeline. For year one, the Steering Committee has outlined the following timeline:

Month 1:	Establish Steering Committee, secretariat, website
Month 2:	Complete mission statement
Month 3:	Draft strategic plan including priority protocol concepts, governance, and fiscal structure of the organization
Months 4-6:	Circulate strategic plan for greater input from stakeholders Begin fundraising Plan follow-up DR-TB Trials Meeting
Month 12:	2nd Annual DR-TB Trials Meeting

III.C.4. Budget. The Steering Committee will create a budget subcommittee to address this while the plan is being circulated (Months 4-6), and a full budget will be completed by Month 8.

III.C.5. Advocacy. Advocacy to raise awareness of the DR-TB problem and to highlight and address roadblocks to its solution are an essential function of RESIST-TB. The Cambridge Declaration is the beginning of this activity, which needs to be nurtured and promoted. The Steering Committee will establish an Advocacy Subcommittee to identify avenues and strategies for advocacy for improved treatment and prevention of DR-TB.

III.C.6. Fundraising. The Steering Committee will oversee development of fundraising by identifying potential funders/donors, matching elements of the organization's strategic plan to funders' interests and priorities, preparing a marketing strategy and case statements for potential funders, and contacting funders in Months 8-12. These contacts will make the case for support of the DR-TB Trials Movement, evaluate results, and tailor the strategy accordingly.

III.D. Conclusions

The attendees of the Cambridge Conference agreed that promoting awareness of the DR-TB problem, designing and implementing clinical trials to provide the tools needed to control and eliminate DR-TB, and ensuring implementation of these tools in all areas of the world affected by DR-TB were of the highest priority for global public health. This has been formalized in the Cambridge Declaration. To accomplish these goals, an administrative structure has been established to support these efforts. A website has been created (http://ghdonline.org/drtb-trials/) and Committees of dedicated volunteers have begun to address the impediments to improved DR-TB treatment and prevention. The challenges are great, but the need is even greater. Please join us in this effort.

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Annex 1: Cambridge Declaration

THE CAMBRIDGE DECLARATION:
Towards Clinical Trials for Drug-Resistant Tuberculosis
Cambridge, Massachusetts, USA
June 12, 2008

Because

- today millions of people are living with drug-resistant tuberculosis (TB),
- drug-resistant TB, which is transmissible and deadly, represents a public-health emergency,
- universal access to effective TB treatment is unachievable with current tools,
- inadequate treatment of drug-resistant TB leads to the emergence of extensively drug-resistant (XDR) TB, and
- there are huge gaps in our understanding of how to best treat drug-resistant TB,

we express extreme concern that the best available treatments are of limited efficacy and are reaching only a small fraction of people who need them. The others are left to die, with no or inadequate treatment.

On June 10-12, 2008, stakeholders from communities, NGOs, governments, donors, industry, and academia met in Cambridge, Massachusetts, USA, and declared the formation of a movement that will:

- conduct priority clinical trials that test strategies in adults and children:
    - to shorten and improve treatment for drug-resistant TB, and
    - to prevent drug-resistant TB
- mobilize the resources needed for these trials
- build the capacity of trial sites
- report to stakeholders on progress made, and
- ensure that these efforts complement those of other groups, and address the critical unmet needs outlined above.

For more information, to become a signatory, or to join protocol-writing groups, please contact: drtbworkshop@gmail.com.

SIGNATORIES, 2 July 2008

1. Ms. Paula Akugizibwe, AIDS and Rights Alliance for Southern Africa, Namibia
2. Dr. Elijah Amooti, African Eye Trust, England
3. Mr. Sidney Atwood, Brigham and Women's Hospital, USA
4. Dr. Renuka Babu, Medicine in Need, USA
5. Dr. Jaime Bayona, Socios En Salud-Sucursal Peru, Peru
6. Dr. Mercedes Becerra, Harvard Medical School, USA

7. Dr. Nulda Beyers, Desmond Tutu TB Centre, South Africa
8. Dr. Cesar Bonilla, National Health Strategy for TB Prevention and Control, Peru
9. Dr. Maryline Bonnet, Epicentre / Médecins Sans Frontières, Switzerland
10. Dr. William Burman, Denver Public Health, USA
11. Dr. Jose A. Caminero, International Union against Tuberculosis and Lung Disease, France
12. Dr. Peter Cegielski, U.S. Centers for Disease Control and Prevention, USA
13. Dr. Richard Chaisson, Johns Hopkins University School of Medicine, USA
14. Dr. Frank Cobelens, KNCV Tuberculosis Foundation, The Netherlands
15. Dr. Theodore Cohen, Brigham and Women's Hospital, USA
16. Dr. Margareth Dalcolmo, Helio Fraga Reference Center - FIOCRUZ / MoH, Brazil
17. Dr. Charles Daley, National Jewish Medical and Research Center, USA
18. Dr. Manfred Danilovits, Tartu University Lung Clinic, National Tuberculosis Program, Estonia
19. Mr. Karel De Beule, Tibotec, Belgium
20. Dr. Victor De Gruttola, Harvard School of Public Health, USA
21. Dr. Mary Ann DeGroote, Colorado State University, USA
22. Dr. Tine De Marez, Tibotec, Inc., USA
23. Dr. Ashwin Dharmadhikari, Brigham & Women's Hospital, USA
24. Ms. Nancy Dianis, Westat, USA
25. Dr. Anne Donnelly, Project Inform, USA
26. Dr. Kelly Dooley, Johns Hopkins University School of Medicine, USA
27. Dr. Kathleen Eisenach, University of Arkansas for Medical Sciences, USA
28. Dr. Gerald Friedland, Yale University School of Medicine, USA
29. Dr. Robert Gerety, Medicine in Need, USA
30. Dr. Ann Ginsberg, Global Alliance for TB Drug Development, USA
31. Dr. Howard Grossman, Fenway Community Health, USA
32. Dr. Abdul Hamid Salim, Damien Foundation, Bangladesh
33. Mr. Mark Harrington, Treatment Action Group, USA
34. Dr. Martin Hirsch, Harvard Medical School, USA
35. Dr. Timothy Holtz, U.S. Centers for Disease Control and Prevention, USA
36. Dr. Robert Horsburgh, Boston University School of Public Health, USA
37. Dr. Gary Horwith, Sequella, Inc., USA
38. Dr. Frauke Jochims, Médecins Sans Frontières, Switzerland
39. Dr. Salmaan Keshavjee, Harvard Medical School, USA
40. Dr. Michael Kimerling, University of Alabama at Birmingham School of Medicine, USA
41. Dr. Mette Klouman, The Norwegian Heart and Lung Patient Organisation, Norway
42. Dr. Serena Koenig, Brigham and Women's Hospital, USA
43. Dr. Kitty Lambregts, KNCV Tuberculosis Foundation, The Netherlands, and MDR-TB Working Group of the Stop TB Partnership, Switzerland
44. Dr. Vaira Leimane, State Centre of Tuberculosis and Lung Diseases, Latvia
45. Dr. Christian Lienhardt, International Union Against Tuberculosis and Lung Disease, France
46. Dr. Pushpa Malla, National Tuberculosis Centre, National Tuberculosis Program, Nepal
47. Dr. William Mac Kenzie, U.S. Centers for Disease Control and Prevention, USA
48. Dr. Helen McIlleron, University of Cape Town, South Africa
49. Dr. Charles Mgone, European and Developing Countries Clinical Trials Partnership, Netherlands
50. Dr. Fuad Mirzayev, World Health Organization, Switzerland

51. Prof. Denis Mitchison, St. George's Hospital, UK
52. Dr. Carole Mitnick, Harvard Medical School, USA
53. Dr. Edward Nardell, Brigham and Women's Hospital, USA
54. Dr. Eric Nuermberger, Johns Hopkins University School of Medicine, USA
55. Mrs. Carol Nyirenda, Treatment Advocacy and Literacy Campaign, Zambia
56. Dr. Thomas Nyirenda, European and Developing Countries Clinical Trials Partnership, South Africa
57. Ms. Lesley Odendal, Treatment Action Campaign, South Africa
58. Dr. Charles Peloquin, National Jewish Medical and Research Center, USA
59. Dr. Sergey Popov, Moscow Medical Academy, Russia
60. Dr. Alexander Pym, Medical Research Council of South Africa, South Africa.
61. Dr. Lee Reichman, University of Medicine and Dentistry of New Jersey, USA
62. Dr. Hind Satti, Partners In Health, Lesotho
63. Dr. Rajeswari Ramachandran, Tuberculosis Research Centre, India
64. Dr. Francisco Rosas, Vivir. Participación, Incidencia, y Transparencia, A.C., Mexico
65. Dr. Leonard Sacks, U.S. Food and Drug Administration, USA
66. Dr. Jussi Saukkonen, Boston University School of Medicine, USA
67. Dr. Neil Schluger, Columbia University Medical Center, USA
68. Dr. Kwonjune Seung, Brigham and Women's Hospital, USA
69. Dr. Alexander Sloutsky, Massachusetts State Laboratory Institute, USA
70. Dr. Thelma Tupasi, Tropical Disease Foundation, Philippines
71. Dr. Frank van Leth, KNCV Tuberculosis Foundation, The Netherlands
72. Mr. Wim Vandevelde, European AIDS Treatment Group, Belgium
73. Dr. Francis Varaine, Médecins Sans Frontières, France
74. Dr. Andrew Vernon, U.S. Centers for Disease Control and Prevention, USA
75. Dr. Tido von Schoen-Angerer, Médecins Sans Frontières, Switzerland
76. Dr. Diana Weil, World Health Organization, Switzerland
77. Dr. Charles Wells, Otsuka America Pharmaceutical, Inc., USA
78. Dr. Matteo Zignol, World Health Organization, Switzerland

Workshop sponsor-organizers: Boston University School of Public Health, International Union Against Tuberculosis and Lung Disease, KNCV Tuberculosis Foundation, MDR-TB Working Group of the Stop-TB Partnership, Médecins Sans Frontières, Partners In Health/Harvard Medical School, Potts Memorial Foundation, Treatment Action Group, World Health Organization.

Annex 2: Current TB Trial Networks

Existing trial networks include the US Centers for Disease Control and Prevention Tuberculosis Trials Consortium (TBTC), which has focused most recently on trials for treatment of latent tuberculosis infection (LTBI) and shortened standard regimens. With GCP-certified sites on 4 continents (most heavily represented is North America), coordination with the TBTC could provide many benefits. These include potential access to a vast library of study documents (protocols, standard operating procedures [SOPs], manuals of procedures, training materials). The consortium also boasts significant pharmacokinetic (PK)/pharmacodynamic (PD) capacity and expertise, which could support an MDR-TB trials network both in training and possibly laboratory work. Their model has increasingly relied on strong collaboration with animal model researchers and can inform this effort in the optimization of such collaboration. Lastly, through the TBTC, a small Phase II trial of linezolid versus placebo with optimized background therapy for MDR-TB therapy will be launched shortly.

The International Union Against Tuberculosis and Lung Disease (IUATLD) is completing its second trial of short-course therapy that involved 9 sites in high-incidence settings in Asia, Latin America and Africa. The expertise of this unit has also been key to the efforts of the OFLOTUB consortium to carry out a multi-site Phase III trial of TB treatment shortening, in collaboration with WHO/TDR (Special Programme for Research and Training in Tropical Diseases). The IUATLD could offer to the MDR trials effort substantial experience in conducting TB trials in the context of NTPs and bringing these into compliance with GCP and GLC requirements, as well as coordinating trial efforts within the context of routine programmatic TB control efforts.

INTERTB will soon begin a trial of short-course treatment among HIV-infected populations in two sites in Africa. This consortium is working in settings with high HIV-TB coinfection prevalence, and high incidence of TB disease. In light of the substantial MDR-TB/HIV overlap in some regions—including parts of India, Southern Africa, and the former Soviet Union—the experience of this consortium in implementing TB treatment trials in HIV-affected populations would be valuable. Also noteworthy is specialized bacteriologic and statistical modeling expertise, as well as extensive prior experience of consortium founders with building TB networks.

Other groups may provide valuable expertise or insight into these efforts. These include those coordinating TB trials: the OFLOTUB collaboration, researchers at Nijmegen University in Holland, the REMOX collaboration, and the CREATE consortium. Still other specialized benefits would be accrued through collaboration with existing multi-site research programs such as ACTG and other AIDS cohort and clinical trials research groups.

Annex 3: Site Evaluation Parameters

1) Number of eligible participants annually
2) Estimates of relevant characteristics of population (e.g., prevalence of DR-TB [including XDR-TB and MDR-TB], prevalence of HIV coinfection)
3) Ongoing trials and status (recruitment, follow-up, etc.) by site and network
4) (available) Laboratory capacity (e.g., culture [solid or liquid], serial sputum colony counting [SSCC], DST [conventional, liquid, PCR], PK)
5) (available) Hospitalization capacity, outpatient capacity

They will also catalogue existing resources, which can be made available to other efforts. These may include:

1) Protocols, SOPs, work instructions
2) Data management procedures and systems
3) Consent forms
4) Training materials
5) Tools to evaluate site/laboratory capacity

Based on this information, a plan will be elaborated for timing, location, and sequence of execution of Stage I of the DR-TB clinical trials priorities.