

# RESIST-TB:

## Research Excellence to Stop TB Resistance

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### RESIST-TB Response to RFI (NOT-AI-10-015)

#### Introduction

RESIST-TB is an international organization of over 100 clinical trialists, patients, physicians, national TB program directors, research scientists, companies, and regulatory bodies that is dedicated to improving the treatment and prevention of MDR-TB. In this response to NIAID'S RFI, we propose that the NIH clinical trial networks focus on studies that will expeditiously lead to improved treatment regimens for MDR-TB. This is important because MDR-TB and XDR-TB are rapidly expanding threats to world health, and current efforts to improve the treatment of drug-susceptible TB are unlikely to yield results that can be applied to MDR-TB for many years. The expected introduction of several new classes of antimycobacterial agents in the next few years presents a window of opportunity to make great progress in containing and then reversing the epidemic of MDR- and XDR-TB.

#### I. Why is MDR-TB a disease that the NIH networks should study?

**Overview.** The current epidemic of Multidrug-Resistant Tuberculosis (MDR-TB) is a major threat to world health. Nearly 40% of patients with MDR-TB are not cured with current regimens [1], but new drugs to treat TB will soon become available. These drugs, when used in combination regimens, could revolutionize treatment and prevention of MDR-TB. Current studies by individual sponsors are focused on the short-term goal of obtaining licensure for each individual agent. No studies to identify either the best combination regimens or the shortest effective treatment duration are currently planned. However, such regimens offer the prospect of greater simplicity and shorter duration, allowing programs to scale up MDR-TB treatment capacity. The findings from MDR-TB clinical trials will likely also provide important insights for improving treatment of drug-susceptible TB.

Now is an opportune time to readdress performing clinical trials to identify optimal MDR-TB treatment for several reasons. First, through the Green Light Committee of the Stop TB Partnership, more than 100 MDR-TB treatment projects have been approved for treatment around the world. The more experienced programs have demonstrated the feasibility of MDR-TB treatment in resource-limited settings. Second, several new drugs for the treatment of TB that may become available in the next several years are being tested in patients with MDR-TB. These drugs have novel mechanisms of action and are not expected to have cross-resistance with existing anti-TB agents. While these new drugs provide an opportunity to greatly improve MDR-TB treatment outcomes, their inappropriate use could

rapidly lead to drug resistance, potentially wasting decades of drug development work and the significant opportunities these agents represent for breakthroughs in care. Third, recent developments in clinical trial design, successfully implemented in HIV clinical trials, can permit heterogeneity in background treatment regimens and allow for rapid sequential evaluation of new regimens using adaptive trial design. Fourth, because there is much room for improvement between the current 50% of patients with MDR-TB who convert their sputum in two months (leading to cure in 20 months) and the 75-85% of patients with drug-susceptible TB (DS-TB) who convert in two months (leading to cure in 95+% by 6-9 months), studies of biomarkers, diagnostics and emergence of drug resistance in patients with MDR-TB can be undertaken with much smaller sample sizes that parallel studies in DS-TB.

**Dimensions of the MDR/XDR-TB problem.** MDR-TB and Extensively Drug-Resistant Tuberculosis (XDR-TB) are rapidly growing threats to the world's health. A 2010 report from WHO estimated that over 440,000 cases of MDR-TB occurred worldwide in 2008 [1]. WHO has called on governments to commit more resources to MDR-TB treatment, but effective, well tolerated and easily-delivered treatment regimens are not available [2]. Current treatment regimens for MDR-TB cure roughly 60% of patients treated. As many as 20% of those who fail to respond to treatment die of tuberculosis; those who do not die become chronic carriers and spread MDR-TB to others [3]. The costs of caring for MDR-TB are substantially higher than care of drug-susceptible TB and threaten to consume disproportionate program resources.

**Inadequacy of current treatment regimens for MDR-TB.** Current standard treatment regimens for MDR-TB last 18-24 months and are associated with substantial drug intolerance, often leading to default from treatment. Moreover, even in the most experienced hands, failure and death rates are unacceptably high (25-39%) [3]. In the only reported study to date, 21% of those receiving MDR-TB treatment developed resistance to additional drugs [4], and half of those developed XDR-TB. Despite the lack of formal surveillance, XDR-TB has been identified in at least 58 countries, and over 5% of incident cases of MDR-TB are estimated to be XDR-TB [1]. The lack of effective strategies for treatment of MDR-TB highlight the urgent need for controlled clinical trials, but there have been no large-scale randomized trials of MDR-TB treatment.

**Availability of new agents to treat TB.** The first new drug class for the treatment of TB in almost 40 years, TMC-207, is expected to receive approval as early as 2011. Within 4 years, several other new drugs may also become available, including OPC-67683, PA-824, PNU-100480 and SQ-109. These agents have novel mechanisms of action and are not expected to have cross-resistance with existing agents (although OPC-67683 and PA-824 may have cross-resistance with each other). This means that they will be excellent candidates for the treatment of MDR-TB. However, if used alone or introduced sequentially, or under conditions that do not assure adequate adherence to therapy, resistance to each may develop. This did occur in the 1990s with the sequential introduction of new anti-retrovirals for HIV treatment and subsequently with the introduction of fluoroquinolones for TB

treatment. It is therefore essential that new drugs under development be promptly studied in combination.

**Why development of new treatment regimens for drug-susceptible TB will not improve MDR-TB treatment in the foreseeable future.** An important initiative to develop improved regimens for the treatment of drug susceptible-TB (DS-TB) was recently announced. This initiative, the *Critical Path to TB Drug Regimens*, seeks to develop and license new TB treatment regimens containing agents of newly developed classes of antimycobacterials to dramatically shorten treatment of TB. RESIST-TB strongly supports this initiative; over the next 15-20 years, development of new regimens that do not contain INH or rifampin will provide effective treatment for patients with TB, irrespective of resistance pattern. However, in the short run, it is highly unlikely that shortening of DS-TB treatment duration will be possible without inclusion of rifampin in the regimen; this agent is the most potent of the current first-line antimycobacterials and was essential for reducing previous longer duration regimens to the current 6 months. All trials of DS-TB regimens underway contain a member of this class; consequently, results of trials of new regimens will not contribute to improved treatment for patients with MDR-TB until a regimen containing three new classes of agents is developed.

Until such time as a completely new TB treatment regimen has been developed and validated, patients with MDR-TB will continue to receive ineffective regimens, suffer unacceptable rates of failure and death and spread MDR-TB to contacts. Moreover, as new drug classes for treatment of TB come to market, they will be added to current suboptimal regimens, leading to emergence of additional drug resistance, progression to XDR-TB, and the rise of a “new” XDR-TB, in which resistance to the new agent is present in addition to the previously available agents. Therefore, it is neither wise, ethically acceptable, nor scientifically valid to expect that the results of the initiative to develop improved regimens for the treatment of DS-TB is an alternative pathway to development of improved regimens for MDR-TB. Rather, the two initiatives should move forward in parallel.

## **II. What are the long-term goals and short-term opportunities to advance the science of MDR-TB treatment and prevention?**

RESIST-TB has developed a staged approach to development of improved strategies for the treatment and prevention of MDR and XDR-TB. This strategy is divided into three parts. Overall long term goals guide the process, with specific short-term, and middle term objectives. We believe that the short-term studies could be initiated in the next 1-2 years, the middle-term studies could be initiated in 3-4 years and anticipate that the long-term goals could be achieved in 7-10 years.

### **A. Long-term goals for control of MDR-TB and prevention of XDR-TB:**

- A regimen that cures 95% of all MDR-TB patients with less than 5% relapses

- A regimen that lasts 6 months or less
- A regimen that is completely orally administered and easily tolerable
- A regimen that is effective in HIV-infected persons with or without antiretroviral therapy
- A regimen that is effective in children, with pediatric formulations available
- A regimen that can be easily and widely disseminated to national TB programs
- A 2-month preventive regimen, oral and easily tolerated, that can reduce secondary cases of MDR-TB by 90%

**B. Short-term objectives for optimization of companion drugs and preclinical studies:**

- Use animal models to establish likely effective combinations of drugs and optimal durations of treatment and prevention of MDR-TB
- Conduct clinical studies to optimize doses of companion drugs in patients with MDR-TB
- Conduct clinical studies to understand the pharmacokinetics and interactions among new agents, companion drugs, and antiretrovirals
- Advance development of methodologies for TB clinical trials analysis
- Identify potential surrogate markers of response to treatment and treatment failure

The short-term opportunities describe studies that can begin immediately. Furthermore, the results of these are necessary for subsequent clinical trials of efficacy (see Mid-term objectives) and, as such, need to be undertaken as soon as possible.

**Animal models to define optimal companion drugs and shortest effective treatment durations.** Animal models have been helpful in identifying possible combinations of anti-tuberculosis drugs that could lead to treatment shortening for drug-susceptible TB. Beginning the process in animal models and then testing only “winners” in clinical studies reduces the time, cost, and risk involved in testing new regimens. Limited animal work has been done on MDR-TB treatment regimens, but some studies have suggested possible shortening opportunities using late-generation fluoroquinolones and new compounds under development [5, 6]. Systematic study of sustained sterilization of small animal organs using regimens that comprise a late-generation fluoroquinolone, a new compound, PZA, and injectable agent of varying duration could provide guidance for clinical trials of reduced treatment duration. Pre-clinical animal studies can suggest which new drug combinations can be expected to be associated with low failure and relapse rates and acceptable safety profiles. Similarly, improved animal models for study of LTBI can determine if single drug regimens with new classes or combinations are optimal for preventing progression to disease, and what is likely to be the shortest effective treatment duration.

**Optimization of companion drugs.** Optimization of potential companion drugs is essential to both preserve effectiveness and minimize the likelihood of emergence of additional drug resistance. The fluoroquinolone class is the most important group of agents to study in this regard, since it is the most effective class of agents to which MDR-TB isolates remain

susceptible. Interest in optimizing fluoroquinolone use in treatment of MDR-TB has intensified recently. In vitro, animal [7], and some human [8] evidence supports the notion that higher doses of later-generation fluoroquinolones have additional activity when compared to standard doses, may even be useful in the presence of organisms with *in vitro* resistance to first-generation fluoroquinolones [9], and may reduce acquisition of resistance to the drug class. The degree of cross-resistance among members of the fluoroquinolone class should be further elucidated in order to ensure rational use of the class.

The use of fluoroquinolones in treatment of TB in general has not been scientifically driven, leaving major unanswered questions regarding the use of these highly active agents, whose usefulness is slowly being eroded. For example, the role of moxifloxacin in MDR-TB treatment is not established. It is recommended by the WHO as the first choice fluoroquinolone in the treatment of MDR-TB, but an EBA study shows its activity to be indistinguishable from that of high-dose levofloxacin and gatifloxacin. A PK modeling study suggests that the optimal moxifloxacin dose is 800 mg daily, but there are few data on the tolerability of this dose, and none with extended administration. Gatifloxacin has fallen out of favor due to serious dysglycemia events, but dose-dependent killing has been demonstrated in animal models and gatifloxacin is currently being examined for shortening drug-susceptible treatment in a Phase III multisite trial and for shortening drug-resistant treatment in an observational study in Bangladesh; in neither case have serious safety concerns been raised. Studies that explore the relative safety, efficacy, and tolerability of members of this class would yield important information. One example is a Phase II study that explores the relative efficacy and tolerability of increasing doses of levofloxacin and moxifloxacin.

A second drug that needs further study is pyrazinamide (PZA). PZA continues to stimulate considerable clinical and basic science interest when used as a component of MDR-TB treatment regimens. It possesses a number of unique properties, such as the inhibition of energy pathways, that make it truly synergistic with a number of existing agents for TB and an especially attractive candidate to include in combination with new drugs for MDR-TB treatment. Uncertainty about its exact mechanism of action, optimal contribution to regimens (i.e., how long should PZA be included; is the toxicity time-dependent and would tolerability and activity be optimized by intermittent administration of higher doses) persist. In the short-term, animal studies could be conducted to address these questions. For instance, the following combinations could be compared in the mouse model (if M=moxi and Z=PZA and AG=an aminoglycoside or polypeptide such as amikacin or capreomycin): 0.5MAG/4 MAGZ, 2MAGZ/4 MAGZ, 4 MAGZ/2 MAGZ, 2 MAGZ/4 MAGZ, and so forth. Further examination should focus on whether the synergistic effect of PZA with other drugs is based on the timing of PZA administration. More research into the mode of action of PZA is also needed, as well as studies of the development of resistance in both laboratory and clinical strains. Analogs of PZA should be pursued in order to increase activity and, importantly, to reduce toxicity. Further exploration of in vitro modeling methods such as the hollow fiber model should be emphasized in order to optimize the pharmacokinetics

and pharmacodynamics of this drug, as well as to minimize toxicity. Activity and liver toxicity with intermittent high-dose administration could also be examined in the mouse model. Results from these models should inform clinical studies of the role of PZA in combination with new drugs.

A third class of existing agents that need further study is the carbapenem/beta-lactams. A recent study demonstrated that meropenem/clavulanate was highly effective against MDR-TB [10]. Thus, it might be an important addition to MDR-TB treatment and could potentially allow for substantial shortening of treatment duration. Although it is an injectable agent, a Phase 2 study of the effect on 2-month culture conversion of adding this agent to current MDR-TB treatment would determine if this class should be further evaluated. Moreover, orally available beta-lactam antibiotics are widely-available and well-tolerated antimicrobials but used uncommonly in treatment regimens for MDR-TB. In EBA studies, amoxicillin/clavulanate acid shows bactericidal activity against TB when it is dosed thrice daily at 1000/250 mg but, consistent with time-dependent activity, little activity at 3000/750 administered once daily [11, 12]. Preclinical studies in mice, a hollow fiber model, or catheterized guinea pigs would help us determine the pharmacodynamics of this class of drug, the time above MIC ( $T > MIC$ ) needed for optimal activity, and the beta-lactam with the best PK/PD profile given the known safety and tolerability characteristics of these drugs.

Other currently-available drugs with potential for inclusion in an optimized background regimen that merit further study and/or dose optimization include clofazimine, which has remarkable synergistic effects in vivo with pyrazinamide and TMC207 but is poorly understood and complicated to evaluate in animal models, and ethambutol, which is currently given at what is likely the minimum effective dose [13][14, 15]. The current use of injectables is associated with toxicity and tolerability challenges. Yet, for the foreseeable future, the aminoglycosides (and polypeptides) are likely to be an important component of multidrug treatment for resistant TB. Identifying the injectable with optimal activity and evaluating alternative delivery mechanisms (e.g., aerosolized delivery) would represent advances in MDR-TB treatment. Other drugs, whose dose and consequently activity are limited by toxicity (e.g., ethionamide), could also be considered for aerosolized delivery.

**Understanding PK interactions.** For the new drugs that are expected to move into TB treatment, pharmacokinetic (PK) studies are needed to determine the doses that achieve optimal PK parameters in new combination regimens, children, and in HIV infected individuals. Despite the usual proscription of quinolone use in children, both levofloxacin and moxifloxacin are given to children with TB. Moreover, a PK study of moxifloxacin being given to healthy children who were exposed to MDR-TB is currently underway. Once the results of these studies have been analyzed, PK studies will be needed to determine the doses that achieve optimal PK parameters of fluoroquinolones in children with TB. It is also necessary to perform PK studies of the new agents in children to identify pediatric dosing parameters. Both Tibotec and Otsuka have identified such studies as a priority, but have not yet initiated them.

It will also be important to determine the interactions between new agents before moving forward with phase III trials. In addition, studies of interactions with antiretrovirals that are likely to be co-administered are essential, since it is now clear that TB treatment of HIV-infected persons requires relatively prompt initiation of antiretroviral therapy [16]. Examples of the PK studies that will be necessary include researching the interactions of TMC-207 with antiretrovirals and with fluoroquinolones. QT prolongation is a potential side effect of several of the new agents, so the effect of adding moxifloxacin to regimens containing these agents will need to be carefully evaluated and could lead to the use of levofloxacin rather than moxifloxacin (QT prolongation does not occur with levofloxacin at doses up to 1500 mg/day).

**Advance development of methodologies for TB clinical trials analysis.** With regard to new methodologies, there are three major hurdles that impede clinical trials for TB, and MDR-TB in particular: 1) the large sample sizes required for non-inferiority trials; 2) the expected need to evaluate the addition of several new drugs to TB treatment regimens in rapid succession; and 3) the need to perform sequential trials of treatment shortening to arrive at the shortest regimen consistent with acceptable efficacy. Unless new clinical trial designs can be crafted to reduce the numbers of patients needed to address non-inferiority, the role of new agents in regimens and duration shortening, progress towards improved regimens will meet a logjam [17]. Therefore, convening a group of trialists, biostatisticians and representatives of regulatory agencies to explore ways to meet this challenge will be important. RESIST-TB has identified several potential strategies to address these issues that can be put forward for discussion, including pre-specified addition of new study arms, duration-randomized clinical trials, and adaptive trial designs. An RFA to encourage development of new analytic strategies for these problems would also be likely to encourage innovative approaches.

**Identify potential surrogate markers of response to treatment and treatment failure.** The availability of validated surrogate markers could reduce the time and number of patients required for clinical trials. Therefore, identification of promising candidate markers is important, and several groups are currently working in this area (TBTC Biomarkers Working Group, TBRU) Potential markers will need to be evaluated and validated against failure/relapse in phase 3 trials, so such evaluation is a mid-term objective, but developing potential candidates and evaluating them in cohort studies should be a short-term objective. This effort would be greatly aided by the establishment of sputum, urine, and blood specimen repositories with specimens from well-characterized patients with active tuberculosis (including MDR-TB, XDR-TB, and TB/HIV co-infection).

### **C. Middle-term opportunities for clinical trials with one or more new agents**

- Conduct clinical trials to optimize MDR-TB treatment using regimen with one or more new agents

- Conduct clinical trials to optimize MDR-TB prophylaxis using a regimen with one new agent
- Evaluate current biomarkers and surrogate endpoints as predictors of clinical endpoints

**MDR-TB treatment clinical trial.** A high priority is to conduct treatment trials to define the optimal use of one or two of the new agents under development for the treatment of MDR-TB [17]. Such trials can address the use of most advantageous companion drugs and the shortest duration of treatment compatible with an acceptable failure and/or relapse rate. Study outcomes would be failure, relapse, and the emergence of resistance to any study agent. Concept sheets for two MDR-TB treatment trials, developed by a consortium of stakeholders at a Workshop organized by RESIST-TB are included in the appendix to this response. The first concept sheet addresses the scenario that one new agent emerges first, and the second concept sheet addresses the scenario that two new drugs become available simultaneously.

**MDR-TB prevention study.** An equally high priority will be studies to define optimal chemoprophylaxis for high-risk contacts of persons with MDR-TB. Currently, suggested regimens with one or more second-line drugs are based on little evidence and are toxic. Such high-risk contacts include household contacts, children, and HIV-infected persons. An important first step should be assessment of the rates of disease occurring among such high-risk contacts. Several such studies are currently underway or have recently been completed, but not yet published. Once data from heterogeneous populations (including those with high burden of HIV infection) are available, and the PK parameters and necessary drug-interaction studies in children and HIV-infected persons have been completed, a prevention study should be conducted for contacts of MDR-TB patients. Planning for the necessary PK studies should begin soon. This efficacy study will require a sample size larger than the treatment trials and require collaboration with other clinical trials consortia. A concept sheet for an MDR-TB prevention trial with one new agent, also developed at the RESIST-TB Workshop, is also included in the appendix.

**Evaluating current biomarkers and surrogate endpoints as predictors of clinical endpoints.** Promising surrogate markers will need to be evaluated as predictors of clinical outcomes, especially failure and relapse, in prospective randomized Phase III clinical trials. There are a number of immunologic and microbiologic markers that are currently under study and merit such evaluation; examples include 2- and 3-month culture conversion, time to conversion in solid and liquid media, time to detection in liquid medium (MGIT), Antigen cytokine expression, antibodies, and bacterial products (eg., Ag85 in sputum, and urinary LAM) [18]. Any clinical trials that are undertaken should prospectively assess the predictive power of these and other promising markers for clinical endpoints. In addition, the trials should collect sputum, urine, and blood specimens and establish repositories for future evaluation of promising candidate markers.

### **III. What are the long-term goals and short-term opportunities to advance the science of MDR-TB diagnosis, drug susceptibility testing and surrogate marker identification?**

**New diagnostics and drug-susceptibility testing for MDR-TB.** The lack of substantial advances in TB diagnostics for nearly half a century presents an enormous obstacle for routine treatment of all forms of TB and clinical research. Reliance on a diagnostic of 50-70% sensitivity among adult, HIV seronegative populations (and considerably lower in pediatric and HIV-coinfected patients) represents one of the reasons for continued growth of the global TB epidemic. Moreover, clinical research in TB is hampered by the inability to rapidly obtain confident diagnosis of TB, including identification of the drug-susceptibility patterns of the infecting isolate. Consequently, if culture confirmation of the microscopy-based diagnosis and drug-susceptibility test (DST) results are required for inclusion in a study, designs require either anticipation of significant exclusion after enrollment (among patients whose results after 2-3 months do not conform to entry criteria) or significant delay to treatment initiation. Although new, rapid, sensitive diagnostics, including DST, are available, most are appropriate only for reference lab settings. Investment in development of new point-of-care, rapid diagnostics—likely DNA- or RNA-based methods that can both confirm the presence of the mycobacterium complex and establish the drug susceptibility pattern of the infecting isolate—will be essential to curtail the TB epidemic and facilitate clinical research in TB. Support for development of such diagnostics and evaluation of their contribution to reducing the delay in administering appropriate treatment, and ultimately to improving outcomes, will be critical. We have incorporated the use of currently available rapid MDR-TB diagnostics in the design of the proposed clinical studies (see appendix).

**Surrogate Markers.** Of particular benefit will be diagnostics which—in addition to being rapid, sensitive, and useful at point of care—are quantifiable and can be used also to measure response to TB treatment, as a surrogate for clinical outcomes of failure and relapse. Although 2-month culture positivity is a partially validated surrogate marker for failure and relapse after short-course chemotherapy for TB, recent reanalysis of British Medical Research Council trial data indicates that the correlation between surrogate and final endpoint is not consistent across regimens and populations; in some studies, 3-month culture positivity had better trial level surrogacy [19]. As a consequence of the limitations of this endpoint—and a virtual halt in development of new TB diagnostics over several decades—Phase III trials of new anti-TB medications typically require follow-up of study participants for two years after treatment completion, 4 times the length of current standard of care and 6 times the length of experimental regimens. Other candidates for evaluation against clinical outcomes include change in time to positivity in MGIT, time to conversion in liquid and solid media, cytokine expression, antibodies, bacterial products [18].

For MDR-TB treatment, there is no evidence from controlled clinical trials of a surrogate marker that correlates well with clinical endpoints. Limited data from observational studies

do point to higher proportions of sustained cure among patients whose sputum cultures convert within the first six months of treatment [20][21]. The absence of fully validated surrogate markers for clinical endpoints, however, adds considerable time and cost to drug development and optimization research. Without the identification of valid surrogate markers for failure and relapse in treatment of MDR-TB, the pace of treatment improvement will continue to be extraordinarily slow. Consequently, any clinical research supported by NIAID should place a high priority on advancing identification and validation of microbiological and/or immunologic surrogate markers for failure/relapse after MDR-TB treatment. Early-stage trials should try to identify potential markers, more than one of which should be evaluated in each Phase III trial.

#### **IV. What special populations need to be included?**

Four special populations need to be included in trials for the treatment and prevention of MDR-TB: HIV-infected persons (with and without antiretroviral therapy [ART]), chronic as well as recently diagnosed MDR-TB, children and contacts of persons with MDR-TB. 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 to the heterogeneous populations requiring treatment.

**HIV-infected persons.** 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 in some cases, answering study questions will likely require independent sample size calculations for each group. One strategy that has been useful 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. If resources allow, two concurrent studies could enrol into two arms, each fully powered to answer the study question in the respective subpopulation. It is also important to study HIV-infected persons with TB who are on antiretroviral therapy. Such studies require that drug-drug interaction studies between TB drugs and ARVs first be performed to identify any pharmacokinetic interactions or additive toxicities.

**Chronic as well as recently diagnosed MDR-TB.** Persons with MDR-TB who have received previous courses of treatment for TB may have substantially different responses to therapy, compared to persons who acquired MDR-TB primarily and have not received previous treatment. These differences may include more extensive disease, a higher burden of organisms, decreased susceptibility to other antituberculosis agents, and poor penetration of antibiotics into foci of necrotic tissue. These characteristics may have a substantial impact on the outcome of treatment with a new regimen. Therefore, it is essential that new

regimens be evaluated in clinical trials that include such trial subjects, so that the utility of new regimens in these population subgroups can be assessed.

**Children.** Since a substantial number of persons with MDR-TB are children, it is important to plan for the enrolment of children into clinical trials of MDR-TB. Children metabolize drugs differently from adults, so planning for the enrolment of children as part of an overall drug development strategy is essential to ensuring that information about the efficacy and toxicity of these regimens in children is available in a timely fashion

**Close contacts of persons with MDR-TB.** Close contacts of persons with MDR-TB are at greatly increased risk of developing MDR-TB disease. However, there are at present no evidence-based antimycobacterial regimens that can treat latent MDR-TB infection and prevent disease. Several of the new antimycobacterial agents have properties that might make them ideal for this purpose, such as activity against non-replicating organisms, good tolerability and long serum half-lives. Identification of regimens for treatment of latent MDR-TB infection is an important priority for interrupting the primary spread of MDR-TB and preventing future cases of MDR-TB disease. Therefore, clinical trials for the prevention of MDR-TB disease among close contacts of persons with infectious pulmonary MDR-TB should be undertaken.

#### **V. What are the key requirements for capacity at clinical research sites?**

Clinical trials to define the optimal regimen for treatment of MDR-TB will require adequate numbers of sites that can contribute patients, perform laboratory studies, collect and manage data, and follow patients after treatment, so that registration-quality results are obtained. Trials will need to be large (~500 patients per arm) and be enrolled promptly, and results should be generalizable to important subpopulations (such as HIV-infected patients, chronic cases, and children). Therefore, it will be important to maximize the number of potential clinical trial sites. Trials by Tibotec and Otsuka are currently in progress at sites in many countries, including South Africa, Russia, India, Thailand, Brazil, Peru, Latvia, Estonia, China, Korea, the Philippines, Japan and the U.S. However, more sites will be needed to conduct the large multi-site trials needed to optimize MDR-TB treatment and prophylaxis regimens. Extensive investment in clinical trial site capacity should continue and is essential to conducting MDR-TB clinical trials.

Sites must demonstrate sufficient experience with TB and/or TB/HIV clinical research, and satisfy minimum capability criteria summarized below to be considered for conducting MDR-TB clinical research.

- **Treatment of MDR-TB patients with quality-assured drugs.** Having a consistent supply of and system for administering drugs, the quality of which is verified by a stringent regulatory authority or by the Essential Drugs Group at WHO, is crucial in preventing the emergence of additional drug-resistant strains of TB.

- **Recruitment of at least 20 newly-diagnosed MDR-TB patients annually.** Sites should be located in areas with high MDR-TB burden and be able to recruit the appropriate patient population for MDR-TB clinical research.
- **Access to a certified or certifiable laboratory.** Participating laboratories should either possess appropriate certification, or demonstrate the capabilities to become certified by meeting minimum standards.
- **Access to a research pharmacy.** A research pharmacy and the ability to track investigational drugs are crucial to conducting successful clinical trials.
- **Effective TB control Programs.** Ineffective medical management of TB can lead to the emergence of drug-resistant strains, which challenges researchers to find alternative treatment regimens that are safe, effective, and economical.
- **Use of regimens that meet or exceed minimum standards for programmatic management of drug-resistant TB.** Failure to manage TB with effective treatment regimens contributes to the development of drug-resistant strains.
- **Availability of on-site X-ray services.** X-rays may supplement sputum smear and culture tests to aid in diagnosing TB.
- **Use of electronic and/or paper system for recording and reporting diagnosis and treatment of MDR-TB patients.** Documenting and sharing diagnostics and treatment outcomes are vital for surveillance purposes. Additionally a well-organized data management system will contribute to efficiently collecting and managing credible clinical research data.
- **Demonstration of successful participation in clinical research.** Prior experience in conducting clinical research increases the likelihood that site personnel are knowledgeable and familiar with participant recruitment and enrollment, data management and other study-related procedures.
- **Ability to comply with GCP regulations.** Site staff must possess knowledge of or show willingness to participate in trainings on the Guidelines for Good Clinical Practices (GCP). The network will offer GCP training and refresher courses to ensure the protection of study participants' safety and confidentiality, the enrollment only of eligible study participants and adherence to study protocols.
- **Ability to comply with GLP regulations.** FDA regulations for the conduct of laboratory studies follow 21 CFR Part 58, Good Laboratory Practices (GLPs). Laboratory personnel

must have or be willing to acquire adequate GLP training and experience that is documented prior to involvement in clinical research. The network will provide GLP training and refresher courses as needed to ensure compliance with regulations.

- **Capacity for shipping specimens.** Capacity for shipping specimens (raw sputum, culture, isolates, plasma, etc.) must be demonstrated or developed.

**Clinical trial sites.** Based on the above assessment parameters, the table below contains a selection of sites that demonstrate the capacity to conduct MDR-TB clinical trials. To the best of our knowledge, all of these sites can recruit a minimum of 20 patients/year (unless otherwise noted), have strong laboratories, and many have had prior clinical trial experience, with further site assessment information currently being collected. While this list is not exhaustive, it does indicate that global capacity to conduct MDR-TB clinical trials exists. Furthermore, it demonstrates that site capacity development is both possible and necessary: many of the sites below require further capacity-building and still more clinical trial sites must be developed to ensure the requisite numbers to conduct MDR-TB treatment and prophylaxis trials.

<u>Site Location</u>	<u>Institution</u>	<u>PI/Contact Person</u>	<u>Network</u>	<u>TB/MDR-TB Clinical Trials Experience</u>	<u>TB Clinical Trials Lab Capacity</u>
<b>Bangkok, Thailand</b>		Sirinapha Jittimane (sxj47@cwru.edu)		HIV and TB clinical trials	Yes
<b>Botsabelo, Lesotho</b>	Botsabelo Hospital/Partners In Health	Hind Satti (hsatti@pih.org)		MDR-TB treatment	Needs strengthening
<b>Butare, Rwanda</b>	Centre Hospitalier Universitaire-Butare	Michel Gasana (michelgasana@yahoo.fr)		MDR-TB treatment	Needs strengthening
<b>Cambodia</b>	Cambodian Health Committee	Sok Thim (sokthimcipra@online.com.kh)		CAMELIA trial; MDR-TB treatment	Yes
<b>Cape Town, South Africa</b>	Brooklyn Chest Hospital	Andreas Diacon (ahd@sun.ac.za)	PanACEA	MDR-TB treatment	Yes
	Institute of Infectious Diseases &	Mark Hatherill (mark.hatherill@uct.ac.za),	TBRU; South African TB	TB research, vaccine trials	Yes

	Molecular Medicine, University of Cape Town*	Willem Hanekom (willem.hanekom@uct.ac.za)	Vaccine Initiative (SATVI)		
<b>Chennai, India</b>	YRG CARE	Nagalingshwaran Kumarasamy (kumarasamy@yrgcare.org)	ACTG	HIV clinical trials	Yes
<b>Durban, South Africa</b>	CAPRISA	Salim Abdool-Karim (karims1@ukzn.ac.za)	ACTG	Tibotec 208	Yes
	University of KwaZulu Natal	Umesh Laloo (laloo@ukzn.ac.za), Alex Pym (Alexander.pym@mrc.ac.za)	ACTG; TBTC	Study 30	Yes
<b>Ho Chi Minh City, Vietnam</b>	Pham Ngoc Thach Hospital	Nguyen Thi Ngoc Lan (ngoclan0456@yahoo.com)	IUATLD	IUATLD study C	Yes
<b>Johannesburg, South Africa</b>	University of Witwatersrand	Martin Grobusch (martin.grobusch@witshealth.co.za), Neil Martinson (martinson@hivsa.com)	ACTG, TBTC	Tibotec 208	Yes
<b>Kampala, Uganda</b>	Mulago Hospital and affiliated institutions	Roy Mugerwa (profrdm@imul.com)	TBTC	INH Prophylaxis, MDR-TB and HIV Clinical trials	Yes
	Uganda-CWRU Research Collaboration /Case Western University*	Moses Joloba (moses.joloba@case.edu)	TBRU	TB research	Yes
<b>Karachi, Pakistan</b>	Indus Hospital	Aamir Khan (aamirjkh@gmail.com)		MDR-TB treatment	Yes
<b>Lima, Peru</b>	Universidad Peruana Cayetana	Eduardo Gotuzzo (egh@upch.edu)	TBTC	Tibotec 208; Otsuka 204	Yes

	Heredia	u.pe)			
	Hospital Nacional Sergio E. Bernales	Epifanio Sanchez		Otsuka 204	Yes
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	Hospital Nacional Hipolito Unanue			Otsuka 204	Yes
	Hospital Nacional Daniel A. Carrion			Otsuka 204	Yes
<b>Lince, Peru</b>	Asociación Civil Inestigaciones Medicas en Salud	Jorge Sanchez (jsanchez@impactaperu.org)	ACTG	HIV clinical trials	Yes
<b>Manila, the Philippines</b>	Tropical Disease Foundation	Thelma Tupasi (tetupasi@tdf.org.ph)	TBTC	Otsuka 204	Yes
<b>Masan, Korea</b>	National Masan TB Hospital		NIAID Intramural	Otsuka 204	Yes
<b>Moscow, Russia</b>	Central TB Research Institute	V Erokhin (citramn@online.ru)		Tibotec 208	Yes
<b>Mumbai, India</b>	Hinduja Hospital	Zarir Udwardia (zarirfudwardia@gmail.com)		MDR-TB treatment	Yes
<b>Port au Prince, Haiti</b>	GHEKIO	Bill Pape	ACTG	ART, TB prophylaxis & treatment trials	Yes (rebuilding post-earthquake)
<b>Porto Allegre, Brazil</b>	GHC	Breno Santos (breno@ghc.com.br)	ACTG	HIV Clinical Trials	Yes
<b>Pune, India</b>	NARI	Srikanth Tripathy (stripathy@nariindia.org)	ACTG	HIV clinical trials	Yes
<b>Riga, Latvia</b>	MDR Facility: State Agency of TB and Lung Diseases	Vaira Leimane (vaira@tuberculosis.lv)		Tibotec 208, Otsuka 204	Yes
<b>Rio de Janiero, Brazil</b>	Inst. Oswaldo Fiocruz	Margareth Dalcolmo (mpdalcolmo@gmail.com)	ACTG	Tibotec 207 and 209	Yes

<b>Shanghai, China</b>	Shanghai Pulmonary Hospital	He-Ping Xiao, Qing Zhang (zhqi709851@sohu.com)		Otsuka 204	Yes
<b>Tallinn, Estonia</b>	Tartu University Lung Clinic	Manfred Danilovits (Manfred.Danilovits@kliinikum.ee)		Otsuka 204	Yes
<b>Tygerberg, South Africa</b>	Stellenbosch University; Brooklyn Chest Hospital	Anneke Hesselting (annekeh@sun.ac.za), Andreas Diacon (ahd@sun.ac.za)	TBTC, PanACEA	Tibotec 208	Yes

\* May not be able to recruit 20 MDR-TB patients/year, but has strong TB trial capacity.

#### **VI. What clinical laboratory capabilities are needed?**

Laboratories at clinical trial sites should either possess appropriate certification according to international standards or demonstrate the capability to become certified by meeting minimal standards, as well as have access to quality-assurance monitoring. Laboratories suitable for MDR-TB clinical research should be staffed with experienced laboratory technicians who can perform, or who are capable of undergoing the necessary training to perform, the following basic lab tests: microscopic sputum smear examination for acid-fast bacilli and mycobacterial culture. Clinical trial sites should also either be able to perform or have access to quality-assured susceptibility testing to first-line and second-line anti-tuberculosis drugs (rapid PCR diagnostics, Hain test, solid media testing).

In addition to specialized TB lab capacity, laboratories at clinical trial sites should also be able to perform hematology tests (i.e. hemoglobin, hematocrit, white blood cell count), and biochemistry blood tests (i.e. sodium, potassium, creatinin, alanine aminotransferase, aspartate aminotransferase, glucose, thyroid-stimulating hormone). In addition, laboratory technicians must be willing to learn and adhere to study-specific standard operating procedures (SOPs).

#### **VII. What Partnerships and collaborations should be fostered and supported?**

Partnerships should be fostered with all stakeholders in the process, including clinical trials networks, patients, physicians, National TB Program directors, research scientists, companies, and regulatory bodies.

Several initiatives to foster such collaborations have already been launched and should be built upon. Since 2008, RESIST-TB has led an international effort to bring together clinical trialists, patients, physicians, national TB program directors, research scientists, companies, and regulatory bodies to address improving the treatment and prevention of MDR-TB. This has included international meetings specifically devoted to this effort, sessions at broader TB meetings to advocate for clinical research and involve new stakeholders, workshops to develop potential study designs, and inclusion of existing trials consortia on protocol teams, in working groups and at meetings. Collaborations work best when centered around specific projects or protocols.

RESIST-TB has over 100 participating members. Steering and Protocol Committee members have extensive experience in designing, conducting, and analyzing results of clinical trials and observational research in TB, MDR-TB, and HIV. Other strengths include demonstrated success in raising awareness, resources, and standards for management of and research in HIV, TB, and MDR-TB in resource-poor settings. RESIST-TB members have longstanding commitments to collaborative work, which is often conducted across multiple institutions and networks.

Another initiative that will contribute to such collaboration is the STOP TB Working Group on New Drugs/MRC/TBTC/Tibotec TB clinical trials Collaboration Initiative. This initiative had its first meeting at the Cancun International TB conference in 2009, and is being coordinated by Andrew Vernon of CDC. Its focus is standardization of clinical trials forms and coordination of research agendas, and its member consortia (including all of the major TB trials units) are committed to inter-network dialogue.

Existing networks that should be involved include:

- a. **AIDS Clinical Trials Group (ACTG):** ACTG is the world's largest HIV clinical trials organization, playing a major role in defining the standards of care for treatment of HIV infection and opportunistic diseases related to HIV/AIDS around the world.  
**Contact:** Constance Benson, University of California San Diego, San Diego, CA (cbenson@ucsd.edu), Susan Swindells, University of Nebraska Medical Center, Omaha, NE (sswindells@unmc.edu)
  
- b. **Tuberculosis Trials Consortium (TBTC).** The TBTC is funded by the Centers for Disease Control and Prevention (CDC) and is composed of 8 Veterans Administration Medical Centers (VAMC) and 21 non-VA sites, including 6 international sites.  
**Contact:** Neil Schluger, Columbia University College of Physicians and Surgeons, New York, NY (ns311@columbia.edu), Elsa Villarino, CDC/DTBE/TBTC, Atlanta, GA (mev1@cdc.gov)

- c. **NEAT (European AIDS Treatment Network).** NEAT consists of 41 partner institutions from 16 European Countries, along with more than 350 centers, which mainly serve patients with HIV/AIDS in Europe.  
**Contact:** Anton Pozniak, Chelsea and Westminster Hospital, London, UK (anton.pozniak@chelwest.nhs.uk)
- e. **TBNET:** is a network of mostly European, research oriented clinicians, microbiologists, mycobacteriologists and epidemiologists interested in the field of tuberculosis and mycobacterial diseases. The goal of the TBNET is to promote clinically oriented research in the field of tuberculosis in Europe by sharing and developing ideas and research protocols among the members of the network.  
**Contact:** Christoph Lange, Clinical Infectious Diseases Research Center Borstel, Germany (clange@fz-borstel.de)
- f. **Technology, Research, Education and Technical Assistance (TREAT TB):** TREAT TB is an initiative of the Union, with funding support from a five-year USAID Cooperative Agreement that commenced in October 2008. TREAT TB aims to build a successful research partnership model to stimulate changes in international standards and practice in ways that serve country needs. TREAT TB is focused on field evaluations of diagnostic tools, clinical trials of priority research questions and targeted operational research benefitting global, regional and country TB control efforts.  
**Contact:** I.D. Rusen, TREAT-TB/The Union, Paris, France (irusen@theunion.org)
- g. **Pan African Consortium for the Evaluation of Antituberculosis Antibiotics (PanACEA):** PanACEA is an EDCTP-funded consortium that consists of six European research organisations, twelve sub-Saharan clinical trial sites, and three pharmaceutical companies. Its goal is to advance the development of therapeutics for shortening and simplifying TB treatment by (a) supporting regulatory-quality Phase IIa, IIb and Phase III clinical trials, and (b) developing enhanced clinical trial capacity in sub-Saharan Africa.  
**Contact:** Martin Boeree, Radboud University Medical Center, Nijmegen, Netherlands (M.Boeree@ULC.umcn.nl)
- h. **International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT):** The NICHD IMPAACT network includes domestic and international clinical sites that conduct clinical studies related to the treatment and prevention of HIV infection and its complications in infants, children, adolescents, and pregnant women. IMPAACT is a multicenter, multiprotocol collaborative effort between NICHD and the National Institute of Allergy and Infectious Diseases (NIAID). Each Institute funds a network of sites whose investigators work together to achieve common HIV research prevention and treatment goals. NICHD network centers participate in a broad range of clinical studies sponsored by IMPAACT.

**Contact:** Brooks Jackson, Johns Hopkins University, Baltimore, Maryland  
(bjackso@jhmi.edu)

- i. **TB Clinical Diagnostics Research Consortium (CDRC):** The TB CDRC is funded by NIAID and consists of a consortium of scientists, clinicians, and support personnel. In an effort to increase the awareness of scientists and manufactures, the TB CDRC is committed to collecting data on the outcomes of investigational diagnostics and the impacts on TB management in endemic countries with clinical trials sites. The consortium intends to serve as a resource to the TB community in advising scientists and manufacturers and work towards identifying novel diagnostic approaches, including those that target special populations.

**Contact:** Jerry Ellner, Boston Medical Center, Boston, Massachusetts  
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## **IX. Summary**

Unprecedented opportunities exist to improve outcomes of treatment of drug-resistant TB, which is currently successful in only 60% of patients. Studies could easily be initiated in the next year or two to optimize the use of existing drugs, in conjunction with new drugs, and to identify new candidates as surrogate endpoints for clinical outcomes. Studies carried out in patients with MDR-TB will be essential to developing regimens of anti-TB drugs that do not include rifampin, the most important sterilizing agent used in the treatment of drug-susceptible TB. Closely linked to improvement of MDR-TB treatment, is improved and accelerated diagnosis of MDR-TB (identification of causative organism and characterization of resistance profile of the infecting isolate). Diagnostic tools will be essential for enrolling patients in trials as well as for measuring response to MDR-TB treatment. More than 20 clinical trial sites are prepared to participate in these efforts globally, either mature MDR-TB treatment demonstration projects or experienced clinical-trial entities, or both. These include individual venues and various networks presently involved in HIV and/or TB trials. The continued failure to capitalize on these opportunities will assure ongoing transmission and increased MDR-TB morbidity and mortality throughout the developing world.

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## Annex I.

### RESIST-TB Trial Proposal I: PHASE 3 TRIAL PROTOCOL WITH 1 NEW DRUG

Title: Prospective, randomized, double-blinded trial of the efficacy and toxicity of a regimen for MDR-TB treatment containing one new agent

*Objectives:* To evaluate for non-inferior efficacy in MDR-TB treatment a regimen of drug A + Optimized Background Therapy (OBT) for 6<sup>1</sup> months after culture conversion, compared to a regimen of A+OBT for 12 months after conversion.

*Design:* Prospective, randomized, double-blinded controlled trial with two study arms.

*Subjects:* Inclusion: Pulmonary tuberculosis with or without extra-pulmonary TB; male or female patients at least 15 years of age prior to the day of enrollment; able and willing to produce sputum for mycobacterial culture; female patients of childbearing potential must have a negative urine pregnancy test at screening and agree to use a highly effective method of birth control; male patients must agree to use an adequate method of contraception throughout the participation in the trial; Documented evidence of solid or liquid drug susceptibility tests demonstrating resistance to isoniazid and rifampicin and/or a rapid diagnostic test including Cepheid or Lineprobe assay demonstrating resistance to isoniazid and rifampicin; Karnofsky score >20.

Exclusion: A history of allergy to Drug A or any class of drug essential for OBT; requirement for a prohibited medication (depending upon drug A profile); comorbid condition for which drug A is contraindicated such as cardiac arrhythmia; grade 4 elevation of ALT or AST or bilirubin according to DAIDS tables; grade 3 elevation in creatinine; hemoglobin < 6.7 g/dl; for HIV positive patients participants with active, uncontrolled opportunistic infection or comorbidity will be excluded; patients requiring ARVs according to national guidelines who have no treatment options available in the form of at least one drug not previously used; administration of any investigational agent within 1-month prior to screening; any prior treatment with the Drug A.

*Study Arms:*

Arm 1: OBT plus drug A for 6 months after culture conversion.

Arm 2: OBT plus drug A for 12 months after culture conversion.

*Sample Size:* 480 subjects in Arm 1, 480 in Arm 2 = 960 patients. (non-inferiority design for the comparison of arms 1 and 2)

*Primary Endpoints:* Death, treatment failure, absence of culture conversion on solid medium after 6 months of treatment, relapse default.

*Secondary Endpoints:* Time to culture conversion on solid and liquid medium; time to resolution of signs and symptoms; adherence to therapy; PK parameters; and emergence of drug resistance.

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<sup>1</sup> 6 months was chosen as the intervention duration for illustrative purposes. The exact duration will be determined based on results of time to conversion in trials still to be conducted; it may be any duration between 6 and 11 months.

*Analysis:* Per protocol analysis would be the primary analysis; Modified Intent to Treat analysis will also be performed. Planned subgroup analyses will include HIV, children, extent of TB disease, and previous treatment.

## Annex II.

### RESIST-TB Trial Proposal II: PHASE III TRIAL PROTOCOL WITH 2 NEW DRUGS

Title: Prospective, randomized, open label non-inferiority trial comparing efficacy, safety and tolerability of a shortened regimen containing two new agents with standard 18 months of treatment for MDR-TB treatment.

**Background assumptions:** Studies of two new drugs, A and B, have shown accelerated sputum conversion when each of these drugs is added to a background regime for the treatment of MDR TB. One of these drugs has already been licensed, and the other is under study with a dossier being prepared for licensure, for the treatment of MDR TB. Studies have been conducted to show that A and B can be co-administered without any negative drug-drug interactions. Two-month sputum conversion rates following treatment with ABZE (A+B+PZA+EMB) and ABZQ (A+B+PZA+fluoroquinolone) were nearly identical to those observed following administration of HRZE, the standard six-month regimen in drug-susceptible TB.

**Objectives:** To assess efficacy, safety, and tolerability of an MDR-TB treatment-shortening regimen that includes two new drugs for 6 months, compared to 18 months of optimized treatment (which may include regimens containing one of the two new drugs, A or B).

**Design:** Open-label randomized controlled trial for non-inferiority of 2-drug Arm

**Subjects:** Inclusion: Pulmonary tuberculosis with or without extra-pulmonary TB; *M. tuberculosis* isolate within past 3 months resistant to INH and RIF; Karnofsky score >50; Age >2 ; willingness to have HIV testing performed; willingness to attend scheduled follow-up visits and undergo study assessments; women with child-bearing potential must agree to practice an adequate method of birth control or to abstain from heterosexual intercourse during study therapy; Laboratory parameters within 14 days prior to screening (serum creatinine level < 2 times upper limit of normal, Hemoglobin level  $\geq 8.0$  g/dL Platelet count of  $\geq 80,000/\text{mm}^3$ , Absolute neutrophil count (ANC)  $> 1000/\text{mm}^3$ , negative pregnancy test; able to provide informed consent or legally authorized representative able to do so if decision-impaired.

Exclusion: XDR-TB ; Culture-negative TB; pregnant women; contraindications relating to specific A+B toxicity; known hypersensitivity to any study drug; not expected to survive for more than 4 weeks; anticipated surgical intervention for the treatment of pulmonary tuberculosis; participation in another drug trial; treatment with second line TB drugs for >60 days prior to enrollment (but use of first line drugs such as INH, Rifampin, PZA, or ethambutol for at least 7 days immediately prior to enrollment allowed).

**Study Arms:**

Arm 1: 6 months ABZQ (new drugs A and B, plus PZA and a fluoroquinolone)  
Arm 2: 18 months of optimized therapy (may include A or B, but not both).

**Sample Size:** 575 subjects per arm. (non-inferiority design, 80% power,  $\alpha=0.05$ ;  $\delta = 8\%$ ; expected frequency of primary endpoint in control arm = 25%; lost to follow-up = 20%)

**Primary Endpoint:** Combined endpoint of treatment failure, relapse, death, or default while on treatment.

**Secondary Endpoints:** Time to culture conversion on solid and liquid medium; safety and tolerability; adherence to therapy; PK parameters; DR emergence.

**Analysis:** Per protocol and Modified Intention to Treat analysis will be performed. Planned subgroup analyses will include HIV, children, extent of TB disease, and previous treatment.

## Annex III.

### RESIST-TB Protocol III: PHASE III TRIAL PROTOCOL FOR PROPHYLAXIS WITH 1 NEW DRUG

Title: OPTICOM (Optimal Preventive Therapy in Contacts of MDR-TB)

**Objectives:** Compare the safety and efficacy of intervention drug to isoniazid for preventing active TB in household contacts of MDR-TB patients.

**Design:** This will be a randomized, double-dummy, controlled trial. Subjects will be randomized by household (cluster randomization) to receive either Drug A or isoniazid.

**Subjects:** Household contacts of MDR-TB index cases (patients) in whom active tuberculosis has been ruled out; HIV infected and uninfected; children and adults.

Inclusion criteria: Household contact of a known patient with documented, sputum smear-positive MDR-TB; Sleeping in the same dwelling with the index case (dead or alive) regularly within six months of enrollment;  $\geq 6$  months old (age limit to be determined by available PK data for the intervention drug); TST-positive for HIV-negative people over 13 years old; Willing to have HIV test; Informed consent (informed assent for minors).

Exclusion criteria: Current confirmed sputum-positive or clinical TB; Known hypersensitivity to study drugs; Using antibiotics with known anti-TB activity and unable to discontinue (for example, other fluoroquinolones); Liver enzymes  $> 5x$  normal limits; History of treatment with second-line TB drugs within the past 12 months; Pregnant or lactating women; Inability to complete study protocol.

**Study Arms:**

Intervention arm: Intervention drug (duration to be determined by future mouse studies).

Control arm: isoniazid for nine months.

**Sample Size:** This study will enroll 2530 household contacts in each arm, which will have 90% power to detect a 70% reduction in relative risk of developing active TB in the intervention arm, compared to the isoniazid arm.

**Primary Endpoint:** Confirmed TB (specific definitions in children to be decided).

**Secondary endpoints:** Confirmed or probable TB (specific definitions of probable TB in adults and children to be decided); All-cause mortality; Grade 3 or 4 adverse events; Completion of assigned study therapy; DST results in household contacts diagnosed with TB compared to index case; Molecular genotyping of isolates of household contacts diagnosed with TB compared to index case; IGRA response between the two arms; TST response between the two arms.

**Analysis:** Per protocol and Modified Intention to Treat will be performed. Planned subgroup analyses will include HIV, children.

## **Annex IV.**

### **Signatures of Support**

*The signatures below represent individual, not institutional, endorsements of the RESIST-TB response, unless specifically noted.*

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**Institutional endorsements:**

The Stop TB Partnership TB Research Movement

The WHO Stop TB Department

Infectology Centre of Latvia: Clinic of Tuberculosis and Lung Diseases, Latvia

Treatment Action Group, USA