Trials in Developing Countries: Lessons Learned

Challenges in Conducting Tuberculosis Clinical Trials in Developing Countries: Lessons Learned

Tuberculosis (TB) is a global epidemic of considerable proportions. It is also closely entwined with the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). There is a great need for new drugs, vaccines, and diagnostics in this therapeutic area, but there are many challenges in the successful operational execution of the requisite clinical trials in developing countries. This paper reviews these challenges and offers some ‘lessons learned’ in the execution of clinical trials for TB vaccines, treatment, and diagnostics across Africa, Asia-Pacific, Latin America, and eastern Europe over the past 10 years.

To set the scene for these discussions, the paper first provides some background on the disease itself, existing vaccines and drugs, and current research on new products. Extensive references are provided for readers who wish to pursue these topics in greater detail.

The World Health Organization’s Global Tuberculosis Report 2012

Tuberculosis is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. It is also the leading cause of death among those infected with HIV. Given that it is a global public health concern, the World Health Organization (WHO) has monitored TB for many years. The WHO Global Tuberculosis Report 2012 provides their latest information and analysis about the TB epidemic and “progress in TB care and control at global, regional and country levels.” It is an extremely comprehensive report in which data were provided by 204 countries and territories that collectively have more than 99% of the world’s TB cases. Both good news and bad news are reported. Good news includes the following:

- New cases of TB have been falling for several years, and fell at a rate of 2.2% between 2010 and 2011. The TB mortality rate has decreased 41% since 1990 and the world is on track to achieve the global target of a 50% reduction by 2015.
- Mortality and incidence rates are falling in all of WHO’s six regions, and in most of the 22 high-burden countries that account for over 80% of the world’s TB cases.
- Since WHO launched a new global TB strategy and began to systematically monitor progress in the mid-1990s, access to TB care has expanded substantially. Between 1995 and 2011, 51 million people were successfully treated for TB in countries that had adopted the WHO strategy, saving 20 million lives.
- The development of new drugs and new vaccines is progressing. New or re-purposed TB drugs and novel TB regimens to treat drug-sensitive TB and multidrug-resistant TB (MDR-TB) are advancing in clinical trials and regulatory review. Eleven vaccines to prevent TB are moving through development stages.
- Innovations in diagnostics are being implemented. Xpert MTB/RIF, a molecular test that can diagnose TB and rifampicin resistance within 100 minutes (rifampicin is discussed later in this paper), has been rolled out successfully. Between its endorsement by WHO in December 2010 and the end of June 2012, 1.1 million tests had been purchased by 67 low- and middle-income countries, with South Africa being the leading adopter.
- In 2004, WHO recommended the implementation of collaborative TB/HIV activities, and there has been good progress. These activities saved an estimated 1.3 million lives between 2005 and the end of 2011. Globally, 48% of TB patients known to be living with HIV in 2011 were started on antiretroviral therapy (ART), a figure the WHO recommends should increase to 100%. Kenya and Rwanda are top performers in HIV testing and provision of ART.

Despite this progress, however, there are still many alarming statistics, and much work to be done:

- The global burden of TB remains considerable. In 2011, there were an estimated 8.7 million new cases of TB (with 13% of patients co-infected with HIV). Moreover, 1.4 million people died from TB (of which approximately 33% were HIV-positive). Statistics at the regional level show that there are variations within the overall progress that is being made: progress in Europe and Africa, for example, is not as good as in some other regions.
- There are critical funding gaps for TB care and control, and also for research and development (R&D). Between 2013 and 2015, up to US$8 billion per year is needed in low- and middle-income countries: current figures indicate that there will be a funding gap of up to US$3 billion per year. With regard to R&D, US$2 billion per year is needed; the funding gap for 2010 was US$1.4 billion.
- Progress in responding to MDR-TB remains slow. Worldwide, 3.7% of new cases and 20% of previously treated cases were estimated to have MDR-TB. India, China, the Russian Federation, and South Africa have almost 60% of the world’s cases of MDR-TB. The highest proportions of TB patients with MDR-TB are in eastern Europe and central Asia. At the present time, while the standard treatment for TB patients lasts six months, the regimen for most patients with drug-resistant TB takes 20 months. Treatment for MDR-TB is costly, and can have serious side-effects. It is worth noting here that the previous summary discussed the situation in several developing regions of the world. Another example of attention being needed in developing and low-income countries can be found in the overall funding gap for TB care and control. International donor funding is particularly critical in many low-income countries, 25 of which are in Africa, where donors provide more than 60% of current
funding. However, the developed world is not immune to concern about TB. For example, a recent report in the Wall Street Journal cited Dr. Kenneth Castro, Director of the division of TB elimination at the US Centers for Disease Control and Prevention, commenting on his personal concern over a “resurgence of complacency” in the US healthcare community. Rates of MDR-TB in the US remain low, but are starting to slowly increase. Given that TB is both curable and preventable, improving care for and control of the disease is a global moral imperative.

Mycobacterium tuberculosis: Basic Research and Molecular Biology
Tuberculosis is caused by a bacterium (Mycobacterium tuberculosis) that most often (but not always) affects the lungs. The disease is spread from person to person through the air: an infected person expels and propels bacteria into the air via coughing, sneezing, and spitting. A healthy individual only needs to inhale a few germs to become infected. Approximately one-third of the world’s population has latent TB, i.e., a person has been infected by the TB bacteria but is not (yet) ill with the disease and cannot transmit the disease to others. Healthy people infected with TB have a 10% lifetime risk of falling ill with active TB disease. However, persons with compromised immune systems, such as people living with HIV, malnutrition, or diabetes, have a much higher risk of falling ill and, without proper treatment, up to two-thirds of these individuals will die.

A particularly worrisome aspect of TB is that infection does not elicit clinically relevant disease in the majority of individuals, and many who are infected carry asymptomatic disease for decades. Moreover, when an individual progresses to active TB disease, symptoms such as cough, fever, night sweats, and weight loss can be mild for many months. Given that individuals who are ill with the active disease can infect up to 10–15 others through close contact over the course of a year, a given individual with the bacterium can infect hundreds of others before being clearly identified as someone with the disease.

Axel-Robertson and colleagues observed that the mechanisms involved in the natural protection that some individuals develop are not yet well understood. Integration of all disparate observations into a coherent systems biology approach is considered advantageous, and advances in cellular immunology offer promise. These authors noted that biologically relevant mechanisms need to be understood and this knowledge translated into the clinical context of TB infection with three aims: to better understand clinically relevant T-cell responses in individuals protected from TB disease and develop markers of immune protection; to characterise the nature of the immune response in individuals who are not able to contain TB infection; and, ultimately, to characterise markers to gauge response to therapy.

Molecular biological and genomic approaches to understanding various basic aspects of the differences and commonalities among high-burden countries is of vital importance for improving understanding of the development of appropriate scientific approaches to the discovery and development of applicable diagnostics, drugs, and vaccines. As Kim et al. observed, “With further development and refinement, molecular investigations of the genetic factors underlying virulence, pathogenicity, and drug resistance in M. tuberculosis may provide the backbone for the design of drugs, vaccines, and diagnostics.”

Clinical, Epidemiological, and Implementation Sciences
In addition to basic science research, other sciences are required in this field: clinical trial sciences, epidemiological science and data collection, and implementation science. Clinical trial sciences, including both trial design and operational conduct, are discussed in more detail later in this paper. Kim et al. clarified the importance of epidemiological and implementation sciences when addressing TB, observing that “Epidemiological data are essential to properly inform the development of implementation research agendas to ensure that investments in product development are properly paired with in-country science, to facilitate clinical trials and product roll out.” The authors continued that although “implementation research has traditionally been regarded separately from basic and clinical research, the HIV and tuberculosis epidemics exemplify the importance of addressing the ultimate goal -- to use new research developments to deliver better care and end both epidemics.” There has never been a greater need to see the management and treatment of two epidemics in unison. HIV and TB cannot be effectively managed without better pooling of resources for basic science research, clinical trials, epidemiological science and data collection, implementation research, and actual implementation of vaccines, diagnostics and treatments.

Development of Vaccines for Tuberculosis
Currently, the only licensed vaccine for TB is bacille Calmette-Guérin, commonly known by the abbreviation BCG. More than 100 million doses of BCG vaccine are given each year to infants in high-burden countries to protect them from TB, including forms of extrapulmonary TB that can be fatal. However, this vaccine is not indicated for many individuals and its protective efficacy against pulmonary TB is inadequate. Much research is currently being conducted to develop new vaccines. References are provided for further reading.

Currently Available Drugs for Tuberculosis
It is of interest in the present context that a clinical trial for a drug indicated for pulmonary TB, the United Kingdom Medical Research Council’s trial of the effects of the aminoglycoside antibiotic streptomycin on pulmonary TB that was conducted in the mid- to late-1940s, is commonly acknowledged to be the first pharmaceutical randomised clinical trial (RCT). Credit for conducting this RCT is typically given to Sir Austin Bradford Hill and his 14 colleagues (the Streptomycin in Tuberculosis Trials Committee, chaired by Dr Geoffrey Marshall). Participants in the trial were randomised to a control treatment group and a streptomycin drug treatment group. The control treatment was the standard of care for TB at that time, which consisted of bed-rest. Participants in the drug treatment group received streptomycin in addition to bed-rest. Two grams/
day of streptomycin per participant were administered intramuscularly via four injections at six-hourly intervals. The methodology employed for randomisation in this trial differed from that typically employed previously. Control groups had certainly been used in medical research prior to this trial, but often the method of allocating participants to one or two treatment groups was alternate allocation, i.e., simply placing the next individual entering the trial in the alternate treatment group to the one entered by the previous individual.\textsuperscript{34} On this occasion, the randomisation methodology was as follows:\textsuperscript{32}

Determination of whether a patient would be treated by streptomycin and bed-rest (S case) or by bed-rest alone (C case) was made by reference to a statistical series based on random sampling numbers drawn up for each sex at each centre by Professor Bradford Hill; the details of the series were unknown to any of the investigators or to the co-ordinator and were contained in a set of sealed envelopes, each bearing on the outside only the name of the hospital and a number. After acceptance of a patient by the panel, and before admission to the streptomycin centre, the appropriate numbered envelope was opened at the central office: the card inside told if the patient was to be an S or a C case, and this information was then given to the medical officer of the centre.

Compelling evidence of the drug’s efficacy was provided by this trial, and streptomycin subsequently became the first antibiotic treatment for this disease.

Two drugs that followed were the antibiotics isoniazid\textsuperscript{45,46} and rifampicin.\textsuperscript{37,38} Several other drugs are now on the market, and are very much needed since the advent of MDR-TB and extensively drug-resistant TB (XDR-TB). MDR-TB denotes bacillary resistance to at least isoniazid and rifampicin. XDR-TB is MDR-TB with additional bacillary resistance to any fluoroquinolone and at least one second-line injectable drug.\textsuperscript{39} As Chang and Yew observed, “Rooted in inadequate TB treatment and compounded by a vicious circle of diagnostic delay and improper treatment, MDR-TB/XDR-TB has become a global epidemic that is fuelled by poverty, HIV, and neglect of air-borne infection control.” Other drugs include fluoroquinolones (e.g., moxifloxacin),\textsuperscript{40,41} pyrazinamide,\textsuperscript{42,43} linezolid,\textsuperscript{44-46} bedaquiline,\textsuperscript{47,49} and delamanid.\textsuperscript{50,51}

Bedaquiline and delamanid were the first novel compounds for TB developed in highly regulated clinical trials. Prior to these trials the regulations were not as stringent, and no truly new compounds were developed for TB for approximately 40 years. Bedaquiline and delamanid therefore paved the way for the development of novel TB drugs in a highly regulated environment.

Skripconoka and colleagues reported an analysis involving individuals who had previously participated in a randomised, placebo-controlled trial of delamanid and a subsequent open-label extension trial. These individuals were eligible to participate in a 24-month observational study designed to capture treatment outcomes. The authors reported that their analysis suggested that “treatment with delamanid for 6 months in combination with an optimized background regimen can improve outcomes and reduce mortality among patients with both multidrug-resistant and extensively drug-resistant tuberculosis.”\textsuperscript{57}

References are provided for further reading.\textsuperscript{52-59}

New Designs Employed in Tuberculosis Trials

The MRC’s ground-breaking RCT of streptomycin for pulmonary TB was discussed in the previous section. Sixty years later, as seen earlier in this paper, TB remains a serious threat to global public health. With regard to the development of newer study designs that are helpful in the development of new drugs for TB, Phillips and colleagues\textsuperscript{60} noted that “The emergence and rapid spread of multidrug-resistant and extensively drug-resistant tuberculosis have given an increased priority to the development and evaluation of novel drug regimens that are expected to be more effective, less toxic, and increase adherence.” The words ‘drug regimes’ in this quote are important: pharmacotherapy for this disease requires combinations of drugs rather than a single drug. The traditional approach for testing combination therapy has been to conduct multiple Phase 2 RCTs for every potential new drug combination, with promising combinations progressing to Phase 3 trials. Given the expense of each individual trial, there is a very large cost when a false-positive Phase 2 result is obtained, i.e., a drug combination that looked promising in Phase 2 progressing to Phase 3 but not being found to be effective in that trial. Originally, each Phase 2 trial only tested one new regimen at a time and multiple trials were needed to determine which regimen could progress to Phase 3. As investigational sites, patient populations from which to recruit participants for clinical trials, and funds for conducting TB trials are all relatively restricted, the urgency of the need for a novel treatment regimen meant that a different approach was needed.

The multi-arm multi-stage (MAMS) design that has been used in other therapeutic settings\textsuperscript{55,62} offers considerable advantages in this context. Phillips and colleagues\textsuperscript{60} provided an example of this approach. They discussed a three-stage trial that, at commencement, contains five treatment arms, a control drug regimen and four novel drug regimens. Upon inclusion into the trial, therefore, participants are randomised to one of the five treatment arms. Two interim analyses are detailed in the study protocol. When the first interim analysis is conducted at the end of Stage 1, it is determined that novel regimen 4, for example, does not display sufficient efficacy compared with the control regimen to warrant its continuation. That treatment arm is therefore terminated, and all participants subsequently entering the trial are randomised to one of the remaining treatment arms. The second interim analysis is conducted at the end of Stage 2. At this point it is determined that neither novel regimen 1 nor novel regimen 3 display sufficient efficacy compared with the control regimen to warrant continuation. These two treatment arms are therefore terminated, which means that only the control regimen and novel regimen 2 continue until the end of the trial. This design, which involves the dropping of poorly performing novel regimens, offers two benefits. First, drug regimens that were relatively ineffective do not progress to Phase 3 trials. This likely reduces the expense and time costs of false-positives. Second, participant safety is enhanced from the commencement of Stage 2 onwards, since all participants entering the trial once a treatment arm has been terminated for being relatively ineffective are not randomised to receive that treatment. As Phillips
and colleagues noted, “In the next few years at least 4 new drug classes will need evaluation in combination with each other and in combination with the standard drugs to define the best possible treatment.” MAMS designs therefore offer significant advantages in this therapeutic area.

Clinical trial designs in the TB therapeutic area are still evolving. Despite the limited funding available there are more new drugs than one might expect in this indication. The urgency of the need and relative absence of trials in TB over an approximately 40-year period has resulted in TB researchers having to invent the wheel as the needs developed. References are provided for further reading.

Challenges in Clinical Trials and Lessons Learned

Conducting TB trials in geographic regions that are well-experienced in conducting clinical trials (e.g., Europe and the United States) is not a realistic strategy for two reasons. Firstly, the incidence of TB is too low in such countries to allow the necessary recruitment of participants. Secondly, to be of maximum value to developers of these drugs, the trials need to be conducted in regions where the approved products will ultimately be most needed so that the research reflects the efficacy and safety in these populations. The challenge has been the relative lack of research in the TB, and specifically the MDR-TB, therapeutic area in such regions. This has led to the need to involve some clinicians/principal investigators, regulatory authorities and ethics committees, national treatment programme directors, and other governing bodies who are inexperienced in clinical research, which can cause delays in approvals and/or logistical obstacles to the launch of clinical trials in these countries. This conundrum requires identifying the spectrum of challenges that will be met, and the prospective instigation and implementation of strategies to overcome these challenges when commencing TB clinical trials in a new and/or inexperienced country or trial site.

As a result of conducting approximately 15 clinical trials in TB vaccines, treatment, and diagnostics across Africa, Asia-Pacific, Latin America, and eastern Europe over the past 10 years, Quintiles gained valuable experience in meeting these challenges. The following are representative of the challenges faced.

Innovative Study Designs

Innovative designs can be looked upon with scepticism and fear. Clinicians, national TB programme directors, ethics committees, and regulatory authorities are often wary of approving studies that deviate from WHO and country guidelines. There is sometimes concern amongst regulators that they will lose funding from The Global Fund if they allow alternate regimens to be used instead of the standard WHO recommended regimens. The Global Fund is an international financing institution that aids funding of HIV, TB and malaria treatment. Sponsors and contract research organisations (CROs) are well served by engaging with the WHO to obtain endorsement of novel treatment regimens to be tested in clinical trials in support of submissions to national TB programme directors for consideration for the novel regimens to be tested.

Challenges in Securing Access to Background Regimes

Securing access to background treatment regimens requires involvement of national TB programme heads from the outset once the study design is identified. Having access to partners within WHO, if possible via the Global Fund for TB, can also greatly improve openness to collaboration and access to background regimen treatments for trial purposes. National TB programmes are subject to targets in terms of TB treatment outcomes and supplies of background regimens are often limited. Allowing a background regimen to be used as part of a clinical trial, specifically one testing a novel drug regimen, requires buy-in and agreement from the national TB programme heads and/or the Global Fund, and obtaining this agreement can be a time-consuming process.

Securing Appropriate Clinical Trial Sites and Facilities

Facilities to conduct clinical trials are often not available, and even if available some of them have insufficient clinical trial infrastructure or experience. It is therefore necessary to collaborate with established networks with good capacity to conduct studies, such as networks for HIV and malaria, and to network with social initiatives and community resources and non-governmental organisations (NGOs). Additionally, establishing relationships with key opinion leaders and stakeholders is essential (see9). Consideration should be given regarding the budget required to put infrastructure and support in place at inexperienced clinical trial sites. Partnering with a CRO experienced in conducting research in these countries and which has staff on the ground in or near the country can be pivotal to the success of the new trial site.

Challenges Associated with Specialised Mycobacteriology

It is typically difficult to identify appropriately trained laboratories with the infrastructure and experience to conduct the testing needed in this therapeutic area. Shipment of sputum across borders is not ideal and often not viable. Therefore, since sputum is vital to the efficacy outcomes in these trials, identifying appropriate specialised mycobacteriology laboratories with the required facilities, equipment, and experience and then ensuring consistency across all laboratories is critical, and can be extremely challenging in developing countries. Working with CROs that have previous experience in managing this process can make the identification and preparation of laboratories a much smoother process.

Failure in Treatment due to the Inadequate Implementation of an Effective DOTS Programme

The outcome of trials in TB is reliant on long-term adherence to the treatment regimen. Most protocols rely on the WHO-endorsed DOTS (Directly Observed Therapy Short Course), for drug sensitive TB, or DOTS-plus, for MDR/XDR-TB programmes being implemented to support adherence to the drug regimen. Managing DOTS/DOTS-plus can be improved by partnering clinical trial sites with the standard of care for treatment in the respective country. Clinical trials can be of benefit to national TB programmes as they bring additional resources dedicated to supporting patients during their therapy.
participation in the trial. Focussed training of family members, DOTS supervisors (often volunteers in the community), and community advisory boards can further support adherence.

Overcoming Quality Concerns

Be prepared to make additional expert resources available to inexperienced sites. Having a CRO partner that can support sites in appropriate and detailed planning for clinical trials and which has experience in managing TB trials is essential to prevent quality concerns, especially when sites are conducting their first TB trial. The required support is ongoing and an experienced CRO partner will be able to provide the ongoing training and support needed to ensure high quality data and the safety of participants. This includes initial training and refresher courses that maintain the staff’s knowledge and address concerns that have arisen since the last training session. It is also very helpful to maintain a protocol specialist team to work directly with sites so that they always have expertise available to call on.

Preventing Loss of Data/Bias due to Incomplete Participation

Successful treatment often may lead to participant drop-out and loss to follow-up, which leads to attendant data analysis issues and can introduce bias. Structured planning and procedures to mitigate participants being lost to follow-up involve participant and community involvement, education, and the implementation of tools that have proven successful for participant retention following prior TB trials. Drawing on the experience of past trials and sharing these best practices with new trial sites has shown improvement in participant retention. Sites may require additional funding for employing drivers as well as other strategies found to be successful in supporting long-term retention.

Concluding Comments

Tuberculosis remains a global public health issue of great concern: As noted at the beginning of this paper, it is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. The advent of MDR-TB and XDR-TB has further complicated the successful treatment of this disease. Development of new vaccines, drugs, and diagnostics is underway, and new trial designs are being considered, but there remain considerable difficulties in the operational execution of TB trials in the regions of the world where they are most beneficially conducted. Early engagement with experienced sites and an experienced CRO partner will greatly impact the success of the trial as more trials are conducted in more countries to meet the urgent need for new vaccines, diagnostics, and treatment regimens in TB.

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