Title: Methodological considerations for clinical trials for new treatment regimens for MDR-TB

Running head: Methodological considerations MDR-TB trials

Authors: Patrick PJ Phillips

MRC CTU at UCL

Aviation House

125 Kingsway

London

WC2B 6NH

United Kingdom

Patrick.phillips@ucl.ac.uk

+44 207 670 4637

Word Count: 1354

Abstract (108 words)

In stark contrast to the treatment of drug-sensitive TB, the evidence base underpinning global guidelines for the treatment of MDR-TB is very poor. This, with the lack of experience from previous trials and the nature of the disease, means that there are a number of methodological aspects that are particular to trials of new regimens for MDR-TB. These aspects include the weight of evidence required to change policy and practice, the flexibility to make adaptations to an ongoing trial, the choice of patient population, the importance of the internal control, the duration and frequency of follow-up, and particular safety monitoring for novel combinations of new and repurposed drugs.

Introduction

The recommendations from the WHO guidelines for the treatment of TB that new patients with pulmonary drug-sensitive TB (DS-TB) should receive the daily 6 month regimen 2HRZE/4HR are considered *strong recommendations* based on the *highest grade of evidence*(1).

In striking contrast, prior to the phase II trials of bedaquiline(2) and delamanid(3) and others currently ongoing (see www.resisttb.org/?page_id=1602), there have been no late stage randomised controlled trials for the treatment of multi-drug resistant TB (MDR-TB). The recommendations that relate to both the composition and duration of MDR-TB treatment regimens are based on the *lowest quality of evidence* (on a 4 point scale)(4). The primary source of evidence underpinning these guidelines is a meta-analysis consisting entirely of observational studies, most of which employed individualised treatment thereby suffering from a potential for bias by indication(5). Evidence for the efficacy of the WHO recommended regimen under programme conditions is limited; of the estimated 480,000 people who developed MDR-TB in 2013, only 111,000 (23%) were started on treatment with an expected treatment success rate of only 50%(6).

The poor evidence base, the lack of experience from previous trials, and the nature of the disease mean that there are a number of methodological aspects that are particular to trials of new regimens for MDR-TB.

Weight of evidence required to change policy and practice

Since the current WHO guidelines for the treatment of MDR-TB are based on 'very low quality evidence'(4), it is likely that considerably weaker evidence would be required to change policy and practice as compared to what would be required to change that for the treatment of DS-TB. This is evidenced by the uptake in some settings of variants of the 9-month Bangladesh regimen(7) based only on one observational study from a single country(8).

Investigators have a responsibility to current and future MDR-TB patients to deliver a trial to the highest standards of design, conduct and analysis. Nevertheless, it may be justifiable to make concessions in certain areas in order to speed regimen evaluation, taking into consideration regulatory requirements for any future licensing applications. Concessions might include the use of more novel trial designs, or an acceptance that the family-wise type I error rate (the chance of any false positive result among multiple intervention arms) may exceed 5% in a multi-arm trial(9). In the context of limited effective treatment options for MDR-TB, a type II error (a false negative result) would be disastrous. Investigators should therefore be careful that study power is not compromised.

Trial adaptations

Due to the large number of planned trials and an even larger number of observational studies that will be conducted in the new few years, trials should be designed to be flexible enough to adapt to external data. Trials should include multiple intervention arms to maximise the chance of finding an effective regimen(10). Trials do not necessary need to have adaptive designs (although such designs are often more efficient(11)), but investigators should be aware of other studies that are ongoing that have a bearing on their study (perhaps because of similar drugs being studied) and be ready to

consider modifications to treatment arms, eligibility or trial design as necessary. This awareness can be achieved through familiarity with the research community and what is presented at TB conferences, but also clinical trial registries and the list of ongoing MDR-TB trials curated at www.resisttb.org. An example of a successful adaptation is the addition of two arms containing bedaquiline in the STREAM trial (ClinicalTrials.gov Identifier: NCT02409290).

Patient population

As with any trial, the primary objective(s) of the trial will directly determine the patient population to be enrolled in trial. The MDR-TB patient population is, in general, more heterogeneous than the DS-TB patient population and eligibility criteria should therefore not be too restrictive so as to ensure the broadest possible generalizability. The decision to include patients with XDR- and pre-XDR- TB will depend on the trial objectives. In many settings, rifampicin mono-resistant TB is managed in the same way as MDR-TB and consideration should be given to also including these patients in a trial. Patients co-infected with HIV should be included as should those on antiretroviral therapy, with as few restrictions on antiretroviral regimens as possible. However, there are many settings where there is limited HIV-TB co-infection where an improved MDR-TB regimen would be of great benefit even if it cannot be given with certain antiretroviral regimens (only 12% of all new TB cases in 2014 were HIV positive(6)).

Inclusion of individuals from other special populations in MDR-TB trials is encouraged to increase generalizability; children and pregnant women have historically been seriously under-represented in TB trials(12, 13). Broader eligibility criteria will have implications for algorithms for the management of adverse events, processes for informed consent (for children and others unable to give consent), the potential for drug-drug interactions with concomitant medications, inclusion of additional stratification factors at randomisation, and variability in treatment outcomes which may require an increase in sample size.

Internal and external controls

Apart from a few well researched settings, since there are little available data on the performance of currently used regimens, any clinical trial should include an internal control. This is in contrast to an uncontrolled study where the comparison is made against an external control either in similar patients outside the study or against some sort of historical control. Absence of any internal control is "treacherous"(14) as any benefits seen might be due to secular trends or patient selection leading to false inference about the benefits of an intervention. This would result in an ineffective or dangerous treatment being given to patients, and any future research being undermined because of a bogus 'standard of care'. Some have advocated for uncontrolled trials for new treatments for Ebola virus disease(15), although the dangers have been well-articulated(16). There is, however, an important role for uncontrolled trials in more untreatable forms of MDR-TB (such as the NiX-TB trial, ClinicalTrials.gov NCT02333799) where the available treatment options and prognosis is not dissimilar to Ebola, but these should be considered exploratory or 'hypothesis generating' to be followed by randomised controlled trials to generate robust, unbiased evidence.

Choice of control

The WHO guidelines are implemented slightly differently in different settings and there is therefore no such thing as a *universal standard of care* regimen. Due to the paucity of evidence, what is standard of care in one setting may be considered to be inappropriate in another setting due to a perception of inferior efficacy or safety. As new drugs are introduced and new evidence emerges from other trials and observational studies, it is highly likely that international guidelines will change during the 5 or more years that a clinical trial usually takes to complete.

The choice of control will therefore depend on the objectives of the trial and could be the locally used implementation of the WHO guidelines, or a variant of the 9-month 'Bangladesh regimen' (for which there is growing observational data (7, 17)), or another alternative. Use of an internal control

that is inferior to the standard of care is likely to result in an unreliable over-estimate of the efficacy of the intervention regimen. Investigators should consider what impact changing guidelines have on the management of patients within the trial, and also on how the results will be received when the trial is completed.

Duration and frequency of follow-up

It is known that the majority of relapses occur within six months of stopping treatment in clinical trials of DS-TB(18, 19) and results from REMoxTB(20), RIFAQUIN(21) and OFLOTUB(22) have confirmed this. Some groups are therefore designing clinical trials in DS-TB with the primary endpoint 12 months after randomisation (i.e. 6 months after the longest duration regimen being studied).

There are very limited data on the timing of relapse in clinical trials of short-course regimens for the treatment of MDR-TB. Nevertheless, it is probably reasonable to select the primary endpoint for a clinical trial in MDR-TB to be 6-9 months after the longest duration regimen being studied, although crucial to continue to follow-up for a minimum of 18 months post-randomisation for a definitive evaluation of the regimens being studied. A secondary analysis at the time of the primary analysis could be useful to confirm that long-term results are consistent in the subgroup of patients for whom the longer follow-up data is available.

Total duration and frequency of follow-up will depend in part on expected toxicities and pharmacokinetic properties of the drugs being studied. As in DS-TB, for trials of regimens of different durations, the primary endpoint should be at a fixed time from randomisation, rather than from end of treatment, since this is an endpoint that is most relevant to the patient when they are enrolled into the trial. Core research definitions for treatment outcomes in adult drug-resistant TB trials have recently been proposed(23).

Safety Monitoring

Treatment for MDR-TB is a risk-benefit balance between the poorly understood efficacies and toxicities of various second-line drugs. This is somewhat different to DS-TB where the drugs have, for the most part, well-established safety profiles. Any more intensive safety monitoring should be done on patients on all arms so as to avoid biased reporting of adverse events. A central expert clinical team can be useful to (A) provide the best support for patient management to sites as needed, but also (B) to encourage consistent decision-making regarding complex treatment changes due to toxicity and treatment failure between study sites and treatment arms.

Conclusion

Compared with the extensive experience within many groups of conducting trials to evaluate new regimens for the treatment of DS-TB, there is almost no experience of conducting trials to evaluate new regimens for the treatment of MDR-TB. A better understanding will come with more experience, and included here are some methodological considerations in the design and conduct of trials for new regimens for MDR-TB.

References

1.   World Health Organization. Treatment of tuberculosis: Guidelines. 4th edition.: World Health Organization; 2010.
2.   Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371(8):723-32.
3.   Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for Multidrug-Resistant Pulmonary Tuberculosis. N Engl J Med. 2012;366(23):2151-60.
4.   World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update: World Health Organization; 2011.
5.   Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients. PLoS Med. 2012;9(8):e1001300.
6.   World Health Organization. Global Tuberculosis Report 2015. Geneva2015.

7.   Piubello A, Harouna SH, Souleymane MB, Boukary I, Morou S, Daouda M, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis. 2014;18(10):1188-94.

8.   Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis. Am J Respir Crit Care Med. 2010;182(5):684-92.

9.   Wason JM, Stecher L, Mander AP. Correcting for multiple-testing in multi-arm trials: is it necessary and is it done? Trials. 2014;15:364.

10.   Parmar MK, Carpenter J, Sydes MR. More multiarm randomised trials of superiority are needed. Lancet. 2014;384(9940):283-4.

11.   Davies GR, Phillips PP, Jaki T. Adaptive clinical trials in tuberculosis: applications, challenges and solutions. Int J Tuberc Lung Dis. 2015;19(6):626-34.

12.   Nachman S, Ahmed A, Amanullah F, Becerra MC, Botgros R, Brigden G, et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. Lancet Infect Dis. 2015;15(6):711-20.

13.   Gupta A, Mathad JS, Abdel-Rahman SM, Albano JD, Botgros R, Brown V, et al. Toward Earlier Inclusion of Pregnant and Postpartum Women in Tuberculosis Drug Trials: Consensus Statements From an International Expert Panel. Clin Infect Dis. 2016;62(6):761-9.

14.   ICH Expert Working Group. Choice of control group and related issues in clinical trials. ICH Harmonised Tripartite Guideline Current Step. 2000;4:E10.

15.   Adebamowo C, Bah-Sow O, Binka F, Bruzzone R, Caplan A, Delfraissy JF, et al. Randomised controlled trials for Ebola: practical and ethical issues. Lancet. 2014;384(9952):1423-4.

16.   Nelson RM, Roth-Cline M, Prohaska K, Cox E, Borio L, Temple R. Right job, wrong tool: a commentary on designing clinical trials for Ebola virus disease. Am J Bioeth. 2015;15(4):33-6.

17.   Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis. 2014;18(10):1180-7.

18.   Nunn AJ, Phillips PPJ, Mitchison DA. Timing of relapse in short-course chemotherapy trials for tuberculosis [Short communication]. Int J Tuberc Lung Dis. 2010;14:241-2(2).

19.   Johnson JL, Thiel BA. Time until Relapse in Tuberculosis Treatment Trials: Implication for Phase 3 Trial Design. Am J Respir Crit Care Med. 2012;186(5):464.

20.   Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, et al. Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis. N Engl J Med. 2014;371(17):1577-87.

21.   Jindani A, Harrison TS, Nunn AJ, Phillips PP, Churchyard GJ, Charalambous S, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med. 2014;371(17):1599-608.

22.   Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis. N Engl J Med. 2014;371(17):1588-98.

23.   Furin J, Alirol E, Allen E, Fielding K, Merle C, Abubakar I, et al. Drug-resistant tuberculosis clinical trials: proposed core research definitions in adults. Int J Tuberc Lung Dis. 2016;20(3):290-4.