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# Recruitment challenges for clinical trials with novel regimens for drug-resistant tuberculosis



## To the Editor:

Drug resistance is a growing public health problem. The World Health Organization reported an estimated 480 000 new cases of multidrug-resistant tuberculosis (MDR-TB) worldwide in 2013, of which 9% were estimated to be extensively drug-resistant (XDR)-TB. The prevalence of HIV co-infection among TB patients in the African region is high [1]. In South Africa, 65% of TB patients tested for HIV are HIV-positive [2].

Treatment for drug-resistant (DR)-TB is long, costly and arduous with consistently poor outcomes and high default rates [2–5]. New treatment options are slowly emerging through clinical trials, while evidence for existing agents is often scarce [6]. Recruitment of suitable subjects for clinical trials has proven challenging at our research site [7, 8]. This study aimed to estimate the proportion of potentially eligible subjects among the population with DR-TB in our area and the most frequent reasons of nonparticipation in ongoing clinical trials for DR-TB.

We used the example of two recently completed trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT00910871 and NCT00449644) to create a set of commonly applicable demographic, social, medical and TB-related criteria for a trial in DR-TB (table 1). Demographic and social criteria aimed to identify cooperative adults likely to comply with rigid visit schedules and long-term follow-up typical of a phase 3 trial. Medical criteria were to exclude subjects at increased risk of adverse events and those with conditions that could interfere with the treatment outcome end-points. HIV-positive subjects not on antiretroviral treatment were allowed (CD4 cut-off at the time was  $<250$  cells·mL<sup>-1</sup>). TB-related criteria required documented infection with *Mycobacterium tuberculosis* with resistance to isoniazid (INH) and rifampin (RIF), but excluded higher-grade resistance if known, and treatment-naïve status for the current episode.

At the time of data collection all patients diagnosed with DR-TB in the Cape Town Metropole were referred to a regional centre at Brooklyn Chest Hospital (BCH) in Cape Town to be registered and evaluated for treatment. Resistance testing in the state laboratory for INH and RIF was done with line probe assays and phenotypical testing at that time. GeneXpert and line probe assays for agents other than INH and RIF were not yet available. A Task Applied Science research team (TASK) was situated on the premises of BCH. A single TASK physician (S. Siwendu) retrospectively evaluated the case files of each referral to BCH for DR-TB for a 3-month period against the criteria in table 1. If a subject seemed not to qualify, the reasons were noted from the records. Individuals were not contacted for additional

TABLE 1 Evaluation of 421 patients and critical values for exclusion

Criterion	Critical value for exclusion	Excluded n (%)
<b>Demographic</b>		
Age years	>60	12 (2.9)
	<18	8 (1.9)
Incomplete or outdated records	Not allowed	27 (6.4)
<b>Social</b>		
Place of living	>100 km from site and no transport	45 (10.7)
Imprisonment or no fixed abode	Not allowed	28 (6.7)
Member of a gang/criminal organisation	Not allowed	1 (0.2)
Substance abuse	Not allowed	19 (4.5)
Alcohol abuse	Not allowed	35 (8.3)
Previous treatment default	Not allowed	54 (12.8)
Enrolled in other trial	Not allowed	11 (2.6)
<b>Medical</b>		
HIV-positive		
CD4 cell count mL <sup>-1</sup>	<250	105 (24.9)
Antiretroviral therapy	Not allowed	108 (25.7)
Karnofsky score	<50	44 (10.5)
Insulin-dependent diabetes	Not allowed	3 (0.7)
Pregnant or breastfeeding	Not allowed	2 (0.5)
Uncontrolled epilepsy	Not allowed	1 (0.2)
Malabsorption	Not allowed	1 (0.2)
QT prolonging co-medication	Not allowed	27 (6.4)
Other critical co-medication	Not allowed	14 (3.3)
<b>Tuberculosis</b>		
Treatment initiated	Not allowed	343 (81.5)
<2 weeks		139 (33.0)
<4 weeks		236 (56.1)
Extrapulmonary TB	Not allowed	4 (1.0)
No resistance documented	Not allowed	1 (0.2)
Rifampicin monoresistance	Not allowed	72 (17.1)
Pre-XDR-TB	Not allowed	26 (6.2)
XDR-TB	Not allowed	44 (10.5)
MDR-TB treatment failure	Not allowed	43 (10.2)

TB: tuberculosis; MDR: multidrug-resistant; XDR: extensively drug-resistant.

information. If a subject had no obvious reasons for disqualification, we investigated if the TASK unit had indeed evaluated that subject for participation.

The clinical trials active at that time were approved by the South African Medicines Control Council, the local Ethics Board, and the relevant committees of Cape Town City Health and the Department of Health of the Western Cape of South Africa.

From July 1 to September 30, 2010, a total of 421 patients, aged between 5 and 86 years (median±SD 37±12 years), 239 (57%) male, were referred for evaluation. All were culture-positive for *M. tuberculosis*. No record of previous treatment was found in 110 (26%) primary DR-TB cases (MDR-TB: n=95; pre-XDR-TB: n=7; XDR-TB: n=8). The main areas for exclusion were HIV-related (CD4 cell counts <250 cells·mL<sup>-1</sup>, antiretroviral treatment), TB-related (resistance to RIF but not INH, resistance to more agents than INH and RIF) and operational, the latter based on the fact that 343 (81.5%) had been started on treatment before they could be screened and that of 55 referrals (13.1%) that could have qualified only 12 (21.8%, 2.9% of all) were known to and screened by the TASK unit.

This retrospective audit of a large series of consecutive patients referred to a treatment centre for DR-TB showed that <3% were screened for participation in a 2-year clinical trial with a novel agent. This seems low in the face of the great need for novel anti-TB treatments [9]. What can be done to improve this figure?

Many patients will be unequivocally excluded from drug research because of conditions that increase risk or impair compliance with protocol requirements, particularly long-term follow-up. Compromising on safety in the interest of speedy drug evaluation is ethically unacceptable. Yet, there are some areas to contemplate where adaptation in criteria or better preparation could increase participation without increasing risk to participants.

First, the need to seek regulatory approval for a specific indication such as “MDR-TB” could be reconsidered. “TB resistant to RIF”, a growing problem in South Africa and elsewhere [10], would include many more subjects without increased risk and make the results valid to a wider, more practically relevant population. Examples are patients with resistance only to RIF and patients with more extensive resistance for whom a safe and effective background regimen can still be constructed. Second, preparatory interaction studies with commonly used antiretroviral regimens to allow such co-medication would increase both the number of participants and the relevance of the results. Recommendations to use antiretroviral agents early for patients with TB support this [11, 12]. As an alternative to smear-positivity as a proxy for a positive baseline culture (to allow for culture conversion), protocols should consider the late exclusion of participants whose cultures remain negative. Finally, trial protocols with lengthy screening procedures that delay the initiation of treatment are not compatible with the interests of healthcare delivery. It could facilitate collaboration between public healthcare providers and research teams if participants were allowed to be on a background regimen for a limited time that would be modified upon trial participation.

In conclusion, we found that only very few MDR-TB patients were fit for participation in a drug trial for a novel regimen with the criteria applied at the time. Careful consideration of criteria related to HIV infection, antiretroviral treatment, anti-TB treatment and anti-TB drug resistance are critical to make participation more inclusive and to enhance recruitment without compromising safety.

Clinical trials are critical to provide new drugs and regimens not only for high-burden settings, but also for first-world countries striving for TB elimination [13].



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**Enrolment criteria of TB drug trials should be reconsidered to include relevant patient populations in early phases** <http://ow.ly/U3aoi>

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