Comment for Lancet Respiratory Medicine - ***Clinical trial research in focus*:**

Title:

Multi-drug resistant Tuberculosis – overcoming barriers to conduct of clinical trials in adults and children

Authors:

Alimuddin Zumla[1] PhD.FRCP.FRCPath and Ibrahim Abubakar[2] PhD.FRCP.FFPH

Institutional affiliations:

[1]Division of Infection and Immunity, University College London, and NIHR Biomedical Research centre, UCLHospitals NHS Foundation Trust, London, United Kingdom

[2]Institute of Global Health, University College London, London, United Kingdom

We declare no competing interests

Word count: 1015 words

References: 11

Figure: 1

Corresponding author: Professor Alimuddin Zumla FRCP. Email: a.i.zumla@gmail.com

The WHO 2016 annual report[1] states 'The TB epidemic is larger than previously estimated'. TB causes 1.5 million deaths and 49 million DALYS annually. There were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB) and a significant proportion of them remain undiagnosed and untreated. The current WHO recommended MDR-TB treatment regimen[2] is associated with poor treatment outcomes[1]. The regimen is based on no trial evidence of efficacy and may not cover local, evolving TB drug resistance patterns. The lengthy duration of treatment (12 to 24 months), drug toxicity and side effects including the painful injectable drugs. Importantly, many MDR-TB patients who survive, suffer long term lung damage and functional disability, and are unable to return to gainful employment.[3] This has been a neglected area of TB patient management and requires urgent attention.

There are several new TB drugs in development. An expanding portfolio of a range of adjunct host-directed therapies[4] are becoming available and will require evaluation in randomized clinical trials (RCTs) for improving treatment outcomes, and to minimize and alleviate lung damage, reduce duration of MDR-TB therapy, and prevent development of further drug resistance. Thus there are a growing number of RCTs in development. There is also an urgent need to enable these RCTs to be performed in as short as time as possible, so that treatment regimens which show improved efficacy and safety can be made available quickly and widely. No doubt this will be a long and arduous process.

There are formidable challenges and burning issues (**Figure 1)** regarding the conduct of randomized clinical trials (RCTs) that need to be addressed and overcome to effect a step-up change in the current dismal global status quo of MDR-TB. There is a need to reach global consensus on the optimal design of MDR-TB clinical trials.[5-8] Previous and some ongoing trials rely on large sample sizes and are of lengthy followup duration in order to produce convincing evidence base of efficacy of new TB drugs and regimens. Reducing large sample sizes and trialling more than one new TB drug in the same trial using the multi-arm, multi-stage (MAMS) design will allow maintaining flexibility to adapt to other data becoming available while trial in progress[6]. Variants of MAMS trials design need to be developed and refined further to optimise them. A Bayesian adaptive randomization design may allow a specified effect size from a reduction in overall sample size.[9]

The WHO guidelines for MDR-TB treatment[2] are implemented slightly differently in different settings and may change over time. Thus there is an absence 'Control regimen'. Since new MDR-TB regimens will need to work across a range of TB drug resistances and co-morbidities and should be generically

effective at population level, there should be careful selection of relevant MDR-TB patient population groups. Eligibility criteria should be less restrictive and trial populations need to reflect heterogeneity.

A longstanding bugbear across RCTs evaluating new TB drugs/regimens is the variation in terminology, case definitions, laboratory protocols, laboratory and clinical endpoints and trial design which makes comparisons between trials data difficult. Recent initiatives have focussed on developing harmonization across trials by developing universal consensus on terminology, case definitions, laboratory and clinical endpoints and trial designs.[5-9] Lack of accurate tools and biomarkers to predict treatment failure and relapse, and to stratify patients into high, medium and low 'risks of relapse' also prolong duration of trials. More investments into development of new biomarkers and trialling of new immunological and molecular biomarkers are required.[10]

Evaluation of new drugs requires more frequent followup over a long period of time in order to evaluate toxicity (including interactions with HIV drugs), side effects and risk of relapse.[5] This compromises patient adherence and increases trial duration. Universal standards and consensus for minimum duration and frequency of followup for toxicity interpretation of toxicity, side effects and safety of new TB drugs/regimens compared to existing ones is required.

Historically excluded groups with MDR-TB in RCTs include children, patients with HIV coinfection and pregnant women, will require specific attention. Several barriers exist in conduct RCTs in children and these need to be overcome.[7] Efficacy and safety from adult trials can be expanded to children after pilot pharmacokinetic and bioavailability studies. With the growing burden of MDR-TB in children and in HIV-co-infected patients a range of trials are required to define optimal regimens for MDR-TB treatment and these will face the conventional issues of pharmacokinetics of new TB drugs; TB/HIV drug interactions, toxicity, and selection of the appropriate pediatric study population, case definition for TB in the absence of microbiological confirmation, and new strategies for integrating children into adult tuberculosis trials[7].

Social and operational aspects have been neglected from being incorporated into TB clinical trials protocols. Mandatory inclusion of social and operational determinants in clinical trial protocols that could optimise adherence and improve treatment outcomes of success of MDR-TB failure. Proactive engagement of community leaders, HCWs and TB patient and advocacy groups (concept, trial and

dissemination phases). Lack of community leaders, healthcare workers and end user engagement in developing clinical trial protocols also hinders clinical trial enrolment and followup. Proactive engagement of community leaders, policy makers, HCWs and TB patient and advocacy groups from concept, to conduct of trial and dissemination of results).

Development of capacity in low and middle income high TB endemic countries[11] for conduct of locally led MDR-TB clinical trials has been slow and neglected. There is a dire need for building TB clinical trials capacities in high TB endemic countries. All currently registered TB trials on WHO databases are led by the western groups exposing the continuing dominance by the north despite the burden of disease disproportionately affecting the south. Further capacity for conduct RCTs in countries in Africa, Asia and South America with a high disease burden ought to be developed urgently empowering leadership from local scientists, community leaders and policy makers. High MDR-TB endemic countries such as China, India and Brazil have the resources to develop high grade capacities for MDR-TB clinical trials and provide much needed leadership to effect a stepup change from the current status quo, and lead the next generation of clinical trials

Author declarations: We declare no competing interests

REFERENCES

1. WHO Global Tuberculosis Report 2016.WHO/HTM/2016.13. 1-214.

2. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. Geneva: World Health Organization; 2016. Available from: http://www.who.int/tb/MDRTBguidelines2016.pdf. (Accessed 26th February, 2017)

3. Wallis RS, Maeurer M, Mwaba P, Chakaya J, Rustomjee R, Migliori GB, Marais B, Schito M, Churchyard G, Swaminathan S, Hoelscher M, Zumla A. Tuberculosis--advances in development of new drugs, treatment regimens, host-directed therapies, and biomarkers. *Lancet Infect Dis*. 2016 Apr;16(4):e34-46

4. Zumla A, Rao M, Wallis RS, Kaufmann SH, Rustomjee R, Mwaba P, Vilaplana C, Yeboah-Manu D, Chakaya J, Ippolito G, Azhar E, Hoelscher M, Maeurer M; Host-Directed Therapies Network consortium. Host-directed therapies for infectious diseases: current status, recent progress, and future prospects. *Lancet Infect Dis*. 2016 Apr;16(4):e47-63

5. Mitnick C, Rusen ID, Bain LJ, Horsburgh J. Issues in design and interpretation of MDR-TB clinica trails: report of the first Global MDR-TB clinical trials landscape meeting. *BMC Proceedings* 2015: 9: Suppl 8: 51 http://www.biomedcentral.com/1753-6561/9/S8/S1

6. Phillips PPJ. Methodological considerations in clinical trials for new MDR-TB treatment regimens. *Int J Tuber Lung Dis* 2016: 20(10):54-57

7. McAnaw SE, Hesseling AC, Seddon JA, Dooley KE, Garcia-Prats AJ, Kim S, Jenkins HE, Schaaf HS, Sterling TR, Horsburgh CR. Pediatric multidrug-resistant tuberculosis clinical trials: challenges and opportunities*. Int J Infect Dis.* 2016 Dec 9. pii: S1201-9712(16)31643-5. doi: 10.1016/j.ijid.2016.11.423. [Epub ahead of print]

8. Furin J, Alirol E, Allen E, Fielding K, Merle C, Abubakar I, Andersen J, Davies G, Dheda K, Diacon A, Dooley KE, Dravnice G, Eisenach K, Everitt D, Ferstenberg D, Goolam-Mahomed A, Grobusch MP, Gupta R, Harausz E, Harrington M, Horsburgh CR, Lienhardt C, McNeeley D, Mitnick CD, Nachman S, Nahid P, Nunn AJ, Phillips P, Rodriguez C, Shah S, Wells C, Thomas-Nyang'wa B, du Cros P.
Drug resistant tuberculosis clinical trials: proposed core research definitions in adults. *Int J Tuberc Lung Dis*. 2016 Mar;20(3):290-4. doi: 10.5588/ijtld.15.0490.

9. Cellamare M, Milstein M, Ventz S, Baudin E, Trippa L, Mitnick CD. Bayesian adaptive randomization in a clinical trial to identify new regimens for MDR-TB: the endTB trial. *Int J Tuberc Lung Dis.* 2016 Dec 1;20(12):8-12. doi: 10.5588/ijtld.16.0066.

10. Petruccioli E, Scriba TJ, Petrone L, Hatherill M, Cirillo DM, Joosten SA, Ottenhoff TH, Denkinger CM, Goletti D. Correlates of tuberculosis risk: predictive biomarkers for progression to active tuberculosis. *Eur Respir J*. 2016 Dec;48(6):1751-1763

11. Tupasi T, Gupta R, Danilovits M, Cirule A, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, Gao M, Awad M, Gentry LM, Geiter LJ, Wells CD. Building clinical trial capacity to develop a new treatment for multidrug-resistant tuberculosis. *Bull World Health Organ*. 2016 Feb 1;94(2):147-52. doi: 10.2471/BLT.15.154997.