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Corresponding Author: Mr. Saiam Ahmed, MSc

Corresponding Author's Institution: University College London, MRC Clinical Trials Unit, Institute of Clinical Trials and Methodology

First Author: Saiam Ahmed, MSc

Order of Authors: Saiam Ahmed, MSc; David Moore, MD; Camus Nimmo, MBBS; Andrew Nunn, MSc; Thomas Yates, PhD

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Linezolid for drug-susceptible tuberculosis

We question why linezolid would be included in a regimen for drug-susceptible tuberculosis (DS-TB) as described by Jung Kyu Lee et al[1] given its known toxicity profile. Regardless of the underlying premise, we have significant concerns about the manner in which the data have been analysed, presented, and the conclusions that have been drawn.

It is unclear why certain patients were excluded from the modified intention to treat (mITT) analysis. For example, those who did not take adequate trial medication should have been included in the mITT population.

Although participants were enrolled on the basis of being Xpert positive, only 285 (74%) were subsequently found to be culture positive at baseline. Therefore, the mITT population includes participants who were culture negative at enrolment and consequently could not contribute to the primary outcome of culture conversion. Therefore, the numbers at risk in Figure 2 are clearly incorrect.

Too much weight is given in the paper the per-protocol (PP) analysis, a biased assessment not appropriate in a trial with a superiority hypothesis. This overemphasis has influenced the authors' conclusions that there is a potential role for linezolid in treating DS-TB as they have focused on an analysis that does not properly reflect the treatment effect of the regimen.

Selecting regimens to take forward into treatment shortening trials is a complex decision. For the reasons we outline above, we do not think the authors' conclusions are supported by the data. The capacity to undertake randomised controlled trials in tuberculosis is currently severely limited, therefore it is critical that these trials are properly designed, analysed and reported.

REFERENCES

[1] Lee JK, Lee JY, Kim DK, et al. Substitution of ethambutol with linezolid during the intensive phase of treatment of pulmonary tuberculosis: a prospective, multicentre, randomised, open-label, phase 2 trial. *Lancet Infect Dis* 2019; **19**(1): 46-55.