Ascertainment Bias in TB Treatment Trials

Can Systematic Assessment of Objective Endpoints Solve It?

Multicenter, open-label, noninferiority treatment trials for tuberculosis (TB) are particularly challenging when it comes to the unbiased ascertainment of outcomes in settings in which there may be inadequate microbiological data available. The approach described by Kurbatova and colleagues (pp. 1376–1382) in this issue of the *Journal* (1), which was employed in Study 31/A5349 (2), has the potential to considerably reduce ascertainment bias by standardizing *1*) the triggers for which a workup for possible poor treatment response (PPTR) should be performed and *2*) the procedures involved in that workup.

Study 31/A5349 defined PPTR triggers as one or more of the following: a positive smear or culture result ⩾17 weeks after randomization, worsening signs or symptoms of TB, worsening radiographic evidence of TB, and the investigator considering extending treatment or initiating a new regimen for TB. These triggers were very sensitive in detecting an unfavorable TB outcome: 133 of 144 unfavorable TB outcomes had a PPTR event. All 11 without a PPTR event had been lost to follow-up by month 12; their inability to be detected did not reflect a failure of the PPTR approach as much as the challenge of retention. The vast majority of the PPTR triggers were microbiological, objective, and unlikely to be affected by knowledge of treatment assignment. The distribution of their presentation was variable across arms. Smear-positive microscopy after 17 weeks occurred more frequently in the experimental groups (48.0% in the rifapentine-moxifloxacin arm and 38.9% in the rifapentine arm) compared with the control arm (30.9%). Cultures positive for *Mycobacterium tuberculosis* were a PPTR trigger in 47.5% of control participants, 34.6% of rifapentine-moxifloxacin–arm participants, and 31.5% of rifapentine-arm participants.

Standardized PPTR evaluation procedures in Study 31/A5349 included a review of interval medical history and adverse events, symptom assessment, chest radiography, collection of three sputum samples (at least one early in the morning; all ⩾4 h apart) before changing TB treatment, collection of biomarker specimens, contact with the central study clinician, and completion of the relevant case report form. The report demonstrates variable, but relatively high, compliance with the PPTR procedures. Sputum sample collection was more complete in the experimental arms than in the control arm. The target of three collections in 1 week was achieved in 72.1% of the population overall and in 66.2% of those in the control arm. At least two samples were collected in 82.4% of those with a PPTR event: 77.7% of the control-arm participants, 84.9% of rifapentine-moxifloxacin participants, and 83.3% of rifapentine-arm participants. A larger proportion of control-arm participants with triggers had no sputum sample collected for evaluation, 10.1%, compared with 6.1% in the rifapentine-moxifloxacin arm and 8.8% in the rifapentine arm. Time to PPTR was also shorter in the experimental arms than in the control arm. These findings suggest that factors other than the occurrence of a PPTR trigger may have influenced provider response to the trigger.

Any reduction in ascertainment bias afforded by PPTR may be especially important in the current TB trial era, which, compared with historical precedent, is characterized by increased local clinical decision-making. In Study 31/A5349, for example, local investigators retain discretion to change study treatment in consultation with central trial clinicians or without such consultation if necessary to protect the participant's well-being. This practice is consistent with that in many contemporary trials (e.g., ReMoxTB [Rapid Evaluation of Moxifloxacin in Tuberculosis], STREAM [Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with Multi-Drug-Resistant Tuberculosis], and endTB [Evaluating Newly Approved Drugs for Multidrug-Resistant Tuberculosis]) (3–5). It is distinct from early BMRC trials, in which the central coordinating center retained more control over decisions to change treatment (6). Site investigator consideration of a change to study treatment is the most subjective of the PPTR triggers. As noted, this trigger occurred more frequently in experimental arms than in the control arm. Consideration of change alone was not sufficient to result in change except in cases in which rapid action was necessary for the participant's well-being. PPTR called for collection of additional microbiological and clinical information and consultation with a central clinical advisor before a treatment regimen change. Ultimately, treatment was changed or restarted for a clinical diagnosis of recurrence or adverse events more frequently in the rifapentine-moxifloxacin (3.0%) and rifapentine (2.5%) arms than in the control arm (1.1%). Changes for other reasons were less common in the experimental arms than in the control arm (2). Although employing the PPTR approach likely reduced these differences, residual ascertainment bias cannot be ruled out; no data were presented to inform the relationship among PPTR triggers, completed PPTR evaluations, and treatment change. Complementary strategies are likely to be required to further reduce ascertainment bias, to account for it in assigning treatment outcomes, or to address it in analysis. The estimand framework applied to trials of TB treatment may be helpful because it permits clear distinction between treatment changes that are considered intercurrent events and offers different analysis strategies depending on the perspective to be highlighted (7).

With the exception of treatment change, commonly collected trial endpoints are generally objective. In their comprehensive review of the history of BMRC [British Medical Research Council] clinical trials, Fox and colleagues highlighted the importance of this endpoint attribute: "the central analysis of results based largely on blinded

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objective laboratory results and blinded radiographic readings, with disclosure to participants only when the trial had been completed, was successful in preventing bias" (6). Kurbatova and colleagues test this hypothesis with the addition of a resource-intensive effort to standardize the conditions for evaluation of nonresponse and the approach to its evaluation. However, the continued emphasis on "objective" endpoints does have important, unintended consequences: the general health status, degree of respiratory disability, and quality of life are unknown for participants at the end of treatment and follow-up. Potential effects in the differences of regimen duration or composition on the massive global burden of post-TB morbidity (8) (recently dubbed post-TB lung disease) (9) are not considered. Although unblinded trials will always be at risk of bias in treatment-outcome assignment, strategies analogous to PPTR could be explored to permit the valid measurement of important patient-reported outcomes (10).

The PPTR approach represents an important attempt to balance competing priorities in TB trial implementation: the ethical obligation for the treating physician/investigator to act in the best interest of the study participants and the integrity of the trial. PPTR implementation requires significant cost and time. Notably, the requirements for the number of sputum samples and the interval between their collection, and the consultation with a central study clinician, preferentially before any change, can result in a several-day delay between the trigger and resolution even though site investigators were not required to wait for all the results to become available before modifying treatment. Nevertheless, PPTR offers a particularly useful framework for sites with limited prior trial experience and for experienced sites where investigators may need reminders of the importance of uniformity in the application of criteria and processes for outcome assessment. It highlights the importance of investment in training (and retraining) in the systematic application of trial procedures. PPTR makes a substantial improvement in the ability to minimize ascertainment bias in unblinded noninferiority trials of shortened TB treatment. Further refinement to simplify the process and reduce residual bias will improve its utility. ■

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