Reference

1. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, *et al*. Standardization of spirometry 2019 update: an official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 2019;200:e70–e88.

Reply to Haynes *et al.*

From the Authors:

The history of spirometry standards over the past 45 years has included recommendations based on expert opinion when peer-reviewed evidence was not available. For the 2019 update of the American Thoracic Society/European Respiratory Society (ATS/ERS) spirometry standards (1), the task force did an extensive literature review searching for studies that examined the effects of recommendations in past technical standards and either validated or invalidated such recommendations.

The 2005 ATS/ERS spirometry standards (2) recommended that if a filter were used with a spirometer, it also must be used when the spirometer was tested. No published evidence to the contrary was found up to 2019, and the recommendation was continued in the 2019 standards. Haynes and colleagues found that including the filter in calibration verifications produced differences up to ±0.7%, which they considered to be not clinically meaningful.

The 2005 standards (2) also recommended that the calibration syringe should "maintain the same temperature and humidity of the testing site," and this recommendation was continued in the 2019 standards. Haynes and colleagues reported that a 1-minute "bear hug" of the calibration syringe produced an increase in measured volume of 0.7% at low flows, which they believed does not appear to have a significant impact.

Although small amounts of error may not be clinically significant on their own, it is the accumulation of errors from all sources that needs to be considered and kept as low as reasonably and realistically possible. This is a prime role in setting technical standards.

Haynes and colleagues have shown that the use of a filter for spirometer calibration and syringe temperature changes can each have an effect on accuracy of up to 0.7%. Thus, if both errors are in the same direction, the cumulative effect of these two factors is up to 1.4%. Considering that the accuracy of the calibration syringe itself is ±0.5% and for the spirometer is ±2.5%, the additional combined degree of error from these two factors could result in recalibrations and calibration verifications having an error up to 4.4%—an increase of 47% from the recommended level in the 2019 spirometry standards.

Are these steps to improve accuracy in spirometry reasonable? The use of a filter in recalibration and calibration verification is generally not onerous, and for many spirometers, the filter is used as the adapter to connect the calibration syringe to the spirometer. However, some filters with newer oval and/or flared mouthpieces may not be as easy to connect to the calibration syringe. In addition, the statement regarding body contact with the syringe was not a "directive" of the 2019 standards but rather a caution to the operator to be aware of this potential source of error and to avoid extensive or prolonged bodily contact with the calibration syringe.

We thank Haynes and colleagues for their diligence in reviewing the 2019 update of the ATS/ERS spirometry standards and for contributing evidence for future revisions of the spirometry standards. ■

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Trials of Tuberculosis-Preventive Therapy in People with HIV Infection

To the Editor:

Stout and colleagues have developed an interesting and potentially useful mathematical model addressing some important issues in noninferiority trials of tuberculosis (TB)-preventive therapy (1).

The authors are the co-chairs of the task force that developed the official American Thoracic Society Document entitled "Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement."

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They rightly point out that enrolling individuals with no risk of experiencing an endpoint in such trials may result in a greater likelihood of finding noninferiority. Some of the assumptions used in their model, however, are not appropriate for trials of TB-preventive therapy in people with HIV infection.

Stout and colleagues (1) used participant parameters from the BRIEF TB (Brief Rifapentine Isoniazid Efficacy for Tuberculosis) study, a large, phase-three randomized trial comparing 1 month of isoniazid and rifapentine (1HP) to 9 months of isoniazid in people with HIV infection (2) to assert that a trial in such a population would have an "unacceptably high" probability of declaring noninferiority even if the experimental regimen was in fact inferior to the control regimen. Their explanation for this contention is that a significant proportion of participants in the BRIEF TB study had negative or missing tests for latent TB infection and were, therefore, not at risk of developing TB.

The assumption that people with HIV infection and negative results of a tuberculin skin test (TST) or IFN-γ release assay (IGRA) are not at risk for TB and will not benefit from preventive therapy is incorrect. People with HIV infection are at greatly increased risk of developing TB, particularly in high-burden settings, and preventive therapy has been proved efficacious in the absence of a positive TST or IGRA (3, 4). In the trial of Rangaka and coworkers (3), individuals with advanced HIV infection and negative TSTs or IGRAs who received a placebo experienced significantly higher rates of TB than those who received isoniazid. Of participants in the Temprano study tested by IGRA, only about one-third had positive results, yet those with negative tests who received isoniazid preventive therapy experienced similar reduction in the incidence of TB and death as those who were IGRA-positive (4).

In both arms of the BRIEF-TB trial, individuals with a negative TST or IGRA had rates of TB or death from an unknown cause that were substantially higher than those seen in TST-positive individuals without HIV infection enrolled in the PREVENT TB (Tuberculosis Trials Consortium Study 26) trial, demonstrating their increased risk (5). Additionally, the subgroup analysis of individuals in BRIEF-TB who had positive TSTs or IGRAs demonstrated noninferiority of 1HP to isoniazid, with an upper bound of the 95% confidence interval for the difference in rates being 0.73 per 100 person-years, which not only meets the noninferiority margin set for this trial (1.25 per 100 person-years) but also the noninferiority margin used in the PREVENT TB trial and the ongoing ASTERoiD (Assessment of Safety, Tolerability, and Effectiveness of Rifapentine Given Daily for LTBI) trial (0.75 per 100 person-years) (5, 6).

TB-preventive treatment is essential for achieving global TB control. Although tests of latent TB infection are useful in nonimmunosuppressed patients, it is clear that some populations, such as people with HIV infection and young child household contacts, do not require testing before initiating preventive treatment, a recommendation now endorsed by the World Health Organization (7). Studies of TB-preventive therapy in people with HIV infection must enroll the population that will receive the therapy in real-world clinical practice. The BRIEF TB trial demonstrated noninferiority of 1HP to isoniazid in both the overall population and the subset of those with a positive TST or IGRA, making the results generalizable to all HIV-infected adults and adolescents living in high-burden areas, as well as those with a positive test of latent infection anywhere. Requiring a positive TST or IGRA for enrollment into clinical trials of HIV-infected people seems to us like a step in the wrong direction. ■

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Reply to Swindells *et al.*

From the Authors:

We appreciate the interest in our recent manuscript (1) describing issues in noninferiority trials of latent tuberculosis infection (LTBI)

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