Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Finally, recent data show that the type of oximeter used may even have a higher influence than skin pigmentation (Fig 1).

It is time to harmonize practices for oxygen management worldwide, and more complex guidelines should be used that take into account the skin pigmentation as well as the type of oximeter used. This is also true if oxygen-free days are used as a marker in clinical trials evaluating new treatments. Ignoring these parameters would have an important impact on this new proposed outcome.

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Response

To the Editor:

We thank Dr Lellouche and colleagues for their comments regarding our manuscript.[1] Selecting an outcome measure for clinical trials in COVID-19 and other causes of hypoxemia is complex. We believe that oxygen-free days (OFD) is an important addition to the available clinical trial outcomes, but appreciate the considerations outlined by Dr Lellouche.

First, Dr Lellouche notes that variation in oxygen saturation targets could lead to differences in oxygen weaning and, therefore, differences in OFDs caused by practice patterns rather than pathophysiology. This limitation is correct but applies to all free day outcomes (eg, ventilator-free days, vasopressor-free days, and so forth), which are widely accepted in critical care research. Although practice variation may impact raw values for OFD, randomization in clinical trials would balance this variation between groups and preserve the validity of between-group comparisons.

Second, Dr Lellouche and colleagues highlight that skin pigmentation may affect the accuracy of oxygen saturation measurements using pulse oximetry (Spo_2). If pulse oximeters systematically overestimate Spo_2 compared with Sao_2 in patients with darker skin pigmentation, this could result in supplemental oxygen being weaned more quickly. Addressing this issue is critically important—more for the millions of patients affected in clinical care than for the use of OFDs as a clinical trial outcome, where randomization balances baseline patient characteristics such as skin pigmentation.

The statement by Lellouche et al that "…Spo_2 overestimates Sao_2 by 2% to 3%" in patients with darker skin may be overly simplistic. Measurement error has two components: directional bias and variability. The magnitude of the directional bias in Spo_2 measurement may differ based on the oximeter type and on the patient's Spo_2 value. In data collected by the authors, at Spo_2 values $< 92\%$ and $> 98\%$, no directional bias was present, and at values between 92% and 98%, Sao_2 values relative to Spo_2 were approximately 1% lower for Black patients.[2] Variability is also an important, and underappreciated, contributor to error in Spo_2 measurement.[2-4] At a given Spo_2 value, patients with darker skin are more likely to have either lower *or higher* Sao_2 values. Although directional bias could be corrected with a simple equation (eg, subtract 2% to 3% from the Spo_2), variability must be corrected by improving the device itself.

In summary, we agree with Lellouche et al that harmonizing the approach to supplemental oxygen use across participants and minimizing Spo_2 measurement

error for patients of all skin pigmentations would strengthen trials using OFDs as an outcome.

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Inhaled Corticosteroids and Mortality in COPD

Biases in Randomized Trials

To the Editor:

The meta-analysis of 60 randomized trials by Chen et al[1] in *CHEST* reports that inhaled corticosteroids (ICS) to treat COPD reduce all-cause mortality by 10% (OR, 0.90; 95% CI, 0.84-0.97) and up to 40% in some subgroups.[1] We note from Figure 2 of Chen et al that the pooled results are largely driven by three large trials, SUMMIT, IMPACT, and ETHOS, the latter two contributing 41% and 32% reductions in mortality with ICS use, respectively. However, the design of these triple-therapy trials included patients already treated with maintenance therapy that had to be abruptly discontinued before randomization, which could affect the results.[2,3] Indeed, regular ICS use was withdrawn in 70% to 80% of the patients in IMPACT and ETHOS, who were then randomized to a dual long-acting beta-agonists/ long-acting muscarinic antagonist bronchodilator. There is some evidence that this withdrawal affected the findings of these trials.

First, all-cause mortality was reduced with triple therapy, mainly in the first 3 months after randomization (by 76% in IMPACT and by 63% in ETHOS), compared with dual bronchodilators, with no reduction during the subsequent 9 months.[4] It is difficult to see how ICS could act so quickly and remarkably in preventing all-cause death, with no subsequent sustained benefit. This is more likely an effect of withdrawing ICS in patients who needed it, replaced by a dual long-acting beta-agonists/ long-acting muscarinic antagonist bronchodilator.[3]

Second, the analysis of these two trials, when restricted to the non-users of ICS before randomization, found that mortality was not reduced with triple therapy. Indeed, the hazard ratios of mortality with triple therapy, among non-users of ICS, were 1.25 (95% CI, 0.60-2.59) and 1.49 (95% CI, 0.49-4.55) in IMPACT and ETHOS, respectively, compared with dual bronchodilators.[4]

The suggestion that inhaled corticosteroids could reduce mortality in COPD was first reported in a 2001 observational study, followed by several others, many