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.

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Editor's Note: Authors are invited to respond to Correspondence that cites their previously published work. Those responses appear after the related letter. In cases where there is no response, the author of the original article declined to respond or did not reply to our invitation.

Oxygen-Free Days and the Confounders of Clinical Practice

To the Editor:

In *CHEST* (October 2022), Moskowitz et al[1] describe a new outcome measure for clinical trials focusing on patients with acute hypoxemic respiratory failure, the oxygen-free days,[1] which are related to hospital discharge, an important patient outcome, and hospital length of stay, an important financial outcome. The authors acknowledged several limitations to this end point but may have missed several important confounders. These include the oxygenation target, skin pigmentation, and the type of oximeter used (Fig 1).

Knowledge regarding oxygen therapy has advanced markedly over the last 20 years, with risks associated with hyperoxemia in addition to those more intuitive risks associated with hypoxemia identified. Current recommendations in acutely ill patients, except COPD, suggest targeting an oxygenation range with a low and a high oxygen saturation (Spo_2) limit. In different guidelines, the recommended Spo_2 targets range from 96% ± 2% proposed by the British Thoracic Society[2] to 92% ± 2% proposed by a Canadian group.[3]

In 36 hospitalized patients receiving oxygen therapy, targeting 96% rather than 92% Spo_2 resulted in a twofold increase in oxygen flow.[4] Consequently, clearly for the same patient managed in London, England (recommended Spo_2 between 94% and 98%) or in London, Ontario (recommended Spo_2 between 90% and 94%, if Canadian suggestions are followed), the duration of oxygen therapy and likely hospital length of stay will increase, whereas oxygen-free days will be reduced in London, England.

Similarly, if the recommendation for the Spo_2 target is not adjusted for skin pigmentation, the same issue will present. In a patient with dark skin pigmentation, oxygen will be weaned more quickly, as pulse oximetry (Spo_2) overestimates arterial oxygen saturation (Sao_2) by 2% to 3% compared with light pigmented subjects (Fig 1).[5]

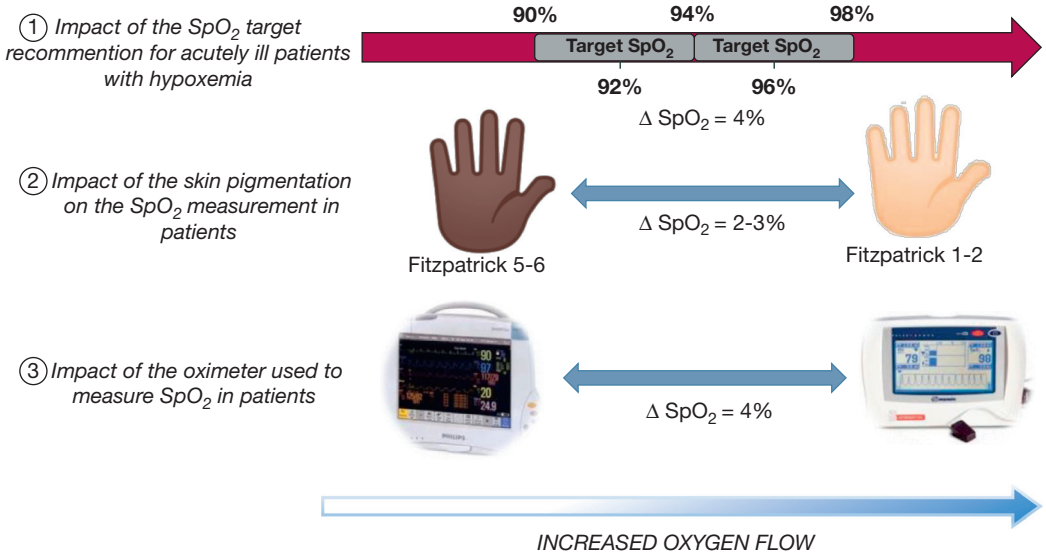

Figure 1 – *Impact of several parameters on oxygen needs: Spo_2 target, skin pigmentation, and type of oximeter used have an impact on the oxygen flow required, and potentially on oxygen therapy duration and associated factors, such as oxygen-free days and hospital length of stay. Extreme situations are presented: ① Spo_2 target recommended by the British Thoracic Society (96% ± 2%)[1] or the one in the rapid BMJ recommendations (92% ± 2%)[2]; ② Skin pigmentation for most pigmented (Fitzpatrick scale 5-6) and less pigmented subjects (Fitzpatrick scale 1-2); ③ Type of oximeter used, with those that overestimated Sao_2 the most and those that underestimated Sao_2 the most (https://openoximetry.org/oximeters). Sao_2 = arterial oxygen saturation; Spo_2 = oxygen saturation.*

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.

François Lellouche, MD, PhD
Marie-Anne Blanchet
Québec, QC, Canada,
Richard D. Branson, MSc RRT
Cincinnati, OH

AFFILIATIONS: From the Centre de recherche, Département de médecine (F. L. and M.-A. B), Institut Universitaire de Cardiologie et de Pneumologie de Québec Université Laval; and the Department of Surgery (R. B.), Division of Trauma & Critical Care, University of Cincinnati.

CORRESPONDENCE TO: François Lellouche, MD, PhD; email: francois.lellouche@criucpq.ulaval.ca

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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