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Dear Editorial team,

We are submitting our letter entitled '**Error without trials: Safe SpO₂ threshold levels may not be derivable from SpO₂ - PaO₂ relationships.**' This is a letter in response to the original article *Durlinger EMJ, Spoelstra-de Man AME, Smit B, de Grooth HJ, Girbes ARJ, Oudemans-van Straaten HM, Smulders YM. Hyperoxia: At what level of SpO(2) is a patient safe? A study in mechanically ventilated ICU patients. J Crit Care. 2017 Jun;39:199-204.*

This submission is being made solely to the Journal of Critical Care. The data presented in the letter were used for analysis in the original article *Ray S, Rogers L, Pagel C, Raman S, Peters MJ, Ramnarayan P. PaO₂/FIO₂ Ratio derived From the SpO₂/FIO₂ Ratio to Improve Mortality Prediction Using the Pediatric Index of Mortality-3 Score in Transported Intensive Care Admissions. Pediatr Crit Care Med. 2017 Mar;18(3):e131-e136.* The data were collected following UK Research Ethics Committee Review (IRAS 191836). The need for individual consent was waived.

We have no conflicts of interest to declare. This work was undertaken at Great Ormond Street Hospital/UCL Institute of Child Health, which received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre's funding scheme.

All the authors have contributed to the submission. GLJ and SR analysed the data, GLJ, SR, PR and MJP contributed and reviewed the final version of the manuscript.

Thank you.

Yours sincerely,

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Error without trials: Safe SpO₂ threshold levels may not be derivable from SpO₂ - PaO₂ relationships.

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Key words:

Hyperoxia, pulse oximetry, saturation, critical care, child

Dear Editor,

We read with great interest the article by Durlinger and colleagues associating a threshold peripheral oxygen saturation (SpO₂) level of >96% with arterial hyperoxia (PaO₂ >125 mmHg) [1]. Given the continuous nature of SpO₂ monitoring, we agree it is important to identify clinically appropriate targets of SpO₂ to guide the clinician in their practice. Although we appreciate this is a small prospectively collected sample, we ask the authors whether any outcome differences were seen between patients with SpO₂ levels above and below 96%. Both de Jonge and Helmerhort et al have shown a U-shaped curve of harm related to admission PaO₂ in adult patients [2,3]. They demonstrated a nadir of risk associated with a PaO₂ of 100-200 mmHg. Therefore a cut-off of 125 mmHg may be too low a threshold for hyperoxia. Preliminary work in children is similar [4].

The determinants of haemoglobin oxygen affinity (pH, temperature, CO₂, 2,3 DPG and fetal haemoglobin) may vary with critical illness. Hence large, heterogeneous datasets may be required to refine our estimate of PaO₂ from SpO₂ thresholds. As part of our clinical studies into the value of permissive hypoxaemia we re-analysed our dataset of blood gas and SpO₂ values collected from children transported to paediatric intensive care over a 3 year period (n=2128 in 1541 children) [5]. The relationship between PaO₂ and SpO₂ could be fitted to a regression equation of the form $SpO_2 = 100(1 - a * e^{(-b * PaO_2)})$ as described by Durlinger, where a=0.91 (95% CI 0.86-0.96) and b=0.05 (95% CI 0.04-0.05) (Figure 1). In this cohort 35 SpO₂ (1.6%) values <95% had corresponding PaO₂ of >100mmHg whilst 39 SpO₂ (1.8%) values <96% had corresponding PaO₂ of >125mmHg. In addition, 14 PaO₂ (0.7%) values <45mmHg had corresponding SpO₂ ≥95%; 12 (0.6%) had SpO₂ ≥96%.

We accept that these values may represent extremes of the population distribution, and may be secondary to a higher fetal haemoglobin fraction in children. Nevertheless, from this large cohort, we have confirmed the wide variability of PaO₂ values for each SpO₂ and therefore we question the reliability of inferring 'safe' SpO₂ thresholds from these values. Rather, we propose that 'safe' SpO₂ levels should be defined by randomised controlled trials comparing liberal versus conservative SpO₂ targets - as piloted by Panwar et al in adults, and currently undertaken in children by our group (Oxy-PICU, clinicaltrials.gov NCT03040570) [6].

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FIGURE 1. Exponential model of relationship between PaO₂ (mmHg) on y axis and SpO₂ (%) on X axis.

Regression line in red with 95% prediction intervals in green. Regression equation: $SpO_2 = 100(1 - a * e^{-b * PaO_2})$. Durlinger's proposed safe limits of SpO₂ =95% and PaO₂ =100mmHg in dashed purple lines.

SpO₂ =96% & PaO₂ =125mmHg safe limits in dashed blue lines.

