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Dear Editorial team,

We are submitting our letter entitled **'Error without trials: Safe SpO_2 threshold levels may not be derivable from SpO_2 - PaO_2 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 SpO_2 threshold levels may not be derivable from SpO_2 - PaO_2 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 (SpO_2) level of >96% with arterial hyperoxia (PaO_2 >125 mmHg) [1]. Given the continuous nature of SpO_2 monitoring, we agree it is important to identify clinically appropriate targets of SpO_2 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 PaO_2 in adult patients [2,3]. They demonstrated a nadir of risk associated with a PaO_2 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, CO_2, 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 SpO_2 values collected from children transported to paediatric intensive care over a 3 year period (n=2128 in 1541 children) [5]. The relationship between PaO_2 and SpO_2 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 SpO_2 (1.6%) values <95% had corresponding PaO_2 of >100mmHg whilst 39 SpO_2 (1.8%) values <96% had corresponding PaO_2 of >125mmHg. In addition, 14 PaO_2 (0.7%) values <45mmHg had corresponding SpO_2 ≥95%; 12 (0.6%) had SpO_2 ≥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 PaO_2 values for each SpO_2 and therefore we question the reliability of inferring 'safe' SpO_2 thresholds from these values. Rather, we propose that 'safe' SpO_2 levels should be defined by randomised controlled trials comparing liberal versus conservative SpO_2 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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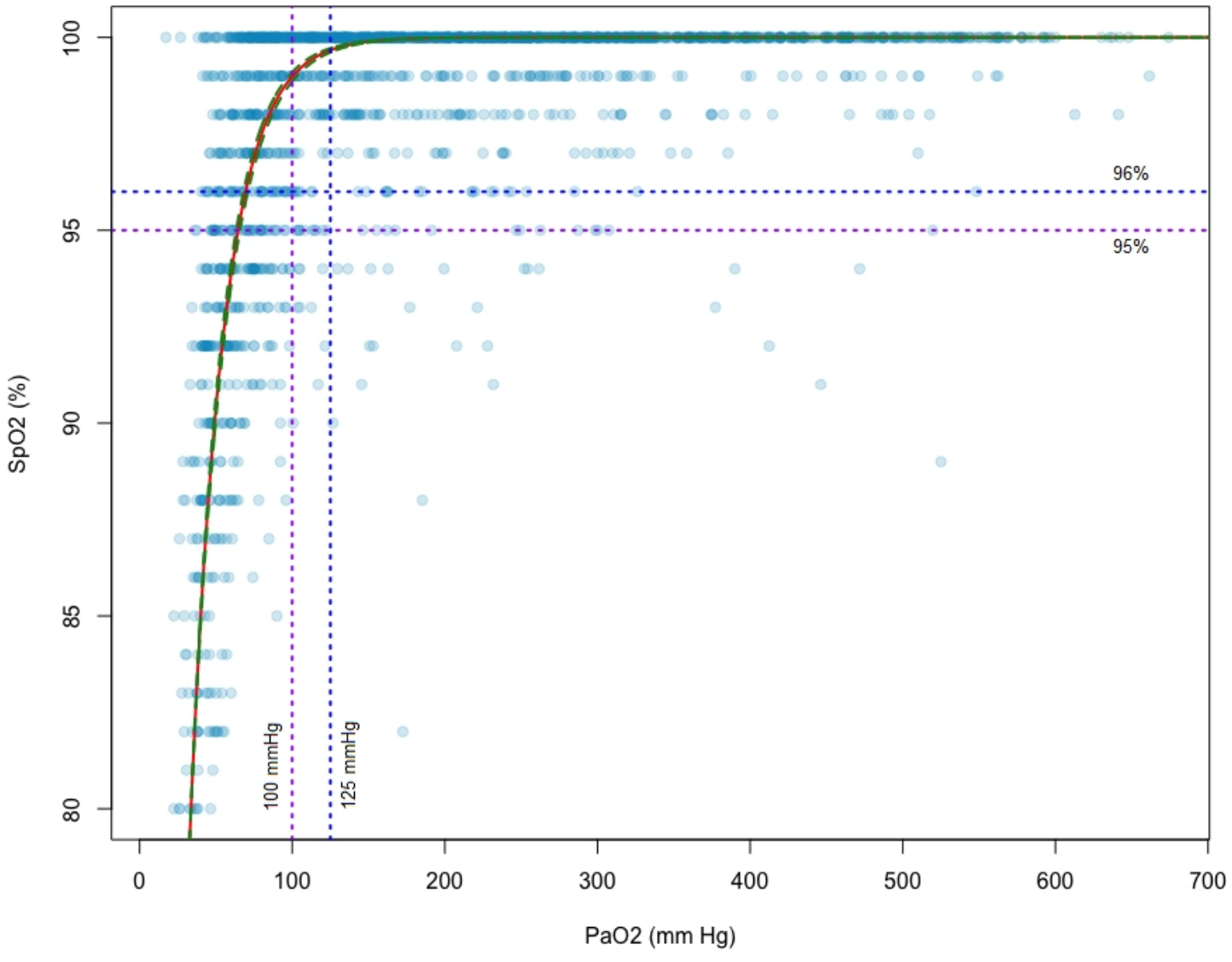
FIGURE 1. Exponential model of relationship between PaO_2 (mmHg) on y axis and SpO_2 (%) on X axis. Regression line in red with 95% prediction intervals in green. Regression equation: $SpO_2 = 100(1 - a * e^{(-b * PaO2)})$. Durlinger's proposed safe limits of SpO_2 =95% and PaO_2 =100mmHg in dashed purple lines. SpO_2 =96% & PaO_2 =125mmHg safe limits in dashed blue lines.


SpO2 (%)
100
95
90
85
80
96%
95%
100 mmHg
125 mmHg
0
100
200
300
400
500
600
700
PaO2 (mm Hg)