

# Performance and safety of the PRICO closed-loop oxygen saturation targeting system in neonates: pragmatic multicentre cross-over study (TarOx Study)

Maria Wilinska,<sup>1,2</sup> Thomas Bachman ,<sup>3</sup> Tomasz Szczapa ,<sup>4,5</sup> Katarzyna Wroblewska-Seniuk,<sup>4,5</sup> Karolina Chojnacka,<sup>4,5</sup> Beata Loniewska,<sup>6</sup> Karolina Olszanska,<sup>6</sup> Beata Rzepecka Weglarz,<sup>7</sup> Katarzyna Janusz,<sup>8</sup> Pawel Piwowarczyk,<sup>2</sup> Wes Onland ,<sup>9,10</sup> G Jeroen Hutten,<sup>9,10</sup> Ruud W van Leuteren,<sup>9,10</sup> Anton H van Kaam<sup>9,10</sup>

**To cite:** Wilinska M, Bachman T, Szczapa T, *et al*. Performance and safety of the PRICO closed-loop oxygen saturation targeting system in neonates: pragmatic multicentre cross-over study (TarOx Study). *BMJ Paediatrics Open* 2024;**8**:e002583. doi:10.1136/bmjpo-2024-002583

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/bmjpo-2024-002583>).

Received 16 February 2024  
Accepted 29 May 2024



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Dr Maria Wilinska; wilinska.maria@gmail.com

## ABSTRACT

**Objective** This study aims to evaluate the performance of the fabian-Predictive-Intelligent-Control-of-Oxygenation (PRICO) system for automated control of the fraction of inspired oxygen (FiO<sub>2</sub>).

**Design** Multicentre randomised cross-over study.

**Setting** Five neonatal intensive care units experienced with automated control of FiO<sub>2</sub> and the fabian ventilator.

**Patients** 39 infants: median gestational age of 27 weeks (IQR: 26–30), postnatal age 7 days (IQR: 2–17), weight 1120 g (IQR: 915–1588), FiO<sub>2</sub> 0.32 (IQR: 0.22–0.43) receiving both non-invasive (27) and invasive (12) respiratory support.

**Intervention** Randomised sequential 24-hour periods of automated and manual FiO<sub>2</sub> control.

**Main outcome measures** Proportion (%) of time in normoxaemia (90%–95% with FiO<sub>2</sub>>0.21 and 90%–100% when FiO<sub>2</sub>=0.21) was the primary endpoint. Secondary endpoints were severe hypoxaemia (<80%) and severe hyperoxaemia (>98% with FiO<sub>2</sub>>0.21) and prevalence of episodes ≥60 s at these two SpO<sub>2</sub> extremes. **Results** During automated control, subjects spent more time in normoxaemia (74%±22% vs 51%±22%, p<0.001) with less time above and below (<90% (9%±8% vs 12%±11%, p<0.001) and >95% with FiO<sub>2</sub>>0.21 (16%±19% vs 35%±24%) p<0.001). They spent less time in severe hyperoxaemia (1% (0%–3.5%) vs 5% (1%–10%), p<0.001) but exposure to severe hypoxaemia was low in both arms and not different. The differences in prolonged episodes of SpO<sub>2</sub> were consistent with the times at extremes.

**Conclusions** This study demonstrates the ability of the PRICO automated oxygen control algorithm to improve the maintenance of SpO<sub>2</sub> in normoxaemia and to avoid hyperoxaemia without increasing hypoxaemia.

## BACKGROUND

Respiratory instability leading to frequent hypoxaemic episodes is a common problem

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Oxygenation targeting in newborn infants is essential but successful manual titration of oxygen is challenging.
- ⇒ Automated control of inspired oxygen is now available and shows great promise, but efficacy and safety may vary between the different available algorithms.

## WHAT THIS STUDY ADDS

- ⇒ In a multicentre study, the fabian-Predictive-Intelligent-Control-of-Oxygenation (PRICO) automated system was shown to be effective and safe in neonates of different maturities among a range of ventilator modalities.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Based on this and other smaller studies, the fabian-PRICO can be routinely used in clinical practice.
- ⇒ Additional research is indicated to evaluate automated oxygen control systems to not only determine how they can be improved but also how their use can be optimised in different clinical environments.

in preterm infants. Therefore, the SpO<sub>2</sub> is continuously monitored, aiming to keep it within a target range by manually adjusting the fraction of inspired oxygen (FiO<sub>2</sub>).<sup>1</sup> However, nurses struggle with this task, and as a result, hyperoxaemia and hypoxaemia are prevalent.<sup>2,3</sup> Both are associated with adverse outcomes in preterm infants.<sup>4–8</sup> Improving oxygen targeting in preterm infants is, therefore, needed.

Modern neonatal ventilators offer the option of automated closed-loop oxygen control (A-FiO<sub>2</sub>). During A-FiO<sub>2</sub>, a software algorithm

adjusts the delivered  $\text{FiO}_2$  based on the measured  $\text{SpO}_2$  and the set target range. Many studies have reported that A- $\text{FiO}_2$ , compared with manual control (M- $\text{FiO}_2$ ), improves the time spent within the target range and reduces the exposure to hypoxaemia and/or hyperoxaemia.<sup>9 10</sup> However, A- $\text{FiO}_2$  control algorithms differ considerably,<sup>11</sup> and therefore, the performance of each algorithm needs to be studied under different conditions before conclusions can be drawn on its relative effectiveness and limitations. The Predictive-Intelligent-Control-of-Oxygenation (PRICO) A- $\text{FiO}_2$  algorithm, introduced in 2016, had only been evaluated in two small single-centre studies.<sup>12 13</sup> Therefore, the aim of this study was to evaluate the efficacy and safety of the PRICO algorithm in a wide range of infants supported with different modes of respiratory support, across multiple centres.

## METHODS

This was a multicentre randomised cross-over study in five European neonatal intensive care unit (NICUs), one in the Netherlands and four in Poland. Potential sites were only considered if they had experience with the Fabian ventilator (Vyair Medical, Mettawa, USA) and A- $\text{FiO}_2$ . The study was sponsored by Vyair and designed as a postmarket clinical follow-up study conducted to fulfil the EU Medical Device Regulations and registered at ClinicalTrials.gov (NCT 04957472). There was no patient or public involvement in designing the study. An independent data safety monitoring committee conducted interim safety reviews masked to the sponsor and the investigators. A contract research organisation managed the study activities including site monitoring and collection of adverse events. This is an independent report from the investigators, which was neither commissioned nor influenced by the sponsor.

### A- $\text{FiO}_2$ system

The PRICO A- $\text{FiO}_2$  option of the Fabian ventilator is available for all invasive and non-invasive respiratory support modalities. PRICO uses a rule-based algorithm, first described by Hütten *et al.*<sup>14</sup> It monitors the  $\text{SpO}_2$  every second using an integrated Masimo pulse oximeter (Masimo Corporation, California, USA). Based on a weighted average of these data, an adjustment in  $\text{FiO}_2$  is made every 30 s, if warranted. When within the set  $\text{SpO}_2$  target range, the  $\text{FiO}_2$  adjustment is  $\pm 1\%$  towards the midpoint. When outside the target range the adjustment varies ( $\pm 1\%$ – $10\%$ ), based on a proprietary algorithm that takes into account the depth and the trajectory of the predicted response to a change in oxygen. In certain conditions (no  $\text{SpO}_2$  reading (drop-out) or exceeding operator set parameters) the system switches off automated control and falls back to manual control at the  $\text{FiO}_2$  previously set by the clinician, while generating an alarm. The system returns to A- $\text{FiO}_2$  control when the condition resolves or after manual reactivation.

## Study population

Infants in the NICU needing a target of 90%–95%  $\text{SpO}_2$ , regardless of weight or gestational age, were eligible for enrolment if they required invasive or non-invasive respiratory support and supplemental oxygen ( $>0.21$ ). Infants were excluded if they had congenital anomalies or uncontrolled haemodynamic instability. In addition, infants were also excluded if the attending physician did not believe participation was in the best interest of the infant, or if parental consent was not obtained.

## Study protocol

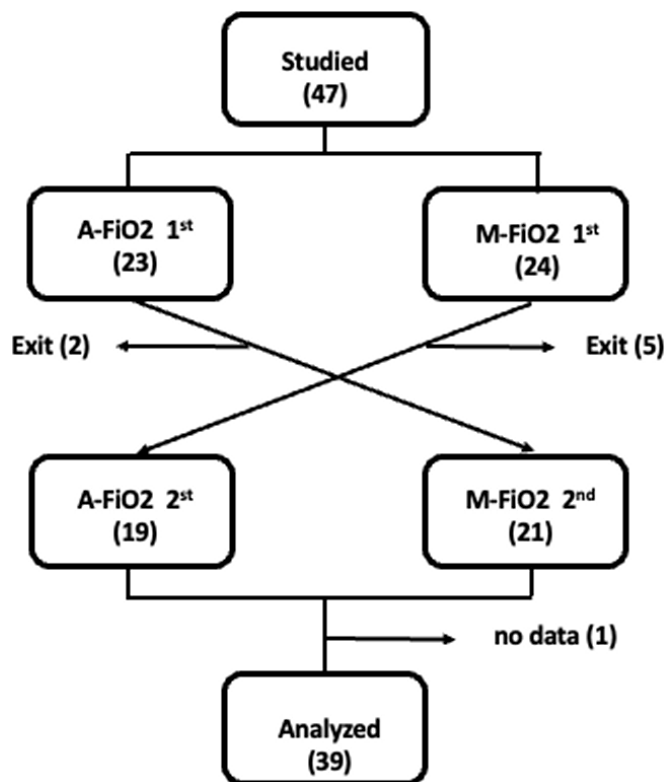
Subjects, a sample of convenience, were assigned to sequential 24-hour periods of A- $\text{FiO}_2$  and M- $\text{FiO}_2$  control in random order. Except for the order of intervention, all other aspects of care, including all PRICO settings (oximeter averaging,  $\text{SpO}_2$  alarm levels and target range thresholds), were according to each unit's standard practice. For infants ready to start caffeine therapy, entry was delayed at least 12 hours to avoid caffeine wash-in effects. Subjects exited the study early if they required a change in the mode of respiratory support, or if the attending physician or the parents withdrew support for participation.

An electronic web-based system (CastorEDC, Amsterdam, Netherlands) was used for the collection of baseline characteristics and subject randomisation. The  $\text{SpO}_2$  values and ventilator settings were recorded on a laptop computer attached to ventilator during both arms of the study. These data were uploaded to the sponsor's study portal and automatically incorporated into a database. The analyses were based on 4 s data points. Remote monitoring reports were automatically generated and sent to the study monitor after each enrolment, with potential inconsistencies adjudicated. Periodic site visits also audited study conduct.

## Endpoints

The proportion of time in normoxaemia was the primary endpoint and specified as  $\text{SpO}_2$  90%–95% with  $\text{FiO}_2 > 0.21$ , plus time 90%–100% with  $\text{FiO}_2 = 0.21$ .<sup>9 15</sup> Avoiding  $\text{SpO}_2$  extremes associated with severe hypoxaemia ( $<80\%$ )<sup>5 16</sup> and severe hyperoxaemia ( $>98\%$  with  $\text{FiO}_2 > 0.21$ )<sup>15 16</sup> were also specified outcomes.

Other descriptive endpoints were (1) the proportion of time in each  $\text{SpO}_2$  bin between  $\leq 80\%$  and 100%, with and without supplemental oxygen; (2) the mean proportion of time above and below normoxaemia; (3) the mean  $\text{FiO}_2$  and  $\text{SpO}_2$ , as well as the median  $\text{SpO}_2$  for the 2 min after oximeter drop-outs; (4) the number of  $\text{FiO}_2$  adjustments and (5) the frequency and duration of episodes outside target range. Episodes were defined as consecutive 4 s data points. Prolonged episodes were defined as those lasting for at least 60 s. Two post hoc analyses were conducted. The time with  $\text{SpO}_2$  between 90% and 95% during supplemental oxygenation was calculated, to assess the impact of differences in time on room air between automated and manual control. In addition,



**Figure 1** Subject accounting. The two patients exited in the first A-FiO<sub>2</sub> arm were at 22 and 24 hours (one was an intubation and the other an operator error (data logging turned off during manual intervention)). The five patients' exits from the first arm of M-FiO<sub>2</sub> were at 8, 19, 21, 24, 24 hours (two were weaned from HFNC, one was intubated and two were withdrawn by the attending). There were no early exits in the second arm during A-FiO<sub>2</sub>. Four patients exited early in the second arm of M-FiO<sub>2</sub> at 5, 12, 14, 15 hours (two were an operator error with collection of SpO<sub>2</sub> data, one withdrawal by attending and one was extubated). FiO<sub>2</sub>, fraction of inspired oxygen; HFNC, high-flow nasal cannula.

the primary outcomes were cross-tabulated by invasive and non-invasive respiratory support. To account for possible transition effects data from the first 10 min and last 5 min of each arm were excluded. All calculations of the proportion of time used time with an SpO<sub>2</sub> signal as the denominator.

Endpoints were unchanged except for the post hoc analyses noted above.

### Statistical considerations

A meta-analysis of 14 similar A-FiO<sub>2</sub> cross-over study cohorts reported that A-FiO<sub>2</sub> improved time within the SpO<sub>2</sub> target range by 12.9%.<sup>9</sup> We determined that we would be able to detect a 4% ( $\pm 6\%$  SD) difference between A-FiO<sub>2</sub> and M-FiO<sub>2</sub> with an alpha of 5% and a power >90% with 40 infants. Assuming 15% would not complete the study, an enrolment of 47 patients was specified.

Based on intention to treat, all subjects with exposure to both interventions of any duration were included in the analyses. The three outcome endpoints were also

**Table 1** Baseline enrolment

Subjects	39
Gender (% female)	18/39 (54)
Gestational age (weeks <sup>days</sup> )	27 <sup>4</sup> (26 <sup>3</sup> –30 <sup>0</sup> )
Birth weight (grams)	980 (800–1335)
Age at entry (days)	7 (2–17)
Weight at entry (grams)	1120 (915–1588)
Indication for respiratory support	
RDS	20 (51%)
Respiratory Insufficiency	8 (21%)
BPD	6 (15%)
Other	5 (13%)
Surfactant (%)	33 (85%)
Caffeine (%)	25 (64%)
Antibiotics (%)	36 (63%)
Vasoactive drug (%)	6 (15%)
Invasive ventilation	12 (31%)
SIPPV/SIMV/HFO	7/4/1
Non-invasive support	27 (69%)
DuoPAP/CPAP/HFNC/NIPPV	12/10/4/1
Initial FiO <sub>2</sub> (%)	32 (22–43)
Previous use A-FiO <sub>2</sub> (%)	8 (21%)
First arm A-FiO <sub>2</sub> (%)	21 (54%)

Continuous parameters are presented as median (IQR) RDS, BPD, SIPPV, SIMV, HFO, DuoPA, CPAP, HFNC, NIPPV.

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; DuoPAP, two level positive airway pressure; FiO<sub>2</sub>, fraction of inspired oxygen; HFNC, high-flow nasal cannula; HFO, high-frequency oscillation; NIPPV, nasal intermittent positive pressure ventilation; RDS, respiratory distress syndrome; SIMV, synchronised intermittent mechanical ventilation; SIPPV, synchronised intermittent positive pressure ventilation.

calculated for all enrolled subjects, as a sensitivity analysis to determine if their exclusion affected the results.

Variables and differences between paired variables were tested for normality (Shapiro-Wilk test), which showed that nearly all were not normally distributed. Therefore, non-parametric tests were used to evaluate the difference between automated and manual control periods (Wilcoxon signed-rank or Mann-Whitney for paired and nonpaired data, respectively). To facilitate comparison to previous and inclusion in future meta-analyses, times in, above and below the target range are reported as mean and SD. For consistency of presentation, other parameters are reported as median and IQR. A two-tailed  $p < 0.05$  was considered statistically significant for all comparisons. 95% CI in the difference in mean was determined for the primary outcome. Statistical tests were conducted with XLSTAT V.11.5 (Lumivero, New York, USA).

**Table 2** End points

	A-FiO <sub>2</sub>	M-FiO <sub>2</sub>	P value
<b>n</b>	<b>39</b>	<b>39</b>	<b>na</b>
Primary			
% time 90%–95% or above without O <sub>2</sub>	74±22	51±22	<0.001
% time SpO <sub>2</sub> <80%	0 (0–1)	0 (0–1)	ns
% time SpO <sub>2</sub> >98% with suppl O <sub>2</sub>	1 (0–3.5)	5 (1–10)	<0.001
Secondary			
% Time 90%–95% with FiO <sub>2</sub> >0.21*	63±20	40±21	<0.001
% Time>95% with FiO <sub>2</sub> >0.21*	16±19	35±24	<0.001
% Time SpO <sub>2</sub> <90%	9±8	12±11	<0.001
Episodes<80% ≥4 s per day	9.0 (4.6–39)	16 (8.5–40)	0.041
Episodes<80% ≥60 s per day	1.0 (0.0–2.5)	1.0 (0.0–5.4)	ns
Episodes>98% with FiO <sub>2</sub> >0.21 per day	41 (15–123)	142 (44–253)	0.002
Episodes>98% ≥60 s with FiO <sub>2</sub> >0.21 per day	2.2 (0.0–9.0)	13.0 (3.9–29)	0.003

The values are presented as mean±SD or median (IQR).

\*Calculated as %time with time in supplemental oxygen as the denominator.

FiO<sub>2</sub>, fraction of inspired oxygen; n/a, not applicable; ns, not significant.

## RESULTS

Patients were enrolled between January and October 2022. Centres enrolled between 6 and 12 infants, accounting for a total of 47 infants. Eight subjects were excluded from the analysis: seven were not exposed to both control methods, and in one, no data were captured due to a technical problem (figure 1). Thus, 39 subjects, exposed to both A-FiO<sub>2</sub> and M-FiO<sub>2</sub>, were included in the final intention-to-treat analyses.

The characteristics of the study population are shown in table 1. Most of the subjects were less than 2 weeks at enrolment. More than half were less than 1000 g when enrolled, and a quarter between 2900 and 4160 g. A total of 27 infants (69%) were receiving noninvasive support

(13 intermittent nasal positive pressure ventilation, 10 continuous nasal positive airway pressure, 4 high-flow nasal cannula (HFNC)) and the remaining 12 infants (31%) were supported by invasive mechanical ventilation. Eight infants (21%) were receiving A-FiO<sub>2</sub> before study entry.

The primary outcome, time within normoxaemia and time at SpO<sub>2</sub> extremes are detailed in table 2. During A-FiO<sub>2</sub> control, the time in normoxaemia was higher than during manual control (74%±22% vs 51%±22%, respectively; p<0.001, mean difference 23%, 95% CI 16% to 30%). A-FiO<sub>2</sub> was associated with a decrease in time with SpO<sub>2</sub>>98% when receiving supplemental oxygen (1% (IQR 0%–3.5%) vs 5% (IQR 1%–10%), p<0.001.

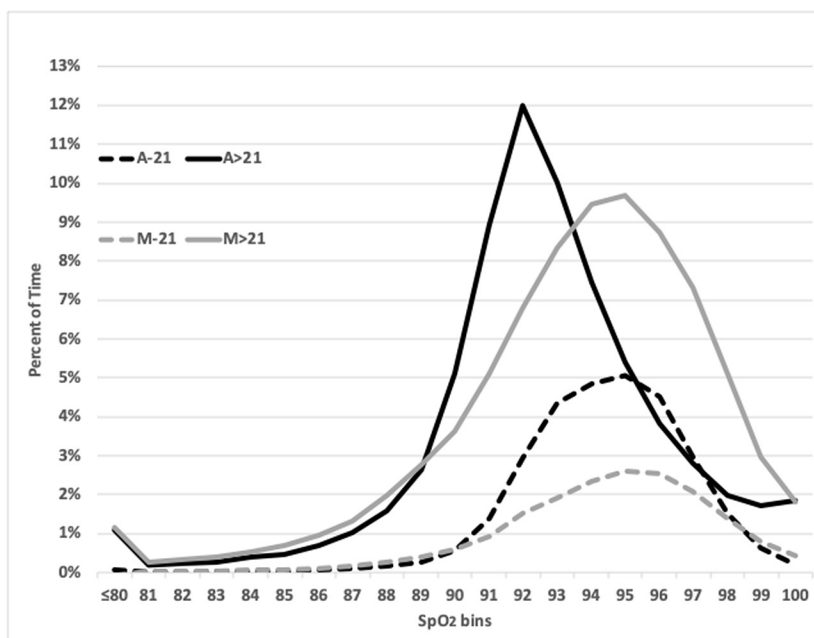
**Table 3** Overview of intervention

	A-FiO <sub>2</sub>	M-FiO <sub>2</sub>	P value
<b>n</b>	<b>39</b>	<b>39</b>	<b>na</b>
Duration of intervention (hour)	23.7 (23.7–23.9)	23.7 (23.6–23.9)	ns
Mean SpO <sub>2</sub> (%)	92.9 (92.4–94.6)	94.0 (92.2–95.4)	0.025
SpO <sub>2</sub> dropouts (per day)	11 (5–16)	10 (6–16)	ns
Median SpO <sub>2</sub> after drop-out (%)	92 (91–95)	90 (87–92)	ns
Mean FiO <sub>2</sub> (%)	26 (23–40)	26 (23–27)	ns
Time in FiO <sub>2</sub> =0.21 (%)	17 (2–51)	3 (0–27)	0.019
FiO <sub>2</sub> flushes per day	4 (1–15)	1 (0–5)	0.025
Manual FiO <sub>2</sub> adj per day	8.0 (4.5–12)	30 (17–106)	<0.001
Auto FiO <sub>2</sub> adjustments per hour	80 (50–108)	n/a	n/a

The values are presented as median (IQR). SpO<sub>2</sub> after dropout reflects subsequent 2 min. The flush function permits the clinician to trigger an increase in FiO<sub>2</sub> for a short period of time and can be used to preoxygenate or respond to a marked hypoxaemia. The level of FiO<sub>2</sub> and duration of flush are both set by the operator.

FiO<sub>2</sub>, fraction of inspired oxygen; n/a, not applicable; ns, not significant.





**Figure 2** Histogram SpO<sub>2</sub> with and without supplement O<sub>2</sub>. Histogram constructed with the mean of the subjects' SpO<sub>2</sub> in each bin. The grey lines are M-FiO<sub>2</sub> and the black A-FiO<sub>2</sub>. The dashed lines are during periods without supplemental oxygen and the solid with supplemental oxygen. FiO<sub>2</sub>, fraction of inspired oxygen.

Exposure to SpO<sub>2</sub><80% was low in both arms and not significantly different. The first post hoc analysis, which included all enrolled subjects (ie, those not exposed to both A-FiO<sub>2</sub> and M-FiO<sub>2</sub>), was consistent with these findings. Finally, these results were similar for infants supported non-invasively or invasively (post hoc results in online supplemental materials).

Secondary descriptive endpoints were consistent with the primary outcome findings. As shown in table 2, there were fewer total episodes and fewer prolonged episodes of hyperoxaemia during A-FiO<sub>2</sub>. In addition, there was no difference in number of prolonged episodes of hypoxaemia. There was, however, a slight reduction in the total number of severe hypoxaemic episodes associated with A-FiO<sub>2</sub>.

Table 3 provides information on the course of the interventions. During A-FiO<sub>2</sub>, automatic adjustments of FiO<sub>2</sub> were quite frequent (80/hour (IQR: 50–108), but manual adjustments were markedly lower than during M-FiO<sub>2</sub> (8.0/day (4.5–12) vs 30/day (17–106), p<0.001). The median FiO<sub>2</sub> and SpO<sub>2</sub> were similar in the two arms. However, during A-FiO<sub>2</sub> the infants spent more time on room air, with a slightly lower median SpO<sub>2</sub> (92.9% (92.4%–94.6%) vs 94.0% (92.2%–95.4%) p=0.025). The SpO<sub>2</sub> histogram in figure 2 shows the SpO<sub>2</sub> distribution during periods with and without supplemental oxygen. When receiving supplemental oxygen, there was a shift towards normoxaemia during A-FiO<sub>2</sub>, which is more apparent than the small difference in SpO<sub>2</sub> medians (table 3). As expected during periods without supplemental oxygen, both histograms shifted to the right with similar and limited hypoxaemia exposure.

There were four adverse events reported during the study period, two in each treatment arm. A detailed description can be found in online supplemental material. In addition, four subjects spent more time in normoxaemia during manual control.

## DISCUSSION

We conducted a multicentre pragmatic cross-over study to evaluate the performance of the PRICO A-FiO<sub>2</sub> system. We found that this A-FiO<sub>2</sub> system markedly increased time in normoxaemia which was mainly driven by a reduction in time spent in hyperoxaemia.

The difference in the mean time in the target range (23% (95% CI 16% to 30%)) is slightly higher than reported in two systematic reviews which included 14 studies investigating eight different A-FiO<sub>2</sub> systems.<sup>9 10</sup> The subgroup meta-analysis in one review, including only those studies using a target range of 90%–95% as we used, showed a difference of 18% (95% CI 5% to 32%).<sup>9</sup> Our finding is within these confidence limits. In addition to differences in the A-FiO<sub>2</sub> algorithms, the larger treatment effect might be related to manual oxygen titration practices, staffing levels and inclusion of bigger infants.

To date, three other studies have investigated the efficacy of the PRICO system in infants. These studies<sup>12 13 17</sup> reported a median improvement of the time within the target range between 6% and 16%, again considerably lower than this study. This larger difference between A-FiO<sub>2</sub> and M-FiO<sub>2</sub> seems to be mediated on the one hand by a higher percentage of time within the target range during A-FiO<sub>2</sub> with a lower percentage of time



within the target range in the M-FiO<sub>2</sub>. While all studies, including ours, tended to reduce time above and below the target range, there was considerable variation in the reduction at SpO<sub>2</sub> extremes in the different studies. Two suggested a more prominent effect in reducing the time in severe hypoxaemia<sup>13 17</sup> while our study showed better performance of A-FiO<sub>2</sub> in avoiding severe hyperoxaemia. One study reported a decrease in severe hypoxaemia but did not report exposure to severe hyperoxaemia.<sup>12</sup> Although it is unclear what caused these differences in performance, it is important to emphasise, that there were important differences between the studies which may have impacted the efficacy of both automated and manual FiO<sub>2</sub> control. One study by Dijkman *et al*, only included infants on HFNC, which allows for a large leak at the nasal interface.<sup>13</sup> Two of the previous studies used a broader SpO<sub>2</sub> target range (88%–95%)<sup>13 17</sup> and a shorter measurement period (8 hours),<sup>17</sup> which may also have impacted performance. Finally, there were differences in the patient characteristics, such as gestational age, respiratory support modalities and the postnatal age at inclusion. Overall, these findings suggest that the relative effectiveness of an A-FiO<sub>2</sub> system is not fixed but will vary between different patients, target ranges and modes of respiratory support. As an example, two recent reports suggest the relative effectiveness of A-FiO<sub>2</sub> compared with M-FiO<sub>2</sub> is most marked in unstable infants.<sup>17 18</sup>

Although most of the focus when evaluating the performance of an A-FiO<sub>2</sub> system has been on the time in the intended SpO<sub>2</sub> target range, what happens with oxygenation during those episodes outside the target range is also of clinical importance. Especially, prolonged periods in extreme hyperoxaemia and hypoxaemia have been associated with neonatal morbidity in the short term and long term.<sup>5 8</sup> We found that the differences between A-FiO<sub>2</sub> and M-FiO<sub>2</sub> in per cent time at SpO<sub>2</sub> extremes were consistent with the number of prolonged episodes. This finding is consistent with other reports,<sup>5 19</sup> further supporting the premise that reducing prolonged episodes outside target range is associated with improved time in the target range and leads to potential long-term benefits of A-FiO<sub>2</sub>.

Besides, the benefit of improved SpO<sub>2</sub> control, A-FiO<sub>2</sub> also promises to reduce nursing stress and labour. Only one of the previous studies of PRICO reported on the reduction in manual FiO<sub>2</sub> adjustments.<sup>12</sup> They reported a modest decrease of nine adjustments per day. In contrast we found a decrease of 22 per day (30–8). Clearly, the need for manual adjustments is dependent on the stability of the infant, which probably also explains the large IQR during manual control (upper quartile 106 adjustments/day) compared with automated control (upper quartile 12 adjustments/day).

We found no difference in the response to SpO<sub>2</sub> drop-outs between A-FiO<sub>2</sub> and M-FiO<sub>2</sub>, suggesting PRICO's fall-back to a clinician's set FiO<sub>2</sub> level is as effective as nursing response. Others have suggested the importance of the response to drop-outs,<sup>20</sup> but we are unaware of published

evaluations of the effectiveness of other A-FiO<sub>2</sub> fall-back strategies for periods without reliable SpO<sub>2</sub> readings.

Our report has some strengths and limitations. First of all, it enrolled more subjects than most evaluations of A-FiO<sub>2</sub> systems. Also, the enrolment was not restricted to extremely preterm infants. In addition, it reflects a multicentre experience. While its cross-over design is the typical approach for evaluating the performance of an A-FiO<sub>2</sub> system, the differences identified in this type study might not be projectable to routine care. This was a pragmatic study which generally provides a better basis for projection to the impact in routine use, however, the impact of different approaches to respiratory care and settings are confounding. While another strength of the study was the use of A-FiO<sub>2</sub> in different respiratory support modes, the study was only powered to detect an overall difference in performance. Therefore, it was inadequate to evaluate the relative effect of different respiratory support modes. Particularly, additional studies during high-frequency oscillatory ventilation are warranted. Eight of the subjects were being managed by A-FiO<sub>2</sub> when randomised, but a previous study suggests that this probably does not affect our findings.<sup>21</sup> Finally, the study centres were all experienced with both the ventilator and the use of A-FiO<sub>2</sub>, and the finding should be projected to naïve centres cautiously.

## CONCLUSIONS

The study demonstrates the ability of the PRICO automated oxygen control algorithm to improve the maintenance of SpO<sub>2</sub> in normoxaemia and to avoid hyperoxaemia while reducing the need for nursing intervention, in a wide range of preterm infants supported with various respiratory support modalities.

### Author affiliations

<sup>1</sup>Department of Obstetrics and Perinatology, National Medical Institute, Warsaw, Poland

<sup>2</sup>Department of Neonatology, Centre for Postgraduate Medical Education, Warsaw, Poland

<sup>3</sup>Faculty Biomedical Engineering, Czech Technical University in Prague, Kladno, Czech Republic

<sup>4</sup>Neonatal Biophysical Monitoring and Cardiopulmonary Therapies Research Unit, Poznan University of Medical Sciences, Poznan, Poland

<sup>5</sup>Department of Neonatology, Poznan University of Medical Sciences, Poznan, Poland

<sup>6</sup>Department of Neonatology, Pomeranian Medical University in Szczecin, Szczecin, Poland

<sup>7</sup>Department of Neonatology, Ujastek Medical Center, Krakow, Poland

<sup>8</sup>Department of Neonatology, Ujastek Medical Center, Krakow, Poland

<sup>9</sup>Department of Neonatology Emma Children's Hospital UMC, University of Amsterdam, Amsterdam, The Netherlands

<sup>10</sup>Amsterdam Reproduction & Development Research Institute, UMC, Amsterdam, The Netherlands

**Acknowledgements** We wish to recognise the contribution of the independent data safety monitoring committee, CJL Newth, NP Iyer and J Varum. We also want to thank Vyair Medical for sponsoring the study and particularly A Waldmann, K Dudar and R Rava for organising and coordinating it. Finally, we appreciate the confidence the parents of the subjects showed towards our investigators.

**Contributors** All the authors have critically reviewed and the manuscript. The manuscript was written by MW, TB, TS and AvK. MW, TS, BL, BRW and AvK supervised implementation of the study at their sites. In addition to those five, KWS, KC, KO, KJ, PP, WO, GJH and RWvL implemented the study at their site. TB is the guarantor.

**Competing interests** All the authors or their institutions received funding for this and additional projects from Vyair Medical.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by Bioethics Committee at Medical Centre for Postgraduate Education# 49/2021 (103/2021 addition of Poznan). Multicentre study of the safety and effectiveness of routine use of Fabian ventilator with PRICO function to maintain target saturation in the neonatal intensive care unit (date of approval: 06-09-2021 (12-08-2021, addition Poznan) METC AMC, (Medical Ethics Review Committee Academic Medical Centre) filenumber: 2021\_226, ABR prico NL79089.000.21. Multicentre study of the performance of Fabian-PRICO for saturation targeting routine use in NICU (date of approval: 4 March 2022. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. Data are available on reasonable request to the corresponding author.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Thomas Bachman <http://orcid.org/0000-0002-3968-9402>

Tomasz Szczapa <http://orcid.org/0000-0002-5214-2719>

Wes Onland <http://orcid.org/0000-0002-9623-0606>

#### REFERENCES

- Sweet DG, Carnielli VP, Greisen G, *et al*. European consensus guidelines on the management of respiratory distress syndrome: 2022 update. *Neonatology* 2023;120:3–23.
- Hagadorn JI, Furey AM, Nghiem T-H, *et al*. Achieved versus intended pulse Oximeter saturation in infants born less than 28 weeks' gestation: the Aviox study. *Pediatrics* 2006;118:1574–82.
- van Zanten HA, Tan RRGB, van den Hoogen A, *et al*. Compliance in oxygen saturation targeting in Preterm infants: a systematic review. *Eur J Pediatr* 2015;174:1561–72.
- Askie LM, Darlow BA, Finer N, *et al*. Association between oxygen saturation targeting and death or disability in extremely Preterm infants in the neonatal oxygenation prospective meta-analysis collaboration. *JAMA* 2018;319:2190–201.
- Poets CF, Roberts RS, Schmidt B, *et al*. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely Preterm infants. *JAMA* 2015;314:595–603.
- Raffay TM, Dylag AM, Sattar A, *et al*. Neonatal intermittent hypoxemia events are associated with diagnosis of bronchopulmonary dysplasia at 36 weeks postmenstrual age. *Pediatr Res* 2019;85:318–23.
- Di Fiore JM, Bloom JN, Orge F, *et al*. A higher incidence of intermittent hypoxemic episodes is associated with severe retinopathy of prematurity. *J Pediatr* 2010;157:69–73.
- Askie LM, Henderson-Smart DJ, Irwig L, *et al*. Oxygen-saturation targets and outcomes in extremely preterm infants. *N Engl J Med* 2003;349:959–67.
- Abdo M, Hanbal A, Asla MM, *et al*. Automated versus manual oxygen control in preterm infants receiving respiratory support: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med* 2022;35:6069–76.
- Stafford IG, Lai NM, Tan K. Automated oxygen delivery for preterm infants with respiratory dysfunction. *Cochrane Database Syst Rev* 2023;11:CD013294.
- Salverda HH, Cramer SJE, Witlox RSGM, *et al*. Automated oxygen control in preterm infants, how does it work and what to expect: a narrative review. *Arch Dis Child Fetal Neonatal Ed* 2021;106:215–21.
- Dani C, Pratesi S, Luzzati M, *et al*. Cerebral and splanchnic oxygenation during automated control of inspired oxygen (Fio<sub>2</sub>) in preterm infants. *Pediatr Pulmonol* 2021;56:2067–72.
- Dijkman KP, Mohns T, Dieleman JP, *et al*. Predictive intelligent control of oxygenation (PRICO) in preterm infants on high flow nasal cannula support: a randomised cross-over study. *Arch Dis Child Fetal Neonatal Ed* 2021;106:621–6.
- Hütten MC, Goos TG, Ophelders D, *et al*. Fully automated predictive intelligent control of oxygenation (PRICO) in resuscitation and ventilation of preterm lambs. *Pediatr Res* 2015;78:657–63.
- Bachman TE, Iyer NP, Newth CJL, *et al*. Thresholds for oximetry alarms and target range in the NICU: an observational assessment based on likely oxygen tension and maturity. *BMC Pediatr* 2020;20:317.
- Bachman TE, Newth CJL, Iyer NP, *et al*. Hypoxemic and hyperoxemic likelihood in pulse oximetry ranges: NICU observational study. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F274–9.
- Dijkman KP, Goos TG, Dieleman JP, *et al*. Predictive intelligent control of oxygenation in preterm infants: a two-center feasibility study. *Neonatology* 2023;120:235–41.
- Bachman T, Rafl J, LeMoyné R. Comparison of the relative effectiveness of automated Fio<sub>2</sub> control in neonates of differing stability: individual patient analysis. *EPNV Conf* 2023.
- Bachman TE, Onland W, van Kaam AH, *et al*. Frequency and duration of extreme hypoxemic and hyperoxemic episodes during manual and automatic oxygen control in preterm infants: a retrospective cohort analysis from randomized studies. *BMC Pediatr* 2022;22:350.
- Lim K, Wheeler KI, Jackson HD, *et al*. Lost without trace: oximetry signal dropout in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2015;100:F436–8.
- Bachman T, Roubik K. Crossover from automated to manual titration of Fio<sub>2</sub> in the NICU: is there a transition lag? *Clin Technol* 2016;46:37–40.