

ORIGINAL ARTICLE

## Oxygen-Saturation Targets and Outcomes in Extremely Preterm Infants

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### ABSTRACT

#### BACKGROUND

Physiological studies have shown that chronic hypoxemia may occur in preterm infants who require supplemental oxygen for extended periods and that this hypoxemia may contribute to poor growth and development. Anecdotal reports and uncontrolled observational studies have suggested that a higher oxygen-saturation range may be beneficial in terms of growth and development.

#### METHODS

We conducted a multicenter, double-blind, randomized, controlled trial involving 358 infants born at less than 30 weeks of gestation who remained dependent on supplemental oxygen at 32 weeks of postmenstrual age. They were randomly assigned to a target functional oxygen-saturation range of either 91 to 94 percent (standard-saturation group) or 95 to 98 percent (high-saturation group); this target was maintained for the duration of supplemental-oxygen therapy. The primary outcomes were growth and neurodevelopmental measures at a corrected age of 12 months.

#### RESULTS

There were no significant differences between the groups in weight, length, or head circumference at a corrected age of 12 months. The frequency of major developmental abnormalities also did not differ significantly between the standard-saturation group and the high-saturation group (24 percent and 23 percent, respectively,  $P=0.85$ ). There were six deaths due to pulmonary causes in the high-saturation group and one such death in the standard-saturation group ( $P=0.12$ ). The high-saturation group received oxygen for a longer period after randomization (median, 40 days vs. 18 days;  $P<0.001$ ) and had a significantly higher rate of dependence on supplemental oxygen at 36 weeks of postmenstrual age and a significantly higher frequency of home-based oxygen therapy.

#### CONCLUSIONS

Targeting a higher oxygen-saturation range in extremely preterm infants who were dependent on supplemental oxygen conferred no significant benefit with respect to growth and development and resulted in an increased burden on health services.

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**I**MPROVED SURVIVAL OF EXTREMELY PRE-term infants<sup>1</sup> has been associated with an increase in the incidence of chronic lung disease of infancy,<sup>2</sup> currently defined by a continued dependence on supplemental oxygen at 36 weeks of postmenstrual age.<sup>3,4</sup> This increased incidence has become a major clinical challenge, since chronic lung disease has serious health consequences, including poor growth,<sup>5,6</sup> neurologic impairment,<sup>5,7</sup> and pulmonary sequelae.<sup>5,8</sup> These and other factors may account for the higher reported health care costs for these infants than for infants who do not have chronic lung disease.<sup>9</sup>

Physiological studies have shown that infants with chronic lung disease (also known as bronchopulmonary dysplasia) have higher rates of oxygen consumption than infants without chronic lung disease,<sup>10</sup> as well as lower base-line oxygen-saturation levels, leading to more frequent episodes of desaturation.<sup>11,12</sup> In addition, observational studies have suggested that preterm infants who receive greater levels of oxygen supplementation, with either a longer duration of treatment or a higher target blood oxygen level, have improvements in sleep patterns,<sup>13,14</sup> growth, and neurodevelopmental outcomes.<sup>15,16</sup> Because of the uncontrolled nature of the studies, it is not known whether these associations are causal.

A policy of routine targeting of higher oxygen-saturation levels in preterm infants might result in some substantial burdens for the health care system and for parents, by increasing the duration of oxygen therapy in the hospital and the frequency of the need for home-based oxygen therapy. Despite some potential costs and the lack of evidence of long-term benefits, such policies are increasingly being implemented in clinical practice.<sup>17,18</sup> Data from randomized, controlled trials are lacking,<sup>19,20</sup> and the question of the most appropriate oxygen-saturation levels for preterm infants who require supplemental oxygen remains controversial.<sup>21-23</sup>

We conducted the randomized, multicenter Benefits of Oxygen Saturation Targeting (BOOST) trial to determine whether maintaining the oxygen saturation at a level higher than the standard range in extremely preterm infants with a long-term dependence on supplemental oxygen improves growth and neurodevelopmental outcomes. Secondary aims were to determine whether the higher oxygen-saturation levels had other beneficial or adverse physical or psychosocial effects on infants or parents.

## METHODS

### CRITERIA FOR ELIGIBILITY

Infants born at less than 30 weeks of gestational age (determined on the basis of the first day of the mother's last menstrual period, prenatal ultrasonography, or both or, if these data were not available, postnatal clinical assessment) who remained dependent on supplemental oxygen (delivered by any method and at any level) at 32 weeks of postmenstrual age were eligible for enrollment. Dependence on supplemental oxygen at 32 weeks of postmenstrual age, rather than 36 weeks, was used as a criterion for inclusion because it was current clinical practice to choose between the standard target range for oxygen saturation and a higher target range at this point in the infant's life. Criteria for exclusion before randomization included major congenital abnormalities, major surgery or a severe intracranial disorder diagnosed before 32 weeks of postmenstrual age, and a multiple birth in which three or more infants were eligible. The protocol allowed for infants from multiple gestations resulting in two eligible infants to be assigned to the same treatment.

The institutional ethics committees of the eight tertiary perinatal enrollment centers participating in the study approved the trial protocol, and written, informed consent was obtained from a parent or guardian of each eligible infant. Infants were enrolled between September 1996 and September 2000.

### INTERVENTION AND BLINDING

Infants were randomly assigned to a target oxygen-saturation range of either 91 to 94 percent (standard-saturation group) or 95 to 98 percent (high-saturation group), as measured with a pulse oximeter (model N-3000, Nellcor) whose algorithm assesses functional oxygen saturation.<sup>24</sup> Randomization was stratified with the use of a dynamic balancing method<sup>25</sup> to ensure a balance of treatment-group assignments within each stratum defined according to hospital, singleton or multiple birth, and gestational age (22 to 27 weeks or 28 to 29 weeks). Central telephone randomization ensured concealment of the treatment-group assignments.

To make sure that the treatment-group assignments were not revealed, the infants who underwent randomization were assigned a specific study oximeter, which after the calculation of the infant's

oxygen-saturation level in the usual manner, was adjusted to display a value 2 percent higher than the actual saturation in infants in the standard-saturation group or 2 percent lower than the actual saturation in infants in the high-saturation group. Staff members and parents were then asked to target the range of 93 to 96 percent for the infant's oxygen saturation, so that they remained unaware of the actual ranges being targeted. Caregivers were aware that they were using adjusted oximeters and that they were participating in a trial, but they were not aware of the offset level of the individual oximeter. Double-blind targeting of the assigned saturation range was maintained for the duration of the infant's oxygen therapy either in the hospital (in both the enrollment center and other hospitals if necessary) or at home.

Dependence on supplemental oxygen was defined by the continuing need for oxygen therapy in order to maintain the double-blind target oxygen-saturation range of 93 to 96 percent, as measured by the assigned study oximeter. The frequency of monitoring of the saturation (continuous or intermittent), the settings for limits that were to trigger alarms, and the criteria for titrating the amount of ambient oxygen delivered or for ceasing delivery were determined by the attending clinicians and were not specified by the trial protocol.

#### ADHERENCE TO THE PROTOCOL

Compliance with the double-blind target oxygen-saturation range of 93 to 96 percent was assessed with the use of twice-weekly downloading of each infant's oxygen-saturation data, and a report on the distribution of the double-blind saturation levels was placed in the case notes. Clinicians and parents were allowed to violate the protocol either temporarily or permanently if they believed that the infant's condition warranted high-saturation oxygen therapy—for instance, because of serious intercurrent illness, as treatment for prethreshold retinopathy of prematurity, or during surgery.

#### PRIMARY OUTCOMES

The primary outcomes assessed at a corrected age of one year (the chronologic age plus the number of weeks of prematurity) included growth, in terms of the mean weight, the mean length, the mean head circumference, and the proportion of infants with a weight below the 10th percentile,<sup>26</sup> and the presence of a major developmental abnormality, defined

as blindness, cerebral palsy, or a score on the revised Griffiths Mental Developmental Scales that was more than 2 SD below the mean (general quotient, <77).<sup>27</sup> Blindness was defined as a visual acuity in both eyes of less than 6/60.<sup>28</sup> Cerebral palsy was diagnosed if the child had nonprogressive motor impairment characterized by abnormal muscle tone and a decreased range or decreased control of movements, accompanied by neurologic signs.<sup>29</sup>

#### SECONDARY OUTCOMES

The secondary outcomes included the effect of the treatment-group assignment on the duration of oxygen therapy, the duration of assisted ventilation and of the hospital stay, and the frequency of home-based oxygen therapy. Parental stress and parent-infant interaction were assessed by means of validated scales (the Edinburgh Postnatal Depression Scale,<sup>30</sup> the Infant Temperament Questionnaire,<sup>31</sup> the Toddler Temperament Scale,<sup>32</sup> the Parenting Stress Index, Short Form,<sup>33</sup> and the Impact-on-Family Scale<sup>34</sup>). Retinopathy of prematurity was assessed by routine ophthalmic examinations at two-week intervals from enrollment until the resolution of retinopathy, with grading according to the International Classification of Retinopathy of Prematurity.<sup>35</sup> Reports by the parents on the use of health services and rehospitalizations during the first year of life were obtained through quarterly telephone contact by the research nurses, and rehospitalizations were confirmed through a review of the medical records. Causes of death were classified according to the codes of the *International Classification of Diseases, Ninth Revision*,<sup>36</sup> and confirmed on the basis of the hospital discharge summary, a postmortem examination report, a coroner's report, or a death certificate.

#### STATISTICAL ANALYSIS

All data analyses were performed according to the intention-to-treat principle. For continuous data, the treatment effect was calculated by subtracting the value for the standard-saturation group from the value for the high-saturation group, with results for normally distributed data presented as means  $\pm$ SD and results for non-normally distributed data presented as medians with interquartile ranges. Differences between the two groups were assessed with the use of Student's *t*-test or the Mann-Whitney *U* test and are expressed as mean or median differences, respectively, with 95 percent confidence in-

tervals. For categorical data, the chi-square test was used, and the treatment effects are expressed as relative risks in the high-saturation group as compared with the standard-saturation group, with 95 percent confidence intervals. For analyses involving small numbers of events, Fisher's exact test was used, and exact confidence intervals were calculated for odds ratios, as approximate relative risks. All P values are two-sided and have not been adjusted for multiple testing or for correlation between the outcomes in siblings, since only 25 pairs of siblings were included (a total of 50 infants), representing 14 percent of the infants, and they were distributed approximately equally between the two groups.

The required sample size was calculated to ensure detection of clinically important effects on the primary outcomes: a reduction from the base-line estimate of 47 percent to 30 percent in the proportion of infants with a weight below the 10th percentile at a corrected age of 12 months, and a reduction in the frequency of major developmental abnormalities from 23 percent to 12 percent.<sup>37</sup> To achieve 80 percent power with a two-sided alpha level of 0.05 and a 1:1 ratio of infants in the two groups, approximately 150 infants were required in each group.

An independent safety monitoring committee, comprising a pediatric ophthalmologist, a neonatologist, and a pediatric respiratory physician-epidemiologist, all of whom were unaware of the treatment-group assignments, assessed adverse outcomes, including death, at five prespecified time points. The stopping rules were never breached.

## RESULTS

### PARTICIPANTS

Of the 703 infants who were eligible during the enrollment period, 158 met the criteria for exclusion before randomization. A total of 187 of the remaining 545 eligible infants were not enrolled (consent was not obtained for 122 infants, and the parent or guardian was not approached for 65 infants). There were 333 infants who underwent individual randomization, and an additional 25 eligible multiples were assigned to the same group as their sibling, for a total of 358 individual infants receiving one of the two treatments for whom outcomes were analyzed. A total of 178 infants were assigned to the standard-saturation group (target oxygen saturation, 91 to 94 percent) and 180 to the high-saturation group (target oxygen saturation, 95 to 98 percent). The two groups were well balanced in terms of the base-line characteristics of the infants and the mothers (Table 1). The intervention continued for a median of 17.5 days (interquartile range, 7.0 to 41.0) in the standard-saturation group and 40.0 days (interquartile range, 20.5 to 73.0) in the high-saturation group ( $P < 0.001$ ).

### ADHERENCE TO THE PROTOCOL

Figure 1 shows the two distributions of the actual saturation levels. The median for each group was within the desired target range. Permitted protocol violations for open targeting of the oxygen saturation occurred relatively infrequently (on 54 occasions), generally for short periods (median, 7 days; interquartile range, 3 to 17), and the occurrences were equally distributed between the two groups.

### PRIMARY OUTCOMES

The rate of ascertainment of primary outcomes was 93 percent in the standard-saturation group (165 of 178 infants) and 93 percent in the high-saturation group (168 of 180 infants). The median age at the assessment of the primary outcomes did not differ between the two groups (a corrected age of 12.1 months [interquartile range, 11.8 to 12.7] in the standard-saturation group and a corrected age of

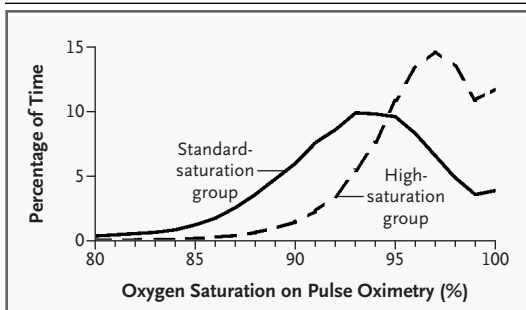
**Table 1. Base-Line Characteristics of the Infants and Mothers.\***

Characteristic	Standard-Saturation Group (N=178)	High-Saturation Group (N=180)
Birth weight — g	918±229	916±231
Gestational age at birth — wk	26.6±1.7	26.5±1.6
<28 Wk of gestation at birth — no. (%)	124 (70)	132 (73)
Male sex — no. (%)	92 (52)	97 (54)
Singleton birth — no. (%)	133 (75)	129 (72)
Born in tertiary care center — no. (%)	163 (92)	172 (96)
Surfactant treatment — no. (%)	138 (78)	137 (76)
Patent ductus arteriosus — no. (%)	94 (53)	91 (51)
Total duration of parenteral nutrition — days		
Median	13.5	13.0
Interquartile range	9.0–20.0	9.0–20.0
Antenatal corticosteroids — no. (%)	148 (83)	149 (83)
Score on the Edinburgh Postnatal Depression Scale†	10.7±5.7	10.0±5.3
Maternal educational level >high school — no. (%)	60 (34)	64 (36)
Maternal occupation score‡	4.5±1.4	4.6±1.3

\* Plus-minus values are means ±SD.

† Scores range from 0 to 30, with higher scores indicating greater severity of depressive symptoms.<sup>30</sup>

‡ Data are the scores on Daniel's occupation scale<sup>38</sup>; scores range from 1 to 7, with lower scores indicating higher occupational prestige.



**Figure 1. Smoothed Frequency Distribution of Actual Oxygen-Saturation Values on Pulse Oximetry during Oxygen Therapy after Randomization.**

The saturation values were sampled every 10 seconds during intermittent downloads performed approximately twice weekly and lasting 8 to 24 hours each. The median oxygen saturation was 93 percent in the standard-saturation group (interquartile range, 90 to 96) and 97 percent in the high-saturation group (interquartile range, 94 to 98).

12.2 months [interquartile range, 11.9 to 12.9] in the high-saturation group).

There were no significant differences between the two groups in the mean weight, length, or head circumference at 38 weeks of postmenstrual age (Table 2). In addition, at a corrected age of 12 months, there were no significant differences in the measurements of weight, length, or head circumference; the proportion of infants who were small for their age; or the proportion of infants with a major developmental abnormality (Table 2). Our data also showed no significant difference between the two groups in the frequency of developmental scores that were more than 1 SD but less than 2 SD below the mean (relative risk associated with the higher oxygen-saturation target, 1.08; 95 percent confidence interval, 0.69 to 1.69; P=0.70). When the primary outcomes were examined in the subgroup of 256 infants born before 28 weeks of gestation, the differences between the two treatment groups remained nonsignificant and were similar

**Table 2. Measures of Growth and Development.\***

Outcome	Standard-Saturation Group	High-Saturation Group	Mean Difference (95% CI)	Relative Risk or Odds Ratio (95% CI)†	P Value
<b>38 Wk of postmenstrual age</b>					
Weight — g	2345±429	2369±428	24.0 (–66 to 113)		0.60
Length — cm	44.2±3.2	44.2±3.2	0.0 (–0.6 to 0.7)		1.00
Head circumference — cm	33.1±2.2	32.9±1.9	–0.2 (–0.7 to 0.2)		0.26
<b>12 Mo of corrected age</b>					
Weight — kg	9.10±1.5	9.25±1.6	0.15 (–0.2 to 0.5)		0.33
Length — cm	74.0±3.9	74.1±4.1	0.1 (–0.8 to 1.0)		0.77
Head circumference — cm	46.3±2.0	46.3±1.9	0.0 (–0.4 to 0.4)		1.00
Weight below 10th percentile — no./total no. (%)	61/165 (37)	55/168 (33)		0.89 (0.66 to 1.19)	0.42
Length below 10th percentile — no./total no. (%)	42/162 (26)	41/164 (25)		0.96 (0.67 to 1.40)	0.85
Head circumference below 3rd percentile — no./total no. (%)	5/165 (3)	8/165 (5)		1.63 (0.46 to 6.47)	0.57
Major developmental abnormality — no./total no. (%)‡	40/166 (24)	39/168 (23)		0.96 (0.66 to 1.42)	0.85

\* Plus-minus values are means ±SD. Denominators are the numbers of infants for whom growth measures or major developmental abnormalities could be assessed at 12 months of corrected age. CI denotes confidence interval.

† The value for a head circumference below the 3rd percentile is an odds ratio; other values are relative risks.

‡ Major developmental abnormalities were blindness, cerebral palsy, or a general quotient on the revised Griffiths Mental Developmental Scales that was more than 2 SD below the mean.

in magnitude to those in the whole cohort (data not shown).

**SECONDARY OUTCOMES**

The proportion of infants who were still dependent on supplemental oxygen at 36 weeks of postmenstrual age was 46 percent in the standard-saturation group and 64 percent in the high-saturation group (P<0.001) (Table 3). Similarly, the proportion of infants requiring home-based oxygen therapy was sig-

nificantly lower in the standard-saturation group than in the high-saturation group (17 percent vs. 30 percent, P=0.004) (Table 3). The duration of oxygen supplementation was significantly higher in the high-saturation group: the postmenstrual age at the cessation of oxygen therapy was 35.4 weeks in the standard-saturation group and 37.9 weeks in the high-saturation group (P<0.001) (Table 3). There were no significant differences between the two groups in the median total duration of assisted ven-

**Table 3. Rates of Adverse Outcomes among the Infants.\***

Outcome	Standard-Saturation Group (N=178)	High-Saturation Group (N=180)	Relative Risk or Odds Ratio (95% CI)†	Median Difference (95% CI)	P Value
Dependence on supplemental oxygen at 36 wk of postmenstrual age — no. (%)	82 (46)	116 (64)	1.40 (1.15 to 1.70)		<0.001
Home-based oxygen therapy — no. (%)	30 (17)	54 (30)	1.78 (1.20 to 2.64)		0.004
Duration of oxygen therapy after randomization — days				17 (12 to 23)	<0.001
Median	17.5	40.0			
Interquartile range	7.0 to 41.0	20.5 to 73.0			
Postmenstrual age at cessation of oxygen therapy — wk				2.3 (1.3 to 3.3)	<0.001
Median	35.4	37.9			
Interquartile range	33.4 to 39.7	35.4 to 45.1			
Duration of assisted ventilation after randomization — days				0 (-4 to 4)	0.95
Median	14.0	14.0			
Interquartile range	7.0 to 28.0	6.0 to 35.0			
Postnatal corticosteroids — no. (%)	89 (50)	104 (58)	1.16 (0.95 to 1.40)		0.14
Diuretics for chronic lung disease — no. (%)	78 (44)	93 (52)	1.18 (0.95 to 1.47)		0.14
Length of hospital stay after randomization — days				2 (-1 to 5)	0.24
Median	50.0	50.0			
Interquartile range	39.0 to 60.0	42.0 to 61.5			
Postmenstrual age at discharge from hospital — wk				0.29 (-0.14 to 0.86)	0.15
Median	39.1	39.1			
Interquartile range	37.4 to 40.4	37.9 to 40.8			
Postmenstrual age at time of fully oral feeding — wk				0.00 (-0.43 to 0.43)	0.91
Median	37.7	37.7			
Interquartile range	36.6 to 39.0	36.4 to 38.9			
Worst retinopathy of prematurity — no. (%)					
<Stage 3	150 (84)	158 (88)	1.04 (0.96 to 1.13)		0.34
Stage 3 or 4	28 (16)	22 (12)	0.78 (0.46 to 1.31)		0.34
Ablative retinal surgery for severe retinopathy of prematurity — no. (%)‡	20 (11)	11 (6)	0.54 (0.27 to 1.10)		0.09
Death (after randomization) — no. (%)	5 (3)	9 (5)	1.82 (0.53 to 7.05)		0.41

\* CI denotes confidence interval.

† The value for death is an odds ratio; all other values are relative risks.

‡ Data are for infants who underwent cryotherapy or laser therapy for threshold retinopathy of prematurity, usually stage 3 with dilatation of the posterior retinal vessels (referred to as “plus” disease).

tilation after randomization, the rate of use of postnatal corticosteroids or diuretics, the length of the hospital stay after randomization, the postmenstrual age at discharge, or the time before the infant was able to be fed entirely orally (Table 3).

There were no significant differences between the groups in the rates of retinopathy of prematurity of any stage or in the frequency of the need for ablative retinal surgery (in 20 of 178 infants in the standard-saturation group [11 percent] and 11 of 180 infants in the high-saturation group [6 percent],  $P=0.09$ ) (Table 3). All the infants who underwent ablative retinal surgery were born before 28 weeks of gestation, and all but one of these infants retained vision in at least one eye. The rate of ablative retinal surgery among infants born before 28 weeks of gestation was 16 percent (20 of 124 infants) in the standard-saturation group and 8 percent (11 of 132 infants) in the high-saturation group (relative risk, 0.52; 95 percent confidence interval, 0.26 to 1.03;  $P=0.06$ ).

There was no significant difference between the two groups in the number of infants who died: five infants in the standard-saturation group and nine in the high-saturation group (Table 3). Of these

deaths, one in the standard-saturation group was due to pulmonary causes, as compared with six in the high-saturation group ( $P=0.12$ ). The number of infants who were rehospitalized and the number of health service visits per infant during the first year of life did not differ significantly according to the treatment group (Table 4). There were also no significant differences between the two groups in the measures of maternal postnatal depression, infant or toddler temperament, parental stress, or effects on the family (Table 4). Follow-up rates for these tests ranged from 71 to 77 percent.

## DISCUSSION

Our double-blind, randomized trial showed no evidence that the targeting of a functional oxygen-saturation range of 95 to 98 percent rather than a range of 91 to 94 percent had a beneficial effect on growth or development in preterm infants with a long-term dependence on supplemental oxygen. The targeting of higher oxygen-saturation levels resulted in a 40 percent increase in the proportion of infants who were still receiving oxygen therapy at 36 weeks of postmenstrual age and a 78 percent increase in the

**Table 4. Use of Health Services in the First Year of Life and Psychosocial Measures in Parents and Infants.\***

Outcome	Standard-Saturation Group	High-Saturation Group	Relative Risk (95% CI)	Difference between Groups (95% CI)†	P Value
Infant rehospitalized — no./total no. (%)	82/171 (48)	92/170 (54)	1.13 (0.92 to 1.39)		0.34
No. of health service visits/infant				3.8 (−0.8 to 8.5)	0.11
Median	27.5	31.3			
Interquartile range	25.1 to 30.4	27.3 to 34.8			
Scores on psychosocial measures‡					
Edinburgh Postnatal Depression Scale (mother)	5.9±5.1	6.5±4.8		0.6 (−0.6 to 1.8)	0.32
Infant Temperament Scale	2.3±0.7	2.4±0.7		0.1 (0.0 to 0.3)	0.06
Toddler Temperament Scale	3.2±0.6	3.1±0.6		−0.1 (−0.2 to 0.1)	0.59
Parenting Stress Index, Short Form	71.7±20.6	72.9±21.1		1.2 (−3.9 to 6.3)	0.65
Impact-on-Family Scale	40.0±11.0	39.8±11.7		−0.2 (−3.0 to 2.6)	0.89

\* Plus-minus values are means  $\pm$ SD. Scores on the Edinburgh Postnatal Depression Scale<sup>30</sup> range from 0 to 30, with higher scores indicating a greater severity of depressive symptoms. Scores on the Infant Temperament Scale<sup>31</sup> range from 1 to 6, with a mean ( $\pm$ SD) of 2.5 $\pm$ 0.64; higher scores indicate a more difficult temperament. Scores on the Toddler Temperament Scale<sup>32</sup> range from 1 to 6, with a mean of 3.46 $\pm$ 0.62; higher scores indicate a more difficult temperament. Scores on the Parenting Stress Index, Short Form,<sup>33</sup> range from 32 to 160, with a median of 69 (interquartile range, 61 to 79); higher scores indicate greater parental stress. Scores on the Impact-on-Family Scale<sup>34</sup> range from 19 to 76, with a mean of 46.2 $\pm$ 7.6; higher scores indicate increased effects on the family. CI denotes confidence interval.

† The mean difference is shown for scores on psychosocial measures; the median difference is shown for health service visits.

‡ The score on the Infant Temperament Scale was obtained at 4 months of corrected age; scores on the other measures were obtained at 12 months of corrected age.

proportion receiving supplemental oxygen after discharge. Hence, one could expect one additional case of home-based oxygen therapy for every eight infants treated if higher target ranges for the oxygen saturation were used routinely.

The finding that oxygen therapy was required for a longer period in the high-saturation group might simply be explained by the fact that a higher target saturation had to be reached for oxygen therapy to be discontinued. However, a higher target oxygen saturation may also be associated with potential pulmonary toxicity. The unexpected finding of excess deaths from pulmonary causes among infants in the high-saturation group — albeit not statistically significant — accords with the findings of the only other trial in which preterm infants were randomly assigned to different target oxygen-saturation ranges, the Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) trial.<sup>39</sup> That trial showed an increased rate of adverse pulmonary sequelae (although not an increased rate of death due to pulmonary causes) among preterm infants with prethreshold retinopathy of prematurity when a higher oxygen-saturation range was targeted.

Oxygen toxicity, particularly in preterm infants, can inhibit lung healing and contribute to ongoing lung injury.<sup>40</sup> In our trial, infants who were still dependent on supplemental oxygen at 36 weeks of postmenstrual age or before discharge did not routinely have oxygen-saturation data collected after a room-air breathing test, and we do not have information on the proportion of infants in the high-saturation group who would not have required oxygen had their oxygen-saturation target been lower. Thus, the cause of the greater oxygen requirement in the high-saturation group remains uncertain.

Although our trial did not have the statistical power to detect differences in secondary eye-related outcomes, the effect of different target oxygen-saturation ranges on retinopathy of prematurity is of interest, since infants were randomly assigned to the different treatments at 32 weeks of postmenstrual age, before threshold retinopathy of prematurity usually develops. The results of both the STOP-ROP trial and our trial suggest the possibility that the need for ophthalmic intervention may be reduced when a higher oxygen-saturation range is targeted in a subgroup of extremely preterm infants with more severe eye disease. However, the differences between the treatment groups were not significant at the  $P < 0.05$  level in our subgroup analysis, and this hypothesis requires confirmation in larger studies.

Our trial addressed only the question of the effects of two different target oxygen-saturation ranges in preterm infants who remained dependent on supplemental oxygen after 32 weeks of postmenstrual age. Hence, these results should not be extrapolated to practice recommendations for preterm infants at earlier postmenstrual ages. The question of the most appropriate oxygen-saturation range for preterm infants treated sooner after birth can be answered only in the context of further large, well-designed, randomized trials with good long-term follow-up.<sup>21</sup>

A possible limitation of the study is that the duration of follow-up may not have been sufficiently long to allow us to detect other clinically important outcomes, such as minor disabilities that may become manifest later in childhood. We found no significant difference in the rates of developmental scores that were more than 1 SD but less than 2 SD below the mean — an outcome that may be a surrogate for later minor disability.<sup>41</sup>

The results of this randomized trial contradict observational reports suggesting that there are benefits of the routine targeting of higher oxygen-saturation levels in preterm infants with a long-term dependence on supplemental oxygen.<sup>13-16</sup> We found no evidence of beneficial effects of higher oxygen-saturation levels on growth or neurodevelopmental outcomes in these infants, but we did find an increased burden on health services.

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