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eNeonatal Review  
Podcast Issue

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## VOLUME 8 – ISSUE 8: TRANSCRIPT

# Featured Cases: Targeting the Ideal Oxygen Saturation

Our Guest Author is Dr. Timothy Stevens, Associate Professor of Pediatrics, Division of Neonatology at Golisano Children's Hospital at the University of Rochester Medical Center.

After participating in this activity, the participant will demonstrate the ability to:

- Describe the evidence establishing appropriate oxygen saturation targets and alarm limits for extremely premature infants in the acute neonatal period,
- Discuss the risks and benefits of supplemental oxygen therapy to achieve oxygen saturation targets among former extremely preterm infants in the convalescent (or recovery) stage of ROP—Retinopathy of Prematurity, and
- Discuss strategies to reduce the frequency of oxygen saturation fluctuations, including alternating periods of hypoxia, in the development of severe ROP.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to Oxygen Saturation in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 8, Issue 7 eNeonatal Review newsletter—[Targeting the Ideal Oxygen Saturation](#).

### MEET THE AUTHOR



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**Next Month's Topic:** Simulation & Training

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**MR. BOB BUSKER:** Welcome to this *eNeonatal Review*<sup>TM</sup> Podcast.

*eNeonatal Review* is presented by the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing. This program is supported by an educational grant from Ikaria and Abbott Nutrition.

Today's program is a companion piece to our Volume 8, Issue 7 *eNeonatal Review* newsletter: Targeting the Ideal Oxygen Saturation.

Our guest is that issue's author, Dr. Timothy Stevens from the University of Rochester Medical Center.

This activity has been developed for physicians, nurses, and respiratory therapists caring for neonates. There are no fees or prerequisites for this activity.

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- Describe the evidence establishing appropriate oxygen saturation targets and alarm limits for extremely premature infants in the acute neonatal period,
- Discuss the risks and benefits of supplemental oxygen therapy to achieve oxygen saturation targets among former extremely preterm infants in the convalescent (or recovery) stage of ROP—Retinopathy of Prematurity, and
- Discuss strategies to reduce the frequency of oxygen saturation fluctuations, including alternating periods of hypoxia-hyperoxia, in the development of severe ROP.

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I'm **BOB BUSKER**, managing editor of *eNeonatal Review*. On the line we have with us Dr. Timothy Stevens, Associate Professor of Pediatrics, Division of Neonatology at Golisano Children's Hospital at the University of Rochester Medical Center in Rochester, New York.

Dr. Stevens has no relevant relationships with commercial supporters to disclose, and his presentation today will NOT include discussion of the off-label or unapproved uses any drugs or products.

Dr. Stevens, welcome to this *eNeonatal Review* Podcast.

**DR. TIMOTHY STEVENS:** Thanks, Bob. It's good to be here with you.

**MR. BUSKER:** An opening comment for us, Doctor?

**DR. STEVENS:** We in neonatology have been seeking the idea oxygen saturation level since the 1940s and '50s, when excessive use of supplemental oxygen was associated with a epidemic of retinopathy of prematurity. We've learned a great deal about appropriate levels of oxygen therapy since that time. And in this podcast, we'll be discussing our current knowledge, as well as some of the gaps in our knowledge that exist as we go forward.

**MR. BUSKER:** Having said that, let's look at how we can apply that current knowledge from a case study perspective. So if you would, please, tell us about our initial case.

**DR. STEVENS:** An 890-gram male infant is born by cesarean section at 27 and two-sevenths weeks' gestation to a mother whose pregnancy was uncomplicated. The Apgar scores were 6 at 1 minute and 8 at 5 minutes. In the delivery room, he has strong respiratory effort, but rapidly develops tachypnea and grunting. He is admitted to the NICU, placed on nasal CPAP and supplemental oxygen. A sepsis evaluation is performed, and IV fluids and antibiotics are started. The blood culture grows *E. coli* within 24 hours.

**MR. BUSKER:** First question, Dr. Stevens: how would you assess this infant's risk of developing severe retinopathy of prematurity?

**DR. STEVENS:** In the *eNeonatal Review* discussing the ideal oxygen saturation, the companion piece to this podcast, we discussed the risk for ROP associated with hyperoxia, hypoxia, and oxygen saturation fluctuations that can be associated with rapidly alternating periods of hyperoxia and hypoxia. Recently, Chen reported interesting epidemiologic data on the risk factors for severe ROP. Their study

included 622 newborns who were less than 30 weeks' gestation. Of these, nearly half developed retinopathy of prematurity.

In a multivariate analysis, gestational age less than 26 weeks, oxygen exposure at 28 days, and neonatal sepsis were the strongest predictors of severe ROP. The association between the level of oxygen exposure and retinopathy of prematurity was strongest among the 23- to 25-week infants, while the infection-associated risk of retinopathy of prematurity was greatest among the 28 to 29-week infants.

**MR. BUSKER:** Just a quick sidebar note to our listeners: links to the Chen study and other studies referred to by Dr. Stevens in this podcast that were not reviewed in the newsletter issue can be found in the transcript version of this program. And now, Doctor, let me ask you: these risk factors — are they additive in their effects on the risk of ROP?

**DR. STEVENS:** In the Chen study, the odds ratio for the joint effect of all three risk factors — gestational age less than 26 weeks, oxygen exposure at 28 days, and neonatal sepsis — the joint effect was greater than would have been expected under either the additive or multiplicative patterns of interaction. This suggests that the three factors are not only independent in their effects, but synergistic in increasing the risk of retinopathy or prematurity.

And I think this fits with what we see clinically, where it is relatively infrequent that infants at 28 weeks' gestation with severe lung disease develop severe retinopathy or prematurity. Typically, infants of this gestational age only develop severe ROP when 2 or more risk factors are present.

**MR. BUSKER:** Hyperoxia — we know it's detrimental to the developing infant retina. Is it as detrimental for infants in the convalescent or recovery period of neonatal care as it is in the early neonatal period?

**DR. STEVENS:** Retinopathy of prematurity develops in two distinct phases, and the effects of oxygen are different in each. In phase one, the retinal hyperoxia and hypoxia are associated with constriction of the fragile retinal vessels, resulting in obliteration of and injury to some of these vessels. In this stage of retinal vessel growth, the retina is relatively quiescent, with very little active maturation. The goal of oxygen therapy in phase 1 ROP is to minimize hyperoxia, hypoxia, and rapidly alternating periods of hyperoxia

and hypoxia, thus stabilizing oxygen delivery to the retina.

In phase 2 retinopathy of prematurity, studies of oxygen therapy have focused on the potential of higher oxygen saturation targets to suppress VEGF production, and thereby suppress the abnormal retinal revascularization, thus reducing the risk of progressive ROP.

**MR. BUSKER:** For the infant you presented, what oxygen saturation targets and saturation alarm limits would you choose and why?

**DR. STEVENS:** This infant is in the early neonatal period. The best data on oxygen saturation targets in this age range come from a recent randomized clinical trial called the Neonatal Research Network's Support study (Support study). In this study, infants were randomized to have oxygen therapy that targeted saturations of either 85% to 89%, the low-saturation group; or 91% to 95%, the high-saturation group. The primary outcome of the study, risk of death or severe ROP, was not different between the treatment groups. However, a 48% reduction in the risk of severe ROP was offset by a 27% greater risk of death in the low-saturation group.

With such a difficult tradeoff between higher incidence of severe retinopathy of prematurity, or greater risk of mortality, the safest approach to oxygen saturation targeting at this time, pending further data, is likely to target oxygen saturations of 88% to 92%, which is the middle ground of a saturation range between a lower saturation alarm limit of 85%, which was used in the Support trial, and an upper limit of 95%. This saturation target range, 88% to 92%, was the consensus saturation targets chosen by the investigators in the Support study.

**MR. BUSKER:** Please tell us more about the upper saturation alarm limit.

**DR. STEVENS:** In studies by Dr. Tin and Dr. Chow and others, oxygen saturation targets exceeding 95% were effective in reducing the incidence of severe retinopathy of prematurity and the duration of oxygen therapy without increasing mortality or neurodevelopmental impairment. Thus, at this point, maintaining oxygen saturations less than 95% is a best practice for most infants less than 32 weeks' gestation.

**MR. BUSKER:** And similarly, the evidence basis for the lower saturation limit.

**DR. STEVENS:** Several studies are available to guide practice in choosing an appropriate lower saturation limit. In the Support study, higher mortality was seen when saturation targets of 85% to 89%, rather than 91% to 95%, were established. Also providing data on this topic, the study by Di Fiore et al looked at the effect of intermittent hypoxic episodes to find its oxygen saturation episodes less than 80% for greater than 10 seconds and lasting less than 3 minutes on the development of retinopathy of prematurity.

Infants in the study were 24 to 27 weeks' gestation and free of major anomalies. Controlling for differences in gestational age, race, sex, multiple birth, and SNAP score, of the number of hypoxic episodes, less than 80% was directly related to the risk of requiring laser retinal surgery for ROP. So, because of the higher mortality with saturation targets of 85% to 89% in Support, and a direct association between the number of desaturation episodes with less than 80% and the risk of severe ROP, a lower saturation limit of 85%, with saturation targets of 88% to 92%, is probably the best approach for most infants less than 32 weeks' gestation.

**MR. BUSKER:** Thank you, Dr. Stevens. Now, please present us with another case.

**DR. STEVENS:** A 750-gram female infant is born by cesarean section at 26 and five-sevenths weeks' gestation to a mother whose pregnancy was uncomplicated. Apgars were 5 at 1 minute and 7 at 5 minutes. In the delivery room, she develops moderate respiratory distress. She is admitted to the NICU, placed on CPAP, supplemental oxygen, IV fluids, and antibiotics.

**MR. BUSKER:** Retinopathy of prematurity is only one of the oxygen-related diseases to which extremely low-birth-weight infants are susceptible. What are some of the others?

**DR. STEVENS:** You're right. Extremely low-birth-weight infants are at risk for a number of morbidities, which can be affected by oxygen toxicity or hypoxia. In the neonatal period, these babies are at risk for bronchopulmonary dysplasia, poor growth, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, and

prolonged hospitalization. In the longer term, they're at risk for neurodevelopmental delays, cerebral palsy, and persistent pulmonary disease, which can lead to frequent respiratory-related rehospitalization in the first years after NICU discharge.

**MR. BUSKER:** I'd like to get into the specifics on some of those conditions you just mentioned. What do we know about the effect of oxygen saturation targets on pulmonary disease in the neonatal period?

**DR. STEVENS:** Cohort studies by Tin and Deulofuet each looked at pulmonary outcomes before and after introducing a practice change that used oxygen therapy to target saturations less than 93%. The Tin study found that babies for whom a lower rather than a higher saturation was targeted, in addition to having less ROP, had a shorter duration of supplemental oxygen and improved growth. The Deulofuet study found that the lower-saturation group had less time and oxygen, less BPD, and less use of steroids to treat BBD, as well as shorter hospitalization.

The only randomized clinical trial on this topic is the Support study by the NICHD Neonatal Research Group. In this study, oxygen saturation targets of 85% to 89%, a low-saturation group, were compared with targets of 91% to 95%. The pulmonary outcome of these infants showed that fewer infants developed bronchopulmonary dysplasia, as measured by the classic definition, oxygen at 36 weeks post-menstrual age, but a similar number of infants with BPD when the physiologic definition of BPD was used.

Recall that the physiologic definition of BPD includes an inability to maintain an oxygen saturation greater than 90% for 30 minutes in room air. These data suggest that there may be no difference between groups in the patients' inherent lung function, such as diffusion capacity or VQ matching. The shorter duration of oxygen in the low-saturation group could simply be attributable to the fact that the clinician accepted a lower saturation value.

**MR. BUSKER:** And the evidence describing oxygen saturation targets and neurologic outcomes?

**DR. STEVENS:** Several studies report neurologic outcome among children managed with higher versus lower oxygen saturation targets. In the cohort study by Deulofuet et al, a higher mental developmental index and a trend toward higher physical

developmental index was seen among babies managed with a low versus a high saturation target. These results must be considered with caution because of a low follow-up rate and the limitations of a cohort study using a before-and-after study design.

The cohort study by Tin et al found similar rates of cerebral palsy in the high- and low-saturation groups. But the randomized, controlled study, the Support study, is currently collecting data on the neurologic outcome of these study patients. The follow-up period will be complete by mid 2011. What we know from the primary trial is that there were no differences in the incidents or severity of IVH or periventricular leukomalacia between study groups.

**MR. BUSKER:** And other common neonatal comorbidities that may be oxygen-related?

**DR. STEVENS:** Well, Bob, several neonatal morbidities are thought to be potentially oxygen-related. These include necrotizing enterocolitis, prolonged length of stay, patent ductus arteriosus, and growth. So looking at each of these separately, for necrotizing enterocolitis in the cohort studies and in Support, its incidence was similar between infants treated with high or low oxygen saturations. For prolonged length of stay, the cohort study by Tin et al showed a shorter length of stay for infants treated with a low rather than a high oxygen saturation target.

Other cohort studies and the Support study, which was the only available randomized trial, found similar lengths of hospital stay in low- and high-saturation groups. As for patent ductus arteriosus, though the ductus arteriosus is very sensitive to oxygen saturations, the Support study did not show a difference in the incidence of PDA between saturation groups. Finally, for growth, the Tin study showed more rapid growth among infants treated with low rather than higher oxygen saturation.

In the Support study, the only randomized trial, the growth velocity was similar between the high- and low-saturation groups.

**MR. BUSKER:** We'll return in a moment with Dr. Timothy Stevens from University of Rochester Medical Center.

**DR. CHRISTOPH LEHMANN:** Hello, I'm Dr. Chris Lehmann. I'm the Director for Clinical Information Technology at the Children's Medical and Surgical

Center at Johns Hopkins and one of the Program Directors for eNeonatal Review.

eNeonatal Review is a CME-accredited program presented by The Johns Hopkins University School of Medicine. eNeonatal Review has two parts: a newsletter delivered by email and podcasts, like the one you are currently listening to. Each presents current, concise, peer-reviewed literature reviews and commentary in areas of importance to neonatologists, NICU nurses, and respiratory therapists working with neonatal patients. Ten thousand of your colleagues have already registered for eNeonatal review. Please join them.

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For more information on registration to receive eNeonatal Review without charge, or to look at archived issues, please go to [www.eneonatalreview.org](http://www.eneonatalreview.org). Thank you.

**MR. BUSKER:** Welcome back to this eNeonatal Review podcast. I'm Bob Busker, managing editor of the program. Our topic is Targeting the Ideal Oxygen Saturation. Our guest is Dr. Timothy Stevens, Associate Professor of Pediatrics from the University of Rochester Medical Center.

We've been looking at how some of the new information Dr. Stevens discussed in the newsletter issue can be applied at the bedside. So if you would, Doctor, please present another case.

**DR. STEVENS:** An 890-gram male infant is born by cesarean section at 27 and two-sevenths weeks' gestation to a mother whose pregnancy was uncomplicated. The early neonatal course was remarkable for E. coli sepsis and respiratory distress syndrome. The baby has required 35% oxygen to maintain oxygen saturations of 88% to 92%, with a lower alarm limit of 85% and an upper limit of 95%. The baby is now 18 days old and experiences frequent oxygen desaturations, requiring the bedside nurse to make frequent oxygen adjustments to maintain saturations in the target range.

The nurse sets the upper alarm limit to 98% to create a buffer against the frequent desaturation episodes. When asked why, she responds that that is the way the anesthesiology group does it in the operating room.

**MR. BUSKER:** Let's focus on the action that nurse took. In your experience, is that common?

**DR. STEVENS:** It is a common practice. Identifying the ideal oxygen saturation, while not yet achieved, is only part of the challenge in managing oxygen therapy to prevent retinopathy of prematurity. There remains a strong bias toward erring on the high side when managing oxygen. A study of intended versus actual oxygen saturations found that the actual oxygen saturations were outside the intended range more than half the time, and during those periods, two-thirds had oxygen saturations that were high.

There are many barriers to achieving the desired oxygen saturation targets, including staff compliance, the belief that pinker is better, and staffing ratios. Lower staffing ratios, nurse-to-patient ratios of one-to-one, are associated with more time in the target oxygen saturation range, in contrast to higher patient-to-nursing ratios of three to one, where the portion of time the baby is in the target saturation range is lower. That was recently shown in a study by Dr. Sink.

**MR. BUSKER:** Do you believe the nurse's decision was the correct one?

**DR. STEVENS:** Not with our current understanding of oxygen saturation levels and risk of severe retinopathy of prematurity. Saturation limits exceeding 95% have been shown to increase the incidence and severity of retinopathy of prematurity. There are many sources of hidden hyperoxia, episodes of hyperoxia that occur in medical practices throughout the hospital that might be unrecognized as a cause of hyperoxia.

These settings might include the operating room, as well as transport of patients between units without the use of blended oxygen, use of 100% oxygen during a nebulized medication delivery, use of 100% oxygen during pre-oxygenation for procedures. Systematic efforts should be made to identify these hidden sources of hyperoxia and to minimize them through use of staff education, blended oxygen, and continuous saturation monitors in all these clinical settings.

At this point, avoiding oxygen saturations exceeding 95% can now be considered a best practice during the acute neonatal period for pre-term infants.

**MR. BUSKER:** If practitioners should not be turning up the oxygen to treat frequent desaturations, what should they do?

**DR. STEVENS:** Oxygenation can be improved with an improvement in alveolar recruitment, such as can be achieved with increasing PEEP on mechanical ventilation or through use of CPAP for those patients who are not on mechanical ventilation. These changes, increasing PEEP and increasing CPAP, should be considered as an alternative to increasing FIO<sub>2</sub> for some patients. Other practices that have been associated with less frequent oxygen desaturations include reducing the ambient noise as well as the number of handlings for the child during routine care. Though such measures are not proven to reduce ROP, it seems reasonable to complement careful oxygen saturation targeting with care practices that limit preventable, transient episodes of hyperoxia or hypoxia.

**MR. BUSKER:** We know many of our listeners may be thinking, the response of this bedside nurse is common in my unit. So my question to you, Dr. Stevens: How would you advise these clinicians about changing unit culture in regard to oxygen saturation targets?

**DR. STEVENS:** NICU staff education is vital. Several educational points are appropriate for our staff. They include education about the limits of pulse oximetry and detecting hyperoxia. In addition, staff should be taught that adjustments in FIO<sub>2</sub> should be small. In the Chow study, increases in FIO<sub>2</sub> by NICU staff obligated close, direct observation until a saturation in the target range was achieved. Similarly, oxygen adjustments were gradual, limited to 2% to 5% per adjustment.

In the Chao study, the project leaders required bedside nurses to sign an agreement acknowledging the change in oxygen saturation targets and their agreement to adhere to the new standards. We've not taken this approach in our own nursery. Instead, we use frequent audits of compliance with oxygen saturation settings, recording both the percentage of time the patients spend below, within, and above the targeted oxygen saturation parameters. Change in

these areas is gradual and takes a persistent, collaborative approach between the medical and nursing services.

**MR. BUSKER:** We've got time, I believe, for one more case. So if you would, Doctor —

**DR. STEVENS:** We'll pick up a case that we discussed before, an 890-gram male infant born by cesarean section at 27 and two-sevenths weeks' gestation to a mother whose pregnancy was uncomplicated. The early neonatal course was remarkable for E. coli sepsis and RDS. Oxygen therapy was managed to maintain saturations of 88% to 92% with a lower alarm limit of 85% and an upper limit of 95%.

At 7 weeks of age, now 34 and two-sevenths weeks post-menstrual age, the baby has zone 2, stage 2 retinopathy of prematurity bilaterally and requires 28% oxygen through a 1/2 liter nasal cannula to maintain oxygen saturations of 90%. His weight gain has been slow, less than our target growth velocity.

**MR. BUSKER:** This baby is more than 34 weeks post-menstrual age. So let's say at this point the clinician wants to improve his growth by liberalizing his supplemental oxygen to achieve higher saturations, say in the range of 98% to 99%. Is there evidence supporting the idea that these higher saturations will improve his oxygenation, help him breathe easier, and promote better growth?

**DR. STEVENS:** This question was carefully addressed in the Benefits of Oxygen Saturation Targeting Study, or BOOST study. This was a randomized, controlled trial involving 258 infants born less than 30 weeks' gestation who were randomized at 32 weeks to 1 of 2 oxygen saturation target ranges. A low group with saturation targets of 91% to 94%, or a high group with saturation targets of 95% to 98%.

The study hypothesis was that supplemental oxygen to achieve higher saturation targets would improve growth in neurodevelopmental outcome. The study found no difference between the high- and low-saturation target groups in mortality, weight gain, length, head circumference, and neural developmental outcome at 12 months of age. The high-saturation group received oxygen for a longer period after randomization, as much as 20 days longer period in oxygen.

In addition, they had a significantly higher rate of supplemental oxygen at 36 weeks post-menstrual age and a significantly higher frequency of home-based oxygen therapy among the higher-saturation group.

**MR. BUSKER:** To reduce the risk of threshold ROP, should the clinician target higher oxygen saturations during the convalescent or recovery period? What does the evidence say about that?

**DR. STEVENS:** This question was carefully addressed in the Supplemental Therapeutic Oxygen for Pre-threshold Retinopathy of Prematurity study, fondly known as STOPROP. This was a randomized controlled trial involving 649 infants born at less than 29 weeks' gestation who had a room air oxygen saturation less than 94% at 36 weeks post-menstrual age. At that age, infants were enrolled and randomized to 1 of 2 oxygen saturation target groups, a low group, 89% to 94%, or a high group, 96% to 99%.

The study hypothesis was that supplemental oxygen to achieve a higher saturation target would slow the progression of pre-threshold to threshold ROP. In the study, there was no difference in the primary outcome, progression of threshold ROP in at least one eye. The investigators found threshold ROP in 48% in the low-saturation group versus 41% in the high-saturation group. After adjustment for baseline and severity of retinopathy of prematurity, plus disease, race, and gestational age, there was no significant difference in the primary outcome.

Among important secondary outcomes, all study eyes at three months corrected age showed similar rates of severe sequelae, including retinal detachments, retinal folds, or macular ectopia, as well as similar rates of progression of ROP.

To answer your question more directly, Bob, the STOPROP study did not find a difference in ophthalmologic outcomes among children measured with a high versus low oxygen saturation target.

**MR. BUSKER:** Now, improving neurodevelopmental outcome — and in particular reducing the risk of cerebral palsy — is there evidence that targeting a higher saturation can help?

**DR. STEVENS:** From the BOOST and STOPROP studies, oxygen saturation targets greater than 95%, beginning at either 32 or 36 weeks post-menstrual

age, were not associated with improvements in growth or neurodevelopmental outcome. Conversely, routine use of supplemental oxygen saturation targets greater than 95% in infants greater than 32 to 36 weeks post-menstrual age was associated with greater risk of pulmonary morbidity. Hence, routine oxygen saturation targets greater than 95% in all infants 32 to 36 weeks post-menstrual age is not recommended.

**MR. BUSKER:** Let's bring in the ophthalmologist. And let's say that this specialist recommends targeting a higher oxygen saturation in some patients with ROP to lessen the risk of progression to threshold ROP. In targeting a higher saturation, what are the tradeoffs?

**DR. STEVENS:** In STOPROP, a post-hoc subgroup analysis of patients with plus disease, which is dilated and torturous vessels in at least two quadrants of the posterior pole, suggests that the infants without plus disease may be more responsive to supplemental oxygen therapy than infants with plus disease. Based on this observation, some ophthalmologists recommend a higher saturation target for patients with pre-threshold ROP.

In terms of tradeoffs, Bob, regardless of ROP severity, infants treated with a higher, rather than a lower, oxygen saturation target were more likely to experience pneumonia and pulmonary exacerbations of bronchopulmonary dysplasia. In addition, these infants had longer hospitalizations, longer periods in oxygen, and greater use of diuretics to treat bronchopulmonary dysplasia.

**MR. BUSKER:** Thank you, Doctor. Now let me ask you to look to the future for us, if you would. What do you see happening that will help improve outcomes in these patients?

**DR. STEVENS:** At this time, Bob, the Support trial is the only randomized control trial of oxygen saturation targeting and clinical outcomes. Several ongoing studies will be completed in the next few years. The authors of these randomized, controlled trials have agreed in advance to share individual-level data, which would allow an individual-level meta-analysis to be performed. Combining the outcomes of these studies will give us much greater power to identify differences in the primary and secondary outcomes for extremely low-birth-weight infants.

A technological advance that is under development and offers a great deal of promise is the use of oxygen controllers, which are automated systems that respond to changes in oxygen saturation with adjustments in the inspired oxygen concentration. These systems have been under development for several years, and their ability to respond appropriately to fluctuations in saturations is getting ever better. Introduction of these at the bedside will offer great potential to improve oxygen saturation targeting and oxygen therapy for our premature infants.

**MR. BUSKER:** Dr. Timothy Stevens from the University of Rochester Medical Center, thank you for participating in this eNeonatal Review podcast.

**DR. STEVENS:** Thank you, Bob. I enjoyed talking with you.

**MR. BUSKER:** This podcast is presented in conjunction with the eNeonatal Review Newsletter, a peer-reviewed, CME/CE-accredited literature review e-mailed monthly to clinicians caring for neonates.

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Thank you for listening.

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## REFERENCES

Chen M, Cital A, McCabe F, Leicht KM, Fiascone J, Dammann CE, Dammann O. Infection, Oxygen, and Immaturity: Interacting Risk Factors for Retinopathy of Prematurity. Neonatology 2010;99(2):125-132.