The SUPPORT, BOOST II, and COT Trials
You Must Understand Usual Care To Safeguard Patients and Make Firm Conclusions

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Clinical Center
National Institutes of Health
Outline

• Facts
  – Usual care at time of trials
  – Outcomes
  – Informed consent
Outline

• **Facts**
  – Usual care at time of trials
  – Outcomes
  – Informed consent

• **Controversy**
  – Criticism
  – Defense
  – Deficiency in the Common Rule?
Timeline

2001-2003
- SUPPORT Study conceived

2005-2009
- SUPPORT enrollment (2006 BOOST II and COT enrollment begin)

2010
- SUPPORT study published NEJM

2011
- OHRP investigation begins
- BOOST II Trial stopped early for harm Published NEJM

2012
- SUPPORT follow-up study published NEJM

2013
- March
- April
- May
- June
- July
- August

- 22nd
- COT study published JAMA
Within the AAP’s recommended SpO₂ range, does targeting the top or bottom half produce the best outcomes for retinopathy of prematurity, neurologic damage, and death?

AAP = American Academy of Pediatrics
Ranges for SpO$_2$ During Usual Care

SpO$_2$ target range recommended by the American Academy of Pediatrics (AAP)

Ranges for $\text{SpO}_2$ During Usual Care

SpO$_2$ target range recommended by the American Academy of Pediatrics (AAP)

- **Neurologic damage, death**
- **Retinopathy of prematurity, blindness**

Ranges for \( \text{SpO}_2 \) During Usual Care

- **Retinopathy of prematurity, blindness**
- **SpO\(_2\) target range recommended by the American Academy of Pediatrics (AAP)**
- **Neurologic damage, death**

Ranges for SpO$_2$ During Usual Care

SpO$_2$ target range recommended by the American Academy of Pediatrics (AAP)

Ranges for SpO$_2$ During Usual Care

What was usual care?

Ranges for SpO$_2$ During Usual Care

What was usual care?

Neonatologists picked **ranges** within the AAP recommended **range**

Ranges for \( \text{SpO}_2 \) During Usual Care

What was usual care?

Oxygen Saturation (%)

Ranges for \( \text{SpO}_2 \)

<table>
<thead>
<tr>
<th>Lower limit</th>
<th>Upper limit</th>
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<tbody>
<tr>
<td>80</td>
<td>100</td>
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</table>

Ranges for SpO₂ During Usual Care

Oxygen Saturation (%)

What were the lower limits?

Ranges for SpO₂ During Usual Care

Lower limit of targeted SpO₂ ranges varied from 80% - 95%.
Ranges for SpO₂ During Usual Care

What were the upper limits?
Ranges for SpO$_2$ During Usual Care

Upper Limits (% NICUs)

Upper limit of targeted SpO$_2$ ranges varied from 92-100%
U.S. surveys of 120 NICUs in 2001 and 40 in 2004, showed that upper limits of targeted SpO\textsubscript{2} ranges were always $\geq 92\%$. 


Did bedside caregivers adhere to intended targeted $\text{SpO}_2$ ranges?
The AVIOx Study in 2004

Ranges for SpO$_2$ During Usual Care

**AVIOx Study Prescribed SpO$_2$ Ranges**

Oxygen Saturation (%)

AVIOx study centers (A-N)

Ranges for SpO$_2$ During Usual Care

AVIOx Study Prescribed SpO$_2$ Ranges

All 14 NICUs followed the 92% upper limit rule

Hagadorn JI. Pediatrics 2006; 118(4):1574–82.
Ranges for SpO$_2$ During Usual Care

AVIOx Study Achieved SpO$_2$ Ranges

Oxygen Saturation (%)

Median and Interquartile Ranges for Achieved SpO$_2$ Ranges
- 75$^{th}$ percentile
- Median
- 25$^{th}$ percentile

AVIOx study centers (A-N)

Hagadorn JI. Pediatrics 2006; 118(4):1574–82.
Ranges for SpO\textsubscript{2} During Usual Care

**AVIOx Study Achieved SpO\textsubscript{2} Ranges**

50% of time achieved SpO\textsubscript{2} kept above the targeted range

AVIOx study centers (A-N)

All centers/patients combined

Hagadorn JI. *Pediatrics* 2006; 118(4):1574–82.
Ranges for SpO$_2$ During Usual Care

SUPPORT Study

Low targeted range
85-89%

AVIOx study centers (A-N)

All centers/patients combined

Oxygen Saturation (%)

Ranges for SpO$_2$ During Usual Care

SUPPORT Study

Low targeted range 85-89%

Within AAP target range for SpO$_2$

Ranges for SpO$_2$ During Usual Care

SUPPORT Study

Usual care: SpO$_2$ upper limit $\geq$ 92%

Low targeted range 85-89%

AVIOx study centers (A-N)

Ranges for SpO₂ During Usual Care

Support Study

Oxygen Saturation (%)

Low targeted range
85-89%

AVIOx study centers (A-N)

NO U.S. NICU reported upper limit as low as 89%

Ranges for SpO₂ During Usual Care

SUPPORT Study

Low targeted range
85-89%

SUPPORT low range below or at the bottom half of prescribed in these 14 NICUs

AVIOx study centers (A-N)

Oxygen Saturation (%)

80
85
90
95
100

Hagadorn JI. Pediatrics 2006; 118(4):1574–82.
Ranges for SpO$_2$ During Usual Care
SUPPORT Study

Low targeted range
85-89%

AVIOx study centers (A-N)

SUPPORT low range below achieved SpO$_2$ in these 14 NICUs

Hagadorn JI. Pediatrics 2006; 118(4):1574–82.
Ranges for SpO$_2$ During Usual Care

SUPPORT Study

Low targeted SpO$_2$ range (85-89%) in SUPPORT below those commonly used in U.S. and E.U.

Low targeted range
85-89%

AVIOx study centers (A-N)
Ranges for SpO\textsubscript{2} During Usual Care

SUPPORT Study

High targeted range
91-95%

AVIOx study centers (A-N)

Oxygen Saturation (%)

All centers/patients combined

Ranges for SpO₂ During Usual Care

SUPPORT Study

High targeted range
91-95%

Within AAP target range for SpO₂


Ranges for SpO₂ During Usual Care

SUPPORT Study

Oxygen Saturation (%)

High targeted range
91-95%

Upper limit of the high targeted range consistent with current practice

Usual care: SpO₂ upper limit ≥ 92%

Ranges for SpO\textsubscript{2} During Usual Care
SUPPORT Study

High targeted range 91-95%

SUPPORT high targeted range consistent with prescribed in these 14 NICUs

Hagadorn JI. *Pediatrics* 2006; 118(4):1574–82.
Ranges for SpO₂ During Usual Care

SUPPORT Study

High targeted range 91-95%

SUPPORT high targeted range consistent with achieved SpO₂ values in these 14 NICUs

Hagadorn JI. Pediatrics 2006; 118(4):1574–82.
Ranges for SpO$_2$ During Usual Care

SUPPORT Study

High targeted range 91-95%

High targeted SpO$_2$ range in SUPPORT indistinguishable from usual care before and during study
Ranges for SpO\textsubscript{2} During Usual Care

**AVIOx Study Achieved SpO\textsubscript{2} Ranges**

![Graph showing oxygen saturation ranges for various AVIOx study centers (A-N).]

- **Oxygen Saturation (%):**
  - 100
  - 95
  - 90
  - 85
  - 80

- **AVIOx study centers (A-N):**
  - N
  - L
  - J
  - G
  - F
  - M
  - K
  - D
  - E
  - B
  - C
  - I
  - A
  - H

- **All centers/patients combined**

References:
- Hagadorn JI. *Pediatrics* 2006; 118(4):1574–82.
Median Achieved SpO$_2$ Values for 14 NICUs During Usual Care

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<thead>
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<th>Mean</th>
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Median Achieved SpO\textsubscript{2} Values for 14 NICUs During Usual Care Compared to the Low and High SpO\textsubscript{2} Arms in Clinical Trials

Randomized clinical trial arms and AVIOXs study centers

Median Achieved SpO$_2$ Values for 14 NICUs During Usual Care Compared to the Low and High SpO$_2$ Arms in Clinical Trials

Randomized clinical trial arms and AVIOXs study centers
Achieved SpO\textsubscript{2} in the low arm significantly lower than both usual care and the high SpO\textsubscript{2} arm

Randomized clinical trial arms and AVIOXs study centers

Percentage of time spent below the indicated SpO$_2$ cutoff for targeted ranges.

Usual care centers:
n = 45 patients

Lower limit of intended range:
Median = 88%
(IQR 85-88%)
Time (%) Spent Below Indicated $\text{SpO}_2$ Cutoff for Targeted Ranges

Percentage of time spend below the indicated $\text{SpO}_2$ cutoff

- **Low $\text{SpO}_2$ arms**
  - $n = 1618$ patients

- **High $\text{SpO}_2$ arms**
  - $n = 1634$ patients

- **Usual care centers**
  - $n = 45$ patients

Lower limit of intended range
- Median = 88%
- (IQR 85-88%)

Time (%) Spent Below Indicated SpO\textsubscript{2} Cutoff for Targeted Ranges

- **Low SpO\textsubscript{2} arms**: n = 1618 patients
- **High SpO\textsubscript{2} arms**: n = 1634 patients
- **Usual care centers**: n = 45 patients

Percentage of time spent below the indicated SpO\textsubscript{2} cutoff

- **<85% (Actual SpO\textsubscript{2})**
  - Lower limit of intended range
  - Median = 88%
  - IQR 85-88%

*p = 0.04*
Time (%) Spent Below Indicated SpO\textsubscript{2} Cutoff for Targeted Ranges

- **Low SpO\textsubscript{2} arms**: n = 1618 patients
- **High SpO\textsubscript{2} arms**: n = 1634 patients
- **Usual care centers**: n = 45 patients

Percentage of time spend below the indicated SpO\textsubscript{2} cutoff

- <85% (Actual SpO\textsubscript{2})
- Lower limit of intended range
  - Median = 88%
  - IQR 85-88%

*p* = 0.04
*p* < 0.0001

Summary

- The Low SpO₂ arm (85-89%) of SUPPORT was below the commonly targeted range.
- Bedside caregivers, outside of the three trials routinely skewed SpO₂ toward the high end of NICU target ranges.
- Babies randomized to the low SpO₂ arm of SUPPORT spent significantly more time below an O₂ saturation of 85%.
Pulse Oximeters in SUPPORT, BOOST II and COT

- Health care providers blinded
- Calibration error in pulse oximeters offset to return false readings to maintain blinding
Pulse Oximeters in SUPPORT, BOOST II and COT

- $\text{SpO}_2$ values between 85% to 95% were offset up to 3% to maintain and blind randomized group assignment
- Displays reverted to true values for $\text{O}_2$ saturations $\leq 84\%$ or $\geq 96\%$
Masimo Pulse Oximeters Used in the Trials: Calibration Error

Masimo calibration curve from 2002 to 2009

- Upper calibration curve adjusted upward for fetal hemoglobin
- Artificial data used to connect two separate calibration curves
- Lower calibration curve not adjusted upward for fetal hemoglobin
All three studies used the same modified pulse oximeters.
BOOST II was done in Australia, New Zealand, and United Kingdom.
COT was conducted primarily in Canada.
Mortality

Trial and Country

BOOST II
Australia

New Zealand

United Kingdom

COT

SUPPORT

Calibration algorithm

Original
Revised
Original
Original
Original
Original

Favors

Low SpO₂ arm
High SpO₂ arm

SUPPORT was conducted in US and started one year before BOOST II and COT

SUPPORT

was conducted in US and started one year before BOOST II and COT

Odds Ratio (± 95% CI)

0.5 1.0 1.5 2.0 2.5
**Mortality**

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<td><strong>SUPPORT</strong></td>
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**SUPPORT and BOOST II in New Zealand used only the original calibration algorithm**

Mortality Odds Ratio (± 95% CI):
- Favors Low SpO₂ arm: 0.5
- Favors High SpO₂ arm: 1.0

Odds Ratio (± 95% CI): 0.5, 1.0, 1.5, 2.0, 2.5
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**Mortality**

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<td>2.0</td>
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**Favors**

- Low
- High

**BOOST II** (Australia and United Kingdom) and **COT** started with the original calibration algorithm, but changed to the revised algorithm halfway through enrollment.
**Mortality**

### Trial and Country Calibration algorithm

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<tr>
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### Favors

- Low SpO$_2$ arm
- High SpO$_2$ arm

- Solid white boxes are odds ratios of survival; horizontal lines are 95% confidence intervals

### Summary

(n=) $I^2$ p-value

All studies (8) 33% 0.17
Mortality

## Trial and Country

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## Summary

- **All studies**: (8) 33% 0.17

## Odds Ratio (± 95% CI)

- No effect line; 95% confidence intervals crossing this line = no significant effect
Trial and Country  | Calibration algorithm
---|---
**BOOST II**
Australia | Original
| Revised
New Zealand | Original
United Kingdom | Original
| Revised
**COT** | Original
| Revised
**SUPPORT** | Original

**Summary** (n=) $I^2$  p-value
All studies  | (8) 33% 0.17

White boxes on this side indicate better survival in high arm.

Mortality

<table>
<thead>
<tr>
<th>Favors</th>
<th>Odds Ratio ($\pm$ 95% CI)</th>
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<tbody>
<tr>
<td>Low SpO$_2$ arm</td>
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<tr>
<td>High SpO$_2$ arm</td>
<td>1.0</td>
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Odds Ratio ($\pm$ 95% CI)
Mortality

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**Summary**

(n=8) $I^2 = 33\%$ p-value 0.17

Odds Ratio ($\pm$ 95% CI)
### Trial and Country

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### Summary

<table>
<thead>
<tr>
<th>All studies</th>
<th>(n=)</th>
<th>I²</th>
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<tr>
<td></td>
<td>(8)</td>
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(No summary, I² >30%)
Mortality

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Summary (n=5)  

- $I^2 = 19.5\%$  
- p-value = 0.29  
- p = 0.80
### Summary

- **Trial and Country**
  - **BOOST II**
    - Australia: Revised
  - United Kingdom: Revised
  - COT: Revised

- **Calibration algorithm**
  - Revised

- **Favors**
  - Low SpO₂ arm
  - High SpO₂ arm

- **Odds Ratio** (± 95% CI)
  - 0.5
  - 1.0
  - 1
  - 1.5
  - 2
  - 2.5

- **Revised**
  - (n=3)
  - $I^2 = 0\%$
  - p-value = 0.65

- **p = 0.002**
<table>
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<th>Trial and Country</th>
<th>Calibration algorithm</th>
<th>Favors</th>
<th>Odds Ratio (± 95% CI)</th>
<th>Summary (n=)</th>
<th>$I^2$</th>
<th>p-value</th>
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<tbody>
<tr>
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<td>Low SpO$_2$ arm</td>
<td>0% 0.44 p = 0.54</td>
<td>(3)</td>
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<td>0.44</td>
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<tr>
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**Summary**: (n=) $I^2$ p-value

Original (studies with revised data) (3) 0% 0.44

Revised (3) 0% 0.65

Interaction p = 0.01
Targeting the bottom half of the AAP recommended SpO$_2$ range can increase mortality, but this effect was variably influenced by the calibration algorithm.
Necrotizing Enterocolitis

Trial and Country | Calibration algorithm | Favors
--- | --- | ---
BOOST II | | 
Australia | Original | Low SpO$_2$ arm
 | Revised | High SpO$_2$ arm
New Zealand | Original | 
United Kingdom | Original | 
 | Revised | 
COT | Original/Revised | 
SUPPORT | Original | 

Summary (n=7) | $I^2$ | p-value
--- | --- | ---
All studies | 0% | 0.95

Odds Ratio (± 95% CI)

Favors

Low SpO$_2$ arm

High SpO$_2$ arm

$p=0.01$
Necrotizing Enterocolitis

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<td>Original</td>
<td></td>
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<tr>
<td>United Kingdom</td>
<td>Original, Revised</td>
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<tr>
<td>COT</td>
<td>Original/Revised</td>
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<tr>
<td>SUPPORT</td>
<td>Original</td>
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</tr>
</tbody>
</table>

Summary (n=7) | I² | p-value |
All studies   | 0% | 0.95    |

Odds Ratio (± 95% CI)
Necrotizing Enterocolitis increased in babies randomized to the bottom half of the SpO2 range recommended by AAP

Effect consistent across all three studies, five countries and the two monitor calibrations used

United Kingdom
- Original
- Revised

COT
- Original/Revised

SUPPORT
- Original

Summary (n=7)
- I²: 0%
- p-value: 0.95

Odds Ratio (± 95% CI)
- p=0.01

Effect consistent across all three studies, five countries and the two monitor calibrations used.
## Retinopathy of Prematurity

### Trial and Country

<table>
<thead>
<tr>
<th>Trial and Country</th>
<th>Calibration algorithm</th>
<th>Favors</th>
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<tbody>
<tr>
<td>BOOST II</td>
<td>Original, Revised</td>
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### Summary (n=7)

- Summary: 55% CI ± 30%
- p-value: 0.04
- (No summary, $I^2 > 30\%$)

### Odds Ratio (± 95% CI)

- 0.5 to 2.0

---

**SpO2**: Oxygen saturation level

**Calibration algorithm**: Adjustments made to the study's methodology.
## Retinopathy of Prematurity

<table>
<thead>
<tr>
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<th>Calibration algorithm</th>
<th>Odds Ratio (± 95% CI)</th>
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<td>Original</td>
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<td>Original</td>
<td>(No summary, I² &gt;30%)</td>
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</table>

Summary (n=) 1² 53% p-value 0.09

Odds Ratio (± 95% CI)

0.5 1.0 1.5 2.0

Calibration algorithm
Retinopathy of Prematurity

Targeting the bottom half of the AAP SpO\textsubscript{2} range inconsistently prevented retinopathy of prematurity (ROP)

Variability in results suggests that unknown cofactor(s) other than the SpO\textsubscript{2} range affected the occurrence of ROP

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<tr>
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<td>0.09</td>
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<tr>
<td>Revised</td>
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<td>51%</td>
<td>0.15</td>
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Odds Ratio (± 95% CI)
SUPPORT 2 year follow-up: “although eye surgery was significantly less frequent in the lower…than…higher-oxygen-saturation group, there were no significant differences … (in) rates of unilateral and bilateral blindness, nystagmus, strabismus, or use of corrective lenses.”


<table>
<thead>
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<th>SUPPORT</th>
<th>Original</th>
<th>Odds Ratio (± 95% CI)</th>
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Odds Ratio (± 95% CI)
Summary

Targeting the low SpO₂ range of 85 to 89%:

- Increased Necrotizing Enterocolitis
- Increased Mortality under some conditions
- Did not necessarily prevent ROP
- After corrective eye surgery, vision differences were no longer present between study arms
Each of the 4 possible combinations of treatments is considered standard care by some units in the United States. All of the treatments (CPAP in the delivery room, delivery room intubation plus surfactant, lower oxygen range, and higher oxygen range) proposed in this study are standard of care at various hospitals like [institution F] in the United States, so there are no predictable increases in risk for your baby.

We will also be looking at the ranges of oxygen saturation that are currently being used with these same babies. All of these saturations are considered normal ranges for premature infants. Sometimes higher ranges are used and sometimes lower ranges are used. All of them are acceptable ranges.

Keeping the level in either end of the normal range is routinely used in the NICU for premature babies. This will determine if your baby will have his/her oxygen saturation level kept in the high or low part of the normal oxygen saturation range. Your infant will have all usual care for infants born before 28 weeks gestation. The oxygen saturation ranges to be used are currently used for usual care in premature infants in the NICU.

Within the range of oxygen which we normally use, your infant will either be on the high end of normal or the low end of normal. … each of the 4 possible combinations of treatments is currently used by some NICUs as their primary approach to treating premature infants. Because all of the treatments proposed in this study are standard of care, there is no expected increase in risk for your infant.

Your baby will have his/her oxygen saturation level kept in the high or low part of the normal oxygen saturation range.

Both of these ranges are within the oxygen saturation range that is currently used for premature infants in the NICU at [institution K]. All of these treatments have been carefully studied and all are used in Newborn ICUs. All of these treatments are currently clinically accepted, but haven't been compared with each other in this manner … For this study, there will be no change in the oxygen saturation range from the one that is currently used in the NICU at [institution K].

Within the range of oxygen that we normally keep babies in (85 to 95%), your baby will either be in the high end or the low end of normal. Your baby will receive all standard care provided to any baby in the Neonatal Intensive Care. The procedures that are being used are standard (routine) treatments used in neonatal intensive care. … To the best of our understanding, there will be no more risks for the baby in this study than are possible for any ill premature baby needing intensive care.

Routine neonatal intensive care will be provided during your baby's participation in the study. Each of the study treatments is already being used by many doctors across the country, there is no predictable increase in risk for your baby.

There are also two oxygen support strategies: 1) a low normal range (85–89%) and 2) a high normal range (91–95%). Because all treatments proposed in this study are currently accepted standard of care, there is no predictable increase in risk to your baby. … because all of the treatments proposed in this study are currently accepted as standard of care, there is no unpredictable increase [in risk] expected.

The oxygen saturation level currently used in the neonatal intensive care units at [institution S] is between 85% and 94%, so both treatment groups (the group for whom the target for oxygen saturation levels will be 85–89% and the group for whom the target for oxygen saturation levels will be 91–95%) will be treated with oxygen in a manner that is very similar to that currently used at both hospitals. The ranges used in this study are in common use in NICU's across the country. Because all of the treatments proposed in this study are standard of care, there is no predictable increase in risk for your baby.
Controversy
March 7, 2013

RE: Human Research Protections under Federalwide Assurance (FWA) 5960

“we determine, that the IRB ... approved informed consent documents ... failed to adequately address the following HHS regulation (Common Rule): A description of any reasonably foreseeable risks and discomforts.”
# Timeline

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## 2013

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Letter from OHRP to lead SUPPORT center
The New York Times
NEW YORK, WEDNESDAY APRIL 10, 2013
FRONT PAGE

Study of Babies Did Not Disclose Risks, U.S. Finds

By SABRINA TAVERNISE

“The risk the consent form did mention was far less significant: abrasion of the infants’ skin by an oxygen monitoring device.”

The researchers had information to know, before conducting the study, that participation might lead to differences in whether an infant survived, or developed blindness, in comparison to had that child not been enrolled in the study.”
“The Department of Health and Human Services needs to investigate how this breakdown occurred. And if the institutions do not offer strong reforms, the agency can suspend their ability to conduct federally financed research on human subjects.”
“When the study was planned, the best evidence showed that lower oxygen targets — even lower than used in the study — resulted in less eye disease without a higher death rate. The finding of a higher death rate in one study group was not anticipated.”
Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation

W Tin, D W A Milligan, P Pennefather, E Hey

Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation

W Tin, D W A Milligan, P Pennefather, E Hey

March 2001
Vol 84 No 2, Pages F106-F110


“Staff always aimed to maintain saturation in the top half of the target range”
An examination of case notes of 295 babies in northern England 1990-1994

Staff always aimed to maintain saturation in the top half of the target range

Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation

W Tin, D W A Milligan, P Pennefather, E Hey

March 2001

Vol 84 No 2, Pages F106-F110

Four target oxygen saturation ranges: 88-98%, 85-95%, 84-94%, and 70-90%

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<thead>
<tr>
<th>Target O₂ saturation</th>
<th>No of babies admitted</th>
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An examination of case notes of 295 babies in northern England 1990-1994

Staff always aimed to maintain saturation in the top half of the target range

Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation

W Tin, D W A Milligan, P Pennefather, E Hey

March 2001
Vol 84 No 2, Pages F106-F110

Mortality was comparable over the four target oxygen saturation ranges: 52.8%, 54.5%, 44%, and 51.6%

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Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation

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Mortality reported here (1990–1994) was double that seen one decade later at the time of SUPPORT (15-25%).


Staff always aimed to maintain saturation in the top half of the target range.

Mortality reported here (1990–1994) was double that seen one decade later at the time of SUPPORT (15-25%).
An examination of case notes of 295 babies in northern England 1990-1994

Staff always aimed to maintain saturation in the top half of the target range

Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation

W Tin, D W A Milligan, P Pennefather, E Hey

March 2001
Vol 84 No 2, Pages F106-F110

Targeting the lowest $O_2$ saturation range 70-90%, mortality was comparable, but ROP was less; 6.2% vs. other 3 ranges (13.5, 15.6, and 27.7%)

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**Timeline**

### 2001-2003
- **SUPPORT Study** conceived

### 2005-2009
- **SUPPORT enrollment** (2006 BOOST II and COT enrollment begin)

### 2010
- **SUPPORT study published** NEJM
- **OHRP investigation** begins

### 2011
- **BOOST II Trial stopped early for harm**
- **Published NEJM**

### 2012
- **SUPPORT follow-up study published** NEJM

### 2013

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- **March 7th**: Letter from OHRP to lead SUPPORT center
- **March 10th**: NYT article on SUPPORT
- **April 15th**: NYT editorial, NYT letter
- **April 18th**: Correspondence
- **May 16th**: NEJM 3 articles published in defense of SUPPORT
- **June**: Editorial, Perspective

**Timeline Details**

- **SUPPORT Study conceived** (2001-2003)
- **SUPPORT enrollment** (2005-2009)
- **SUPPORT study published** NEJM (2010)
- **OHRP investigation** begins (2010)
- **BOOST II Trial stopped early for harm**
- **Published NEJM** (2011)
- **SUPPORT follow-up study published** NEJM (2012)
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- **NYT letter** (2013)
- **Correspondence** (2013)
- **NEJM 3 articles published in defense of SUPPORT** (2013)
- **Editorial** (2013)
- **Perspective** (2013)
Oxygen-Saturation Targets in Extremely Preterm Infants

By CARLO WA et al

“The best evidence available when we planned the study was that oxygen saturations of 70 to 90% were associated with less retinopathy without an increase in mortality.”

ADC Fetal & Neonatal Ed. Tin W et al. 2001;84:F106-F110
EDITORIAL

Informed Consent and SUPPORT

By Drazen JM et al

“...there was no evidence to suggest an increased risk of death with oxygen levels in the lower end of a range viewed by experts as acceptable, and thus there was not a failure on the part of investigators to obtain appropriately informed consent...”
“Given OHRP's study was not involving biological practices at the time the study was that there was no additional risk to being enrolled in the trial. . . . (The trial) should have been eligible for a waiver of documentation of informed consent...
June 4, 2013

RE: Human Research Protections under Federalwide Assurance (FWA) 5960

“...we will conduct an open public meeting on this topic...”

(Held August 2013, 28 speakers)

“...we have put on hold all compliance actions... relating to the SUPPORT case, and plan to take no further action in studies involving similar designs until the process of producing appropriate guidance is completed.”

Correspondence, NYTimes, NYT, NYT editorial, NYT opinion letter, NY Times articles, NY Times editorial, NY Times opinion letter, NYTimes correspondence.
Timeline

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PERSPECTIVE

In Support of SUPPORT – A View from the NIH

By Kathy L. Hudson, Ph.D., Alan E. Guttmacher, M.D., and Francis S. Collins, M.D., Ph.D.

“...each treatment... increased... death mortality... approached their desired... approach...”

“...recent studies showed... expected difference...”

“...no scientific evidence to expect...”

“...saturation levels as low as 70%.”

March 2001-2003
SUPPORT Study conceived

July 2005-2009
SUPPORT enrollment (2006 BOOST II and COT enrollment begin)

June 20, 2013
PERSPECTIVE – A View from the NIH

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“In Support of SUPPORT – A View from the NIH

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“...each treatment... increased... death mortality... approached their desired... approach...”

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“...no scientific evidence to expect...”

“...saturation levels as low as 70%.”

2012
OHRP investigation begins

2012
NSF support study published NEJM

2013
SUPPORT follow-up study published NEJM

June 20, 2013
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“...each treatment... increased... death mortality... approached their desired... approach...”

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“...no scientific evidence to expect...”

“...saturation levels as low as 70%.”
CORRESPONDENCE

The OHRP and SUPPORT

Signed By MORE THAN 40 PROMINENT SCIENTISTS, ETHICISTS, AND CLINICIANS

“There is nothing to indicate that institutional bodies responsible for... SUPPORT failed the standard factors required by the “Common Rule” in approving the study...”
“The U.S. Code of Federal Regulations (45CFR46.116 ‘Common Rule’) includes the following requirements for informed consent: ‘A statement that the study involves research, an explanation of the purposes of the research, . . . a description of the procedures to be followed, and identification of any procedures which are experimental’; ‘a description of any reasonably foreseeable risks or discomforts to the subject’; and ‘a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.’”
The OHRP and SUPPORT – Another View

Signed By MORE THAN 40 PROMINENT SCIENTISTS, ETHICISTS, AND CLINICIANS

"The (SUPPORT) consent forms... failed in each of the elements described above." (of the Common Rule)

"a potential differential in the risks that were being tracked (death, retinopathy of prematurity; and neurologic impairment) was reasonably foreseeable, since determining differential risk was the very purpose of the study."
Nearly 4 years, and no compliance action or guidance has been provided by OHRP to resolve this “controversy”
Summary

• After the NY Times editorial, the controversy became more important than resolving valid concerns about consent documents.

• The focus became winning public opinion, protecting federally funded neonatal research, and having OHRP retract its determinations.
Summary

Understanding Usual care

- SUPPORT, BOOST II and COT Trials
  - RCT of two SpO₂ ranges
  - High arm consistent with usual care (control)
  - Low arm experimental
  - Most comments made by both defenders and critics of SUPPORT were not germane to either the trial design or concerns about consent documents
Potential Solutions

• Clarify Common Rule
  – Distinguish between commonly used and novel or experimental
  – Commonly used therapy, given in a new manner, is experimental

• Guidance for studies reported as “Usual Care”
  – Provide data defining usual care to IRBs
  – Determine whether or not a commonly used therapy might be given in a novel or experimental manner
How to Characterize Usual care

• Literature search
  – Observational studies
  – RCTs
  – Surveys of usual care

• Chart reviews
  – Range of therapy at enrolling hospitals
  – Patient characteristics that determine treatment approach

• Prospective studies
  – Practice surveys
  – Observational cohorts
Science is simply common sense at its best, that is, rigidly accurate in observation, and merciless to fallacy in logic.

Thomas H. Huxley
English Scientist
1825 - 1895
Critical Care Studies of Commonly Used Therapies

- Most of these studies cannot be defined as Comparative Effectiveness Research
- Controls can be protocolized, but need to closely reflect contemporary practices
- Comparing two experimental treatments or a commonly used intervention in two novel ways compromises safety monitoring
Misconceptions

• Comparative Effectiveness Research

In Critical Care, commonly used therapies meeting Comparative Effective Research requirements are not common.

Therapy 1  Interchangeable  Comparable Risks  Therapy 2
Misconceptions

Controls Can’t be “protocolized”

- **SUPPORT**
  - High SpO$_2$ arm; usual care control

- Usual care “control” can be protocolized, but not solely based on tradition, expert opinion, or guidelines

- Provide actual studies or data to IRB, ideally from hospitals enrolling subjects, to support design of the control group
Misconceptions

Comparison of two novel treatments

- Common therapy, but given in novel ways in both arms
- No control group to monitor safety