abstract

OBJECTIVE: Parkland Memorial Hospital (PMH) participated in Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded controlled trial, in which preterm neonates of 240/7 to 276/7 weeks’ gestational age (GA) were randomized in the delivery room (DR) to endotracheal intubation or nasal continuous positive airway pressure. We hypothesized that DR intubation could change in nonenrolled patients at PMH and that the change would be larger than in comparable centers not participating in the trial.

METHODS: The PMH Cohort included eligible but nonenrolled neonates of 240/7 to 276/7 weeks (primary) and noneligible neonates of 28 to 346/7 weeks (confirmatory). A subset (240/7–296/7 weeks) of that cohort was compared with a contemporaneous cohort born in centers participating in or familiar with the trial protocol. We used a Poisson regression model to obtain adjusted relative risks (RRs) of DR intubation or nasal CPAP. A subset (240/7–296/7 weeks) of that cohort was compared with a contemporaneous cohort born in centers participating in or familiar with the trial protocol. We used a Poisson regression model to obtain adjusted relative risks (RRs) of DR intubation or nasal CPAP.

RESULTS: In the PMH cohort (n = 3527), the proportion of DR intubation decreased during or after SUPPORT in the lower GA group (adjusted RR 0.76, 95% confidence interval [CI] 0.59–0.96) and the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70). Compared with the RR for DR intubation in VON, the RR at PMH was smaller in the lower (ratio of RR 0.76, 95% CI 0.65–0.87) and the upper GA group (ratio of RR 0.52, 95% CI 0.39–0.68).

CONCLUSIONS: A center’s participation in an unblinded randomized trial may affect process of care of nonenrolled patients. Pediatrics 2013;132:e960–e970

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KEY WORDS
randomized controlled trial, process of care, unblinded, preterm, endotracheal intubation, birth cohort study, non-enrolled patients

ABBREVIATIONS
BW—birth weight
CI—confidence interval
CPAP—continuous positive airway pressure
DR—delivery room
GA—gestational age
NNT—number needed to treat
NRN—Neonatal Research Network
PMH—Parkland Memorial Hospital
RCT—randomized controlled trial
RD—risk difference
RR—relative risk
SUPPORT—Surfactant, Positive Pressure, and Oxygenation Randomized Trial
VON—Vermont Oxford Network

Dr LeVan conceptualized and designed the study, merged data from all Parkland Memorial Hospital (PMH) databases, participated in the interpretation of the data, drafted the first version of the manuscript, and critically reviewed the revisions; Drs Wyckoff, Heyne, Sanchez, Chalak, and Jaleel conceptualized and designed the study, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Ahn conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Ms Burchfield and Ms Christie collected and entered data into the databases and extracted the data for the PMH cohort, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Soll conceptualized and designed the comparison between the 2 cohorts, participated in the interpretation of the data, and critically reviewed the manuscript; Dr Brion conceptualized and designed the study, conducted statistical analyses for the PMH cohort, participated in the interpretation of the data, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

(Continued on last page)
Outcomes in control patients enrolled in randomized controlled trials (RCTs) may be better than contemporaneous, eligible but nonenrolled patients.\(^1\) Differ- ences in outcomes between enrolled and nonenrolled patients could be a trial effect or a spurious association due to bias.\(^1\) Andersen et al showed that conducting a seeding trial (company-driven trial to entice doctors to pre-
scribe a new drug being marketed by the company) changed some processes of care among participating physicians compared with nonparticipating physi-
cians; however, processes of care for nonenrolled patients were not assessed.\(^3,4\)

The objective of the current study was to evaluate whether a process of care of contemporaneous nonenrolled patients can change during and after recruitment to an unblinded randomized trial, when care providers participating in or fa-
familiar with the trial protocol are un-
aware that data on nonenrolled patients are being collected for a study. We hypothesized (1) that participation of Parkland Memorial Hospital (PMH) in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT), an unblinded RCT comparing processes of care, could be associated with a re-
duction in the proportion of delivery room (DR) intubation in nonenrolled patients, and (2) that the local practice change would be larger than in com-
parable centers not participating in SUPPORT.

**METHODS**

**Setting**

The Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Net-
work (NRN) SUPPORT trial was a multi-
center randomized 2 × 2 factorial trial in which preterm neonates of 24/7 to 27/7 weeks’ gestational age (GA) were randomized at birth to 2 interventions: (1) continuous positive airway pressure (CPAP) initiated in the DR and subse-
quent use of a protocol-driven limited ventilation strategy or DR intubation with surfactant administration, and (2) oxygen saturation targets of 85% to 89% or 91% to 95%.\(^5,6\) The first intervention (CPAP versus DR intubation/surfactant) was unblinded, and its primary out-
come was death or bronchopulmonary dysplasia at 36 weeks’ postmenstrual age.\(^5\) PMH participated in SUPPORT from July 2005 until February 2009.

Data were compiled from 3 prospective databases, including detailed infor-
mation about DR and NICU management with predetermined entry criteria and de-
definitions: the Neonatal DR Resus-
citation Registry (started in 1989), the NICU database (started in 1977), and SUPPORT registry. At PMH, all neonates <35 weeks’ GA by obstetrical assess-
ment are admitted to the NICU and in-
cluded in the Resuscitation Registry and in the NICU database (unless tri-
aged to the newborn nursery if pedi-
atric assessment is >34 weeks’ GA and the infant is otherwise well). These databases provide information on 99.8% of eligible neonates, with high inter-
rater reliability (<1% error); most miss-
ing data points correspond to in-
fants triaged to the newborn nursery (≤6%).

Data for an analysis cohort were ab-
stracted using a before–after study design during 3 consecutive epochs: (1) up to 30 months before SUPPORT initiation, (2) during SUPPORT partic-
ipation, and (3) up to 15 months after trial completion. To account for secular trends in DR intubation, a subset of the PMH cohort was compared with a con-
temporaneous control population in the Vermont Oxford Network (VON), a voluntary collaboration of more than 900 NICUs around the world. The VON includes de-identified data by calendar year on infants with birth weight (BW) of 501 to 1500 g. This study was ap-
proved by the University of Texas Southwestern Medical Center Institutional Review Board.

**Participants**

The PMH cohort included neonates 24/7 to 27/7 weeks’ GA born at PMH before SUPPORT (January 2003–June 2005), during SUPPORT (July 2005–February 2009), and after SUPPORT (March 2009–June 2010) until SUPPORT publication.\(^5,6\) The study included (1) neonates 24/7 to 27/7 weeks’ GA who were eligible for SUPPORT but not enrolled (lower GA group), and (2) noneligible neonates of 28/7 to 34/7 weeks’ GA (upper GA group). The latter was used as a positive control for the lower GA group, in whom selection bias (due to exclusion of patients enrolled into SUPPORT) was possible.\(^7,8\) Exclusion criteria were com-
fort care or major congenital anomalies known at birth, lack of patient record in the DR Resuscitation Registry or the NICU database, and enrollment in SUPPORT.

A subset of the PMH cohort, including all neonates 24/7 to 29/7 weeks’ GA born in 2003 to 2004 (before SUPPORT) and 2006 to 2009 (during/after SUPPORT), was compared with inborn contemporane-
ous neonates born in level IIIb or IIIc North American centers participating in VON. The subset included (1) neonates 24/7 to 27/7 weeks’ GA (lower GA group), and (2) neonates of 28/7 to 29/7 weeks’ GA (upper GA group). We excluded centers participating in SUPPORT or in the VON Delivery Room Management Trial,\(^9\) and neonates who received comfort care in the DR (death without endotracheal intubation), or had severe congenital anomalies. This GA range was selected because infants in this GA range are included in the 501 to 1500 g BW range of VON. PMH was not a member of VON during the study period.

**Comparisons of Interest**

**PMH Cohort**

The primary analysis was the adjusted relative risk (RR) of DR intubation
during/after SUPPORT versus before SUPPORT in the lower GA group. The adjusted RR in the upper GA group was confirmatory and used as a positive control.

Univariate analyses in each GA group evaluated DR treatment (endotracheal intubation, positive pressure ventilation, CPAP), intubation (within the first 4 hours after admission to the NICU or during the first 24 hours of age), surfactant administration, pneumothorax, mortality to discharge from the hospital, chronic lung disease (chronic changes on chest radiograph and supplemental oxygen requirement for at least 28 days), duration of mechanical ventilation, patent ductus arteriosus, necrotizing enterocolitis (stage II or greater, modified Bell classification), severe intraventricular hemorrhage (Papile grade III or IV), periventricular leukomalacia, and severe retinopathy of prematurity (grade 3 or higher, international classification).

**Comparison With VON**

The primary analysis was the comparison of RR (adjusted for baseline variables) of DR intubation (during/after SUPPORT versus before SUPPORT) in the subset of the PMH cohort in the lower GA group with the RR of DR intubation in the contemporaneous VON cohort.

The secondary analyses were (1) the adjusted ratio of RRs for DR intubation in the upper GA group and (2) the adjusted ratio of RRs for any invasive (endotracheal tube or tracheostomy) ventilation.

**Statistical Analysis: PMH Cohort**

**Multivariate Analyses**

In each GA group, the adjusted RRs for DR intubation during/after SUPPORT versus before SUPPORT were calculated using robust Poisson regression in a generalized estimating equation model adjusted for covariates that met the $P < .05$ criterion (backward selection).

Candidate variables selected for modeling were characteristics preceding the decision of DR intubation and shown previously to associate with DR intubation. To avoid collinearity with GA, BW was converted to BW $z$-score. The adjusted risk difference (RD) and number needed to treat (NNT) were obtained from the adjusted RR and the proportion of DR intubation before SUPPORT. The Altman interaction test was used to determine if the adjusted RRs for DR intubation were different between GA groups.

**Univariate Analyses**

Univariate analyses were performed by using $\chi^2$ tests or Fisher’s exact tests for categorical variables, and Student’s $t$ tests or analyses of variance followed by Tukey test, or Kruskal-Wallis test followed by Mann-Whitney test for continuous variables. We analyzed temporal patterns of DR intubation to determine how soon after initiating SUPPORT the proportion of DR intubation changed from baseline; we selected blocks of 15 to 16 months to limit fluctuation due to sample size.

Statistical analyses were performed by using SPSS version 19 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and SAS version 9.2 (SAS Institute, Cary, NC). Statistical significance (2-tailed) was determined based on $P < .05$, except for multiple pairwise nonparametric comparisons, for which we used the Bonferroni adjustment.

The time interval for data abstraction was set to ascertain a sufficient number of registered patients in the PMH cohort to detect changes in DR intubation in the lower GA subgroup using multivariate analysis. Given the ascertainment of data on 200 DR intubations, the analysis set was sufficient to conduct a multivariate analysis with up to 20 independent covariates tested as main effects, with a 2-sided $\alpha$ of 0.05. The duration of the study was set to recruit enough patients to detect changes in DR intubation in the lower GA group by univariate analysis. The effect size was selected as a 33% RR reduction in DR intubation, a conservative estimate compared with the 47% RR reduction in DR intubation in a center in which routine DR bubble CPAP was prospectively introduced in 2000. A sample of 97 patients before SUPPORT and during/after SUPPORT yielded 80% power to detect a reduction in DR intubation from 60% to 40% with a 2-sided $\alpha$ of 0.05.

**Comparison With VON**

A Poisson regression model with robust variance was used for each GA group to obtain adjusted RRs (during/after SUPPORT versus before SUPPORT) for PMH and VON along with the ratio of their RRs. Covariates in the model were infants’ GA, gender, BW, $z$-score, and antenatal steroids. Location (PMH and VON) and epoch (before and during/after SUPPORT) were represented by a 4-level categorical variable in the model, with the appropriate linear contrasts constructed to obtain estimates of RRs and their ratio.

**RESULTS**

**PMH Cohort**

At PMH, a total of 3821 individual patient database records were reviewed, of which 3533 were eligible and 3527 (99.8%) had records in the 3 PMH databases (Fig 1). The analysis cohort comprised 3527 records. In the lower GA group, the percentage of multiple births was lower after SUPPORT (Table 1). In the upper GA group, exposure to antenatal steroids was more frequent after SUPPORT, maternal diabetes was more frequent during SUPPORT, and BW was greater during/after SUPPORT; other differences were clinically insignificant (Table 2).

During SUPPORT, patients in the lower GA group included in the current study...
had a greater GA than contemporaneous patients enrolled in SUPPORT (excluded from the current study), were less likely to have been exposed to antenatal steroids, and were more likely to receive positive pressure ventilation in the DR (Appendix).

**Multivariate Analysis**

Among 3527 neonates, 649 (18%) were intubated in the DR. The proportion of DR intubation significantly decreased during/after SUPPORT versus before SUPPORT, in the lower GA group (adjusted RR 0.76, 95% CI 0.59–0.96, \( P = .02 \)) and in the upper GA group (adjusted RR 0.57, 95% CI 0.46–0.70, \( P < .001 \)) (Tables 3 and 4). In the lower GA group, the proportion of DR intubation decreased from 85% before SUPPORT to 61% during/after SUPPORT (Table 5) (adjusted RD 0.21, 95% CI 0.03–0.34; NNT 5, 95% CI 3–33). In the upper GA group, the proportion decreased from 19% to 10% (Table 6) (adjusted RD 0.08, 95% CI 0.06–0.10; NNT 12, 95% CI 10–18). The decrease in DR intubation was not significantly different in the upper GA group compared with the lower GA group (adjusted ratio of RR 0.75, 95% CI 0.54–1.03).

**Univariate Analyses**

In the lower GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT (\( P = .01 \)) and that of CPAP increased (\( P < .001 \)) (Table 5). Not surprisingly, the proportion of intubation in the NICU within 4 hours after admission increased over time (\( P = .03 \)); however, intubation within 24 hours of life decreased during/after SUPPORT (\( P = .002 \)). The proportion of surfactant administration decreased during SUPPORT (\( P < .001 \)). The proportion of pneumothoraces increased after SUPPORT (\( P = .03 \)). Most pneumothoraces occurred in neonates who were intubated in the DR.

### TABLE 1 Baseline Characteristics in Neonates Born at PMH Between March 2003 and June 2010: Lower GA Group: 24\( ^{6/7} \) to 27\( ^{6/7} \) Weeks’ Gestation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before SUPPORT, ( n = 161 )</th>
<th>During SUPPORT, ( n = 132 )</th>
<th>After SUPPORT, ( n = 76 )</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, wk, mean (SD)</td>
<td>25.8 (1.0)</td>
<td>25.9 (1.1)</td>
<td>25.8 (1.1)</td>
<td>.42</td>
</tr>
<tr>
<td>BW, g, mean (SD)</td>
<td>858 (236)</td>
<td>908 (238)</td>
<td>874 (290)</td>
<td>.24</td>
</tr>
<tr>
<td>Size for age, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small for GA</td>
<td>19 (12)</td>
<td>14 (11)</td>
<td>10 (13)</td>
<td>.52</td>
</tr>
<tr>
<td>Large for GA</td>
<td>19 (12)</td>
<td>25 (19)</td>
<td>12 (16)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>74 (46)</td>
<td>61 (46)</td>
<td>36 (47)</td>
<td>.98</td>
</tr>
<tr>
<td>Multiple birth, n (%)</td>
<td>34 (21)</td>
<td>19 (14)</td>
<td>5 (7)</td>
<td>.01</td>
</tr>
<tr>
<td>Antenatal steroids, n (%)</td>
<td>81 (50)</td>
<td>52 (39)</td>
<td>38 (50)</td>
<td>.14</td>
</tr>
<tr>
<td>Abruptio placenta, n (%)</td>
<td>6 (4)</td>
<td>11 (8)</td>
<td>4 (5)</td>
<td>.25</td>
</tr>
<tr>
<td>Placenta previa, n (%)</td>
<td>5 (2)</td>
<td>1 (1)</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>Maternal diabetes mellitus, n (%)</td>
<td>8 (4)</td>
<td>10 (8)</td>
<td>8 (11)</td>
<td>.11</td>
</tr>
<tr>
<td>Gestational hypertension or preclampsia, n (%)</td>
<td>25 (16)</td>
<td>26 (21)</td>
<td>19 (25)</td>
<td>.19</td>
</tr>
<tr>
<td>Clinic attendance, n (%)</td>
<td>416 (90)</td>
<td>113 (66)</td>
<td>67 (88)</td>
<td>.40</td>
</tr>
</tbody>
</table>

\( * \) Complete data were available for patients in the lower GA group and for GA. \( P \) values on the last column on the right are based on analyses of variance or \( \chi^2 \) analysis (Fisher’s exact tests where needed). Subsequent pairwise comparisons were performed using \( \chi^2 \) tests, Fisher’s exact tests, or Tukey tests, with significance determined using \( P < .025 \) and \( P \) values indicated as * \( P < .025 \). Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

In the upper GA group, administration of DR positive pressure ventilation decreased during/after SUPPORT (\( P = .002 \)) (Table 6). The proportion of intubation within 24 hours of life decreased during/after SUPPORT (\( P < .001 \)).
Comparison Between PMH and VON

We compared data from 576 neonates born at PMH with data from 85 118 contemporaneous neonates born in 1 of 396 North American VON centers (Table 7).

In the lower GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT at PMH (82% vs 60%; adjusted RR 0.74, 95% CI 0.64–0.86) and in VON (85% vs 84%; adjusted RR 0.98, 95% CI 0.98–0.99). The decrease was greater at PMH than in VON (adjusted ratio of RR 0.76, 95% CI 0.65–0.87). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in the VON data. The change over time was not significantly different between PMH and VON.

In the upper GA group, the proportion of DR intubation decreased from before SUPPORT to during/after SUPPORT both at PMH and in VON. The decrease was greater at PMH than in VON (adjusted ratio of RR 0.52, 95% CI 0.39–0.68). The proportion of overall ventilator support did not change significantly from before to during/after SUPPORT in the PMH cohort but changed significantly in VON. The change over time was not significantly different between PMH and VON.

DISCUSSION

In the current study, a change in care process (proportion of DR intubation) was observed in eligible but non-enrolled patients and in noneligible more mature patients soon after SUPPORT initiation and persisted through 16 months of posttrial evaluation. This change in practice at PMH was much larger than in other comparable centers that did not participate in any trial involving random allocation to DR.
intubation, suggesting that the trial participation itself influenced clinical practice well beyond the study participants.

PMH is a high-volume delivery unit with 12,000 to 15,000 deliveries per year. At PMH, the decision whether to intubate is made by resuscitation teams of practitioners who are trained in the neonatal resuscitation program. Teams for neonates with GA of 30 to 35 weeks include a nurse, a respiratory therapist, and a neonatal nurse practitioner or a senior pediatric resident. Teams for lower GA neonates also include a neonatal-perinatal fellow. Additional personnel are available for backup. The same teams provided care to all neonates, whether enrolled into SUPPORT or not. PMH did not have a policy about DR endotracheal intubation; decisions are left to team leaders according to national guidelines for neonatal resuscitation. At PMH before SUPPORT, most preterm neonates <28 weeks GA were intubated in the DR. PMH did not participate in the NRN Feasibility Trial, which preceded SUPPORT. At PMH, the only evident change in DR management was initiation of a resuscitation rotation for fellows in neonatal-perinatal medicine in 2005. The Neonatal Resuscitation Program mentioned the use of CPAP in the DR for preterm neonates in 2006, and included CPAP in the resuscitation algorithm in 2010, however, immediate application of CPAP in the DR at PMH was not recommended for all preterm neonates <32 weeks until May 1, 2011.

The strengths of the current study include large sample size; prospective validated databases thereby minimizing missing data, information bias, and loss to follow-up; stratified analysis yielding internal controls (upper GA group); and multivariate comparison with contemporaneous external controls (comparable VN

### Table 5

<table>
<thead>
<tr>
<th>Care Process or Outcome Variable</th>
<th>Before SUPPORT, n = 161</th>
<th>During SUPPORT, n = 132</th>
<th>After SUPPORT, n = 76</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation in the DR, n (%)</td>
<td>136 (85)</td>
<td>81 (61)**</td>
<td>46 (61)**</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Positive pressure ventilation in the DR, n (%)</td>
<td>140 (91)</td>
<td>106 (80)*</td>
<td>60 (79)*</td>
<td>.01</td>
</tr>
<tr>
<td>CPAP in the DR, n (%)</td>
<td>48 (31)</td>
<td>74 (58)**</td>
<td>48 (63)**</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Intubation in the NICU within the first 4 h after admission to the unit, n (%)</td>
<td>7 (4)</td>
<td>14 (11)</td>
<td>10 (13)</td>
<td>.03</td>
</tr>
<tr>
<td>Intubation during the 24 h of life, n (%)</td>
<td>141 (88)</td>
<td>95 (72)**</td>
<td>56 (73)*</td>
<td>.002</td>
</tr>
<tr>
<td>Surfactant, n (%)</td>
<td>121 (79)</td>
<td>78 (59)**</td>
<td>50 (66)</td>
<td>.001</td>
</tr>
<tr>
<td>Pneumothorax, n (%)</td>
<td>11 (7)</td>
<td>13 (10)</td>
<td>14 (18)*</td>
<td>.03</td>
</tr>
<tr>
<td>Death before discharge, n (%)</td>
<td>43 (27)</td>
<td>34 (26)</td>
<td>18 (24)</td>
<td>.91</td>
</tr>
<tr>
<td>Chronic lung disease, n (%)</td>
<td>83 (52)</td>
<td>61 (48)</td>
<td>43 (57)</td>
<td>.34</td>
</tr>
<tr>
<td>Total no. days intubated (endotracheal tube or tracheostomy) (n = 338); median (quartiles)</td>
<td>10 (2–23)</td>
<td>5 (1–14)</td>
<td>11 (2–28)</td>
<td>.05</td>
</tr>
</tbody>
</table>

### Table 6

<table>
<thead>
<tr>
<th>Care Process or Outcome Variable</th>
<th>Before SUPPORT, n = 852</th>
<th>During SUPPORT, n = 1557</th>
<th>After SUPPORT, n = 549</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation in the DR, n (%)</td>
<td>177 (19)</td>
<td>162 (10)**</td>
<td>47 (9)**</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Positive pressure ventilation in the DR, n (%)</td>
<td>332 (36)</td>
<td>513 (31)*</td>
<td>150 (28)**</td>
<td>.002</td>
</tr>
<tr>
<td>CPAP in the DR, n (%)</td>
<td>314 (34)</td>
<td>588 (36)</td>
<td>194 (36)</td>
<td>.74</td>
</tr>
<tr>
<td>Intubation in the NICU within the first 4 h after admission to the unit, n (%)</td>
<td>43 (5)</td>
<td>82 (5)</td>
<td>28 (5)</td>
<td>.84</td>
</tr>
<tr>
<td>Intubation during the 24 h of life, n (%)</td>
<td>220 (23)</td>
<td>242 (15)**</td>
<td>75 (14)**</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Surfactant, n (%)</td>
<td>105 (11)</td>
<td>131 (8)*</td>
<td>50 (6)</td>
<td>.01</td>
</tr>
<tr>
<td>Pneumothorax, n (%)</td>
<td>29 (3)</td>
<td>40 (2)</td>
<td>12 (2)</td>
<td>.51</td>
</tr>
<tr>
<td>Death before discharge, n (%)</td>
<td>17 (2)</td>
<td>19 (1)</td>
<td>8 (2)</td>
<td>.41</td>
</tr>
<tr>
<td>Chronic lung disease, n (%)</td>
<td>31 (3)</td>
<td>40 (2)</td>
<td>16 (3)</td>
<td>.44</td>
</tr>
<tr>
<td>Total no. days intubated (endotracheal tube or tracheostomy) (n = 694); median (quartiles)</td>
<td>1 (1–3)</td>
<td>1 (0–4)</td>
<td>1 (1–6)</td>
<td>.087</td>
</tr>
</tbody>
</table>

P Values in the last column on the right are based on χ² analysis (Fisher’s exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using χ² tests, Fisher’s exact tests, or Tukey tests, with significance determined by using P < .025, and P values indicated as * P < .025, or ** P < .001. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

### Table 7

<table>
<thead>
<tr>
<th>Care Process or Outcome Variable</th>
<th>Before SUPPORT, n = 952</th>
<th>During SUPPORT, n = 1657</th>
<th>After SUPPORT, n = 549</th>
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<td>242 (15)**</td>
<td>75 (14)**</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Surfactant, n (%)</td>
<td>105 (11)</td>
<td>131 (8)*</td>
<td>50 (6)</td>
<td>.01</td>
</tr>
<tr>
<td>Pneumothorax, n (%)</td>
<td>29 (3)</td>
<td>40 (2)</td>
<td>12 (2)</td>
<td>.51</td>
</tr>
<tr>
<td>Death before discharge, n (%)</td>
<td>17 (2)</td>
<td>19 (1)</td>
<td>8 (2)</td>
<td>.41</td>
</tr>
<tr>
<td>Chronic lung disease, n (%)</td>
<td>31 (3)</td>
<td>40 (2)</td>
<td>16 (3)</td>
<td>.44</td>
</tr>
<tr>
<td>Total no. days intubated (endotracheal tube or tracheostomy) (n = 694); median (quartiles)</td>
<td>1 (1–3)</td>
<td>1 (0–4)</td>
<td>1 (1–6)</td>
<td>.087</td>
</tr>
</tbody>
</table>

P Values in the last column on the right are based on χ² analysis (Fisher’s exact tests where needed) or Kruskal-Wallis tests. Subsequent pairwise comparisons were performed by using χ² tests, Fisher’s exact tests, or Tukey tests, with significance determined by using P < .025, and P values indicated as * P < .025, or ** P < .001. Pairwise comparisons were performed between during SUPPORT and before SUPPORT and between after SUPPORT and before SUPPORT.

95% of data were available; we used the total number available as denominator.
centers not participating in DR trials) with a similar baseline proportion of DR intubation. Secular trends are unlikely to explain the primary results because DR intubation at PMH decreased much more than in other comparable centers. It is unlikely that the current study affected the proportion of DR intubation because when the first data were obtained and presented at a national meeting, the change in practice had already taken place. We did not observe a regression to the mean but instead a sustained reduction in DR intubation at PMH during/after SUPPORT. A differential Hawthorne effect was ruled out because providers were not aware of an observational study of eligible, non-enrolled patients during SUPPORT.7,8 This study was limited to a single institution rather than all NRN centers participating in SUPPORT because the generic database of the NRN includes only the most immature infants; patients in the upper GA group were important in this study as positive controls who were not eligible for SUPPORT and thus not subjected to selection bias. Selection bias at PMH in the lower GA group during SUPPORT is unlikely to explain the observed decrease in DR intubation in nonenrolled patients, because respiratory distress is associated with lower exposure to antenatal steroids,35 and more frequent DR positive pressure ventilation (Appendix) would be expected to increase, rather than decrease, DR intubation. The lower percentage of antenatal steroids among nonenrolled patients could have resulted because of many reasons, including not enough time before delivery.7 Rich and colleagues’ study showed that a significantly larger proportion of eligible infants whose mothers were not approached for consent to SUPPORT had no prenatal steroid exposure.7 The frequency of antenatal corticosteroid administration at PMH is low because preeclampsia and diabetes are considered contraindications.36 Multivariate analyses showed that the RR of DR intubation decreased at PMH and decreased more at PMH than in VON, even taking into account antenatal corticosteroid administration. We were unable to analyze bronchopulmonary dysplasia, or other elements of care process examined in SUPPORT (ie, targeted ventilation strategy and oxygen saturation), which were not included in the PMH databases. In addition, target oxygen saturation values of 88% to 94%, a PMH NICU policy since May 2002,37

![Figure 2](image-url)
was used for nonenrolled patients. Because the study used databases, it was not possible to perform a propensity match, or a cluster analysis of DR team members or individual providers and to obtain their rationale for deciding whether to intubate the trachea. It is possible that the change in DR intubation was related to increased availability of T-piece devices for DR resuscitation, or to training and experience with these devices and DR CPAP.

CONCLUSIONS

A change in process of care was observed in nonenrolled patients during/after recruitment to an unblinded RCT, in the absence of changes in standard care, initiation of a protocol, or previously described trial effect. This suggests that care for patients who are not enrolled in RCTs should routinely be monitored and audited to identify changes in practice that may either be beneficial or detrimental without the evidence from a completed trial. Further studies are needed to investigate the determinants of changes in individual decisions about care process (eg, observations of short-term outcomes versus experience with novel processes of care). A trial design in which centers are randomized to participation in RCTs could further analyze the impact of changes in care process associated with unblinded RCTs.

ACKNOWLEDGMENTS

The first version of the PMH cohort was a poster presentation at the Pediatric Academy Society Meeting, Honolulu, HI, May 4, 2008: Brion LP, Wyckoff MH, Jaleel M, Sanchez PJ, Burchfield J, Christie L. Delivery room practice change following the initiation of the SUPPORT trial. The final version of the PMH cohort was a platform presentation at the Pediatric Academy Society Meeting, Boston, MA, April 28, 2012: LeVan JM, Wyckoff MH, Jaleel MA, Sanchez PJ, Ahn C, Burchfield J, Christie L, Brion LP. Impact of initiating the NICHD Neonatal Research Network SUPPORT Trial on management and outcomes of gestational-age matched non-enrolled patients.

Dr LeVan was a pediatric resident at University of Texas Southwestern Medical Center and was part of the DR team during her rotations at PMH in 2006–2009. Dr Wyckoff was awarded a grant from The American Academy of Pediatrics Neonatal Resuscitation Program (2008–2009), and an Ikaria Investigator Initiated Grant (Nov 2010–Nov 2012). Dr Heyne was, during the study and remains, the follow-up principal investigator of the National Institute of Child Health and Human Development NRN at University of Texas Southwestern Medical Center. Dr Sánchez was, during the study and remains, the site principal investigator of the National Institute of Child Health and Human Development Neonatal Research Network (U10 HD40689) at University of Texas Southwestern Medical Center. Dr Chalak was awarded grant 5 KL2 RR024983–02 from the North and Central Texas Clinical and Translational Science Initiative (9/17/07–5/31/12), a North and Central Texas Clinical and Translational Science Initiative Pilot Grant Award Program (2010–2011), and a grant from the Gerber Foundation (11/17/2011–10/16/2013). Dr Jaleel is a member of the National Quality Forum Perinatal Steering Committee. Dr Brion is the alternate principal investigator of the National Institute of Child Health and Human Development NRN at University of Texas Southwestern Medical Center since April 8th, 2009. Dr Soll is the president and director of clinical trials at the VON.


TABLE 7 Adjusted RR Estimates in Preterm Infants Born With GA 24 to 296/7 Weeks at PMH and in Comparable North American Centers in the VON Before SUPPORT (2003–2004) and During/After SUPPORT (2006–2009)

<table>
<thead>
<tr>
<th>Care Process</th>
<th>GA Group, wk</th>
<th>Location</th>
<th>Before SUPPORT</th>
<th>During/After SUPPORT</th>
<th>Adjusted RR* During/After Versus Before SUPPORT (95% CI)</th>
<th>Ratio of RRs PMH Versus VON (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubated in DR</td>
<td>246/7–276/7</td>
<td>PMH</td>
<td>105/128 (82%)</td>
<td>90/132 (80%)</td>
<td>0.745 (0.644–0.861)</td>
<td>0.757 (0.654–0.875)</td>
<td>.0002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VON</td>
<td>11 728/13726 (85.4%)</td>
<td>29 715/35 447 (83.8%)</td>
<td>0.984 (0.976–0.992)</td>
<td>n = 49 055</td>
<td></td>
</tr>
<tr>
<td></td>
<td>286/7–296/7</td>
<td>PMH</td>
<td>51/86 (59%)</td>
<td>57/198 (29.0%)</td>
<td>0.495 (0.375–0.652)</td>
<td>0.516 (0.391–0.681)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VON</td>
<td>5427/10 008 (54.2%)</td>
<td>13 457/25 928 (51.9%)</td>
<td>0.959 (0.939–0.979)</td>
<td>n = 35 851</td>
<td></td>
</tr>
<tr>
<td>Received any invasive ventilation</td>
<td>246/7–276/7</td>
<td>PMH</td>
<td>119/128 (93.0%)</td>
<td>144/194 (88.0%)</td>
<td>0.952 (0.886–1.023)</td>
<td>0.965 (0.889–1.037)</td>
<td>.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VON</td>
<td>13 158/13 727 (95.9%)</td>
<td>33 469/35 453 (94.4%)</td>
<td>0.986 (0.982–0.991)</td>
<td>n = 49 068</td>
<td></td>
</tr>
<tr>
<td></td>
<td>286/7–296/7</td>
<td>PMH</td>
<td>63/86 (73.0%)</td>
<td>134/198 (68.0%)</td>
<td>0.939 (0.804–1.095)</td>
<td>0.988 (0.846–1.154)</td>
<td>.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VON</td>
<td>7599/13 728 (85.4%)</td>
<td>33 469/35 447 (83.8%)</td>
<td>0.950 (0.937–0.962)</td>
<td>n = 35 855</td>
<td></td>
</tr>
</tbody>
</table>

*RR estimates are adjusted for infants’ GA, gender, z-score for BW (computed within GA and gender), and exposure to antenatal corticosteroids by using robust Poisson regression generalized estimating equation models. Location (PMH and VON) and time period (during/after SUPPORT and before SUPPORT) were represented by a 4-level categorical variable. RRs and the ratio of RR estimates were computed based on the appropriate linear contrast of model parameters.
A. Miller, RN, recruited patients into the SUPPORT and collected data for the study by Rich and collaborators.7,8

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### APPENDIX  Baseline Characteristics of Infants 24 to 27\textsuperscript{6/7} Weeks’ Gestation Born at PMH During SUPPORT (July 2005–February 2009)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SUPPORT, n = 73, Excluded From the Current Study</th>
<th>NONSUPPORT, n = 132, Included in the Current Study</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, wk, mean (SD)</td>
<td>25.3 (1.0)</td>
<td>25.9 (1.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BW, g, mean (SD)</td>
<td>878 (189)</td>
<td>907 (239)</td>
<td>.37</td>
</tr>
<tr>
<td>Size for age, n (%)</td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>Small for GA</td>
<td>1 (1)</td>
<td>14 (11)</td>
<td></td>
</tr>
<tr>
<td>Large for GA</td>
<td>19 (26)</td>
<td>25 (19)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>29 (40)</td>
<td>61 (46)</td>
<td>.23</td>
</tr>
<tr>
<td>Multiple birth, n (%)</td>
<td>12 (16)</td>
<td>19 (14)</td>
<td>.69</td>
</tr>
<tr>
<td>Use of antenatal steroids, n (%)</td>
<td>49 (67)</td>
<td>52 (39)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abruptio placenta, n (%)</td>
<td>3 (4)</td>
<td>11 (8)</td>
<td>.39</td>
</tr>
<tr>
<td>Placenta previa, n (%)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Maternal diabetes, n (%)</td>
<td>6 (8)</td>
<td>10 (8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>15 (21)</td>
<td>28 (21)</td>
<td>1.000</td>
</tr>
<tr>
<td>or preeclampsia, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinic attendance, n (%)</td>
<td>63 (86)</td>
<td>113 (86)</td>
<td>1.000</td>
</tr>
<tr>
<td>Positive pressure ventilation in the DR, n (%)</td>
<td>42 (58)</td>
<td>106 (80)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Significance based on Fisher’s exact tests or Student’s t tests.
Change in Care Among Nonenrolled Patients During and After a Randomized Trial


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DOI: 10.1542/peds.2013-1595

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