Enrollment of Extremely Low Birth Weight Infants in a Clinical Research Study May Not Be Representative

WHAT'S KNOWN ON THIS SUBJECT: The demographics of trials that use antenatal consent may not be representative of the populations that they are intended to study.

WHAT THIS STUDY ADDS: This study analyzes the difference in clinical outcomes between the enrolled and eligible but not enrolled populations of a trial that required antenatal consent.

abstract

BACKGROUND AND OBJECTIVE: The Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) antenatal consent study demonstrated that mothers of infants enrolled in the SUPPORT trial had significantly different demographics and exposure to antenatal steroids compared with mothers of eligible, but not enrolled infants. The objective of this analysis was to compare the outcomes of bronchopulmonary dysplasia, severe retinopathy of prematurity, severe intraventricular hemorrhage or periventricular leukomalacia (IVH/PVL), death, and death/severe IVH/PVL for infants enrolled in SUPPORT in comparison with eligible, but not enrolled infants.

METHODS: Perinatal characteristics and neonatal outcomes were compared for enrolled and eligible but not enrolled infants in bivariate analyses. Models were created to test the effect of enrollment in SUPPORT on outcomes, controlling for perinatal characteristics.

RESULTS: There were 1316 infants enrolled in SUPPORT; 3053 infants were eligible, but not enrolled. In unadjusted analyses, enrolled infants had significantly lower rates of death before discharge, severe IVH/PVL, death/severe IVH/PVL (all < 0.001), and bronchopulmonary dysplasia ($P = .003$) in comparison with eligible, but not enrolled infants. The rate of severe retinopathy of prematurity was not significantly different. After adjustment for perinatal factors, enrollment in the trial was not a significant predictor of any of the tested clinical outcomes.

CONCLUSIONS: The results of this analysis demonstrate significant outcome differences between enrolled and eligible but not enrolled infants in a trial using antenatal consent, which were likely due to enrollment bias resulting from the antenatal consent process. Additional research and regulatory review need to be conducted to ensure that large moderate-risk trials that require antenatal consent can be conducted in such a way as to ensure the generalizability of results. *Pediatrics* 2012;129:480–484

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KEY WORDS

antenatal steroids, clinical research/trials, informed consent, neonatal

ABBREVIATIONS

ANS—antenatal steroids
BPD—bronchopulmonary dysplasia
GA—gestational age
GDB—Generic Database
IVH—intraventricular hemorrhage
NRN—Neonatal Research Network
PVL—periventricular leukomalacia
ROP—retinopathy of prematurity
SUPPORT—Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial

This trial has been registered at www.clinicaltrials.gov (identifier NCT 00233324).

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COMPANION PAPER: A companion to this article can be found on page 576 and online at www.pediatrics.org/doi/10.1542/peds.2011-3455.

The Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely low birth weight infants was a randomized, 2×2 factorial designed multicenter trial conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) (identifier NCT 00233324).[1,2] The trial prospectively compared continuous positive airway pressure and a protocol driven limited ventilatory strategy begun in the delivery room and continuing in the NICU with the early (< hour) intratracheal administration of surfactant followed by conventional mechanical ventilation. Infants were also randomly assigned to a prospective comparison of a lower oxygen saturation target range (85%–89%) with a higher, more conventional target range (91%–95%) until 36 weeks' postmenstrual age or the infant was no longer requiring ventilatory support or oxygen, by using purpose-altered oximeters. Eligible infants were those born at NRN centers at 24 0/7 to 27 6/7 weeks' gestational age (GA), without known major congenital malformations, and with full resuscitation intended. Antenatal consent was required for enrollment.

A prospective cohort study of the antenatal consenting practices of SUPPORT research personnel was conducted during the last half of the trial, and the results were published.[3] As part of the ongoing NRN Generic Database (GDB) observational study, data were collected routinely for inborn infants at NRN centers, including most of those who met the GA eligibility criteria for SUPPORT. These data were used to identify eligible, nonenrolled infants. In this previous analysis, comparisons were made between enrolled versus nonenrolled eligible infants as well as between infants whose mothers were approached versus not approached. Comparing all GDB infants who were eligible for SUPPORT but whose mothers were not approached with those whose mothers were approached for consent revealed that mothers in the latter group were significantly more likely to be older, to have a high school degree, private medical insurance, and at least 1 prenatal care visit. Infants of these mothers were more likely to be non-Hispanic white. Failure to be treated with antenatal steroids (ANS) was >4 times more prevalent among infants who were eligible, but not enrolled in SUPPORT in comparison with those who were enrolled.

In view of these results, we felt that it was essential to determine if the outcomes of infants enrolled in SUPPORT differed in substantial ways from infants enrolled in the GDB during the same period who were SUPPORT eligible but were not enrolled.

Based on the differences in prenatal care and antenatal steroid use between the populations that we had found previously, we postulated that the infants enrolled in SUPPORT would have lower rates of bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), mortality, and death or intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) in comparison with infants of the same GAs who were entered into the NRN GDB during the period of SUPPORT recruitment (February 2005 through February 2009) but not enrolled in the trial. Previous trials have compared contemporaneous controls to study subjects to determine if being in the trial affected outcomes, and have found that enrolled subjects did better overall than their contemporaneous comparison groups.[4,5] Because this trial had no placebo group, we created statistical models that controlled for demographic characteristics and receipt of ANS to test for this trial effect.

METHODS

This analysis compared 1316 infants enrolled in SUPPORT with 3053 infants born at NRN centers that met the eligibility criteria for the SUPPORT trial but were not enrolled. Perinatal characteristics, delivery room interventions, and neonatal outcomes were compared for enrolled and nonenrolled infants in bivariate analyses by using *t* tests and χ^2 tests.

Data for SUPPORT infants were obtained from trial documents and the GDB, and nonenrolled infant data were collected from the GDB only. Because not all of the data collected for the trial subjects were available for nonenrolled infants, severe ROP was defined as retinal detachment or documented surgery during initial hospitalization (up to 120 days of life) for survivors to discharge or transfer. BPD was compared by using the conventional definition of oxygen at 36 weeks' postmenstrual age only, and does not include the NRN physiologic definition of BPD. Severe IVH, PVL, and necrotizing enterocolitis outcomes were based on GDB data.

Logistic regression models were created to test the "trial effect" of enrollment in SUPPORT on outcomes, controlling for GA, birth weight, gender, race, center, and antenatal steroid exposure.

RESULTS

Bivariate analyses of demographic characteristics demonstrated small, but statistically significant differences in GA, birth weight, and race between enrolled and nonenrolled infant groups (Table 1). Receipt of ANS and treatment with prenatal antibiotics were significantly higher for enrolled infants. Infants in the nonenrolled group were significantly more likely to have an Apgar score of <3 at both 1 and 5 minutes, and delivery room interventions, including intubation, compressions, and epinephrine were significantly more frequent in the nonenrolled group (Table 2). In unadjusted analysis of outcomes, infants enrolled in SUPPORT had significantly lower rates of BPD, death

TABLE 1 Demographic Information for Randomly Assigned Versus Nonenrolled Infants

Variable	Enrolled (N = 1316)	Nonenrolled (N = 3053)	Unadjusted P
GA (wk) (mean ± SD)	26.2 ± 1.1	26.0 ± 1.2	<.001
Birth weight (g) (mean ± SD)	830.1 ± 193.2	812.5 ± 191.8	.006
Male	54.1%	52.6%	.373
White, non-Hispanic	39.6%	36.1%	.030
Prenatal antibiotics	78.1%	65.4%	<.001
ANS (any)	96.2%	84.4%	<.001
ANS (full course)	71.7%	49.4%	<.001

before discharge, severe IVH/PVL, and death/severe IVH/PVL in comparison with infants eligible but not enrolled. Rates of severe ROP and necrotizing enterocolitis were not significantly different (Table 3).

In the logistic regression models used to test whether there was a trial effect related to enrollment in SUPPORT, we found that enrollment in the SUPPORT trial itself was not a significant predictor of BPD, severe ROP, death, severe IVH/PVL, or death/severe IVH/PVL when we controlled for GA, birth weight, gender, race, center, and antenatal steroid exposure.

DISCUSSION

When providing the enrollment tables for their trials, authors generally start with an enumeration of eligible subjects, and then describe how many refused, had missing data, etc. This group of eligible subjects is better described as "identified eligible subjects"—in other words, those whom the investigator identified as eligible at the time they would normally be approached for consent. In the SUPPORT study, there were additional mothers who were missed by the investigators because of time of day, rapidity of admission, duration of stay, etc. Because of the nature of the GDB of the NRN, which identifies and tracks all infants fitting broad GA criteria, we were able to look not just at the subjects enrolled in SUPPORT, but also those who were not enrolled or, in some cases, were not even identified as eligible by the research team. This allowed us to make a unique comparison of all infants who were born in NRN centers who met the SUPPORT study criteria, both those who were enrolled and those who were not.

The increased level of prenatal care received by the mothers of infants enrolled in SUPPORT, including receipt of ANS, and the increased frequency of delivery room interventions and poor Apgar scores among nonenrolled infants indicate that SUPPORT infants were less disadvantaged than the overall eligible population. Unadjusted comparisons of outcomes between the 2 groups confirmed that nonenrolled infants had greater incidences of poor neonatal outcomes, including BPD, death, severe IVH/PVL, and death/severe IVH/PVL. The fact that the differences in outcomes between the groups were not significant after controlling for infant characteristics at birth indicates that the birth characteristics, rather than enrollment in the trial itself, were likely responsible for the improved outcomes of enrolled infants.

TABLE 2 Delivery Room Status and Interventions

Variable	Enrolled (N = 1316), %	Nonenrolled (N = 3053), %	Unadjusted P
Apgar <3 at 1 min	24.4	31.9	<.001
Apgar <3 at 5 min	4.4	8.4	<.001
Intubated in DR	63.6	75.8	<.001
Surfactant in DR or NICU	82.5	86.5	<.001
Chest compressions in DR	5.9	9.7	<.001
Epinephrine in DR	3.1	6.0	<.001

DR, delivery room.

Our findings suggest that using antenatal consent to conduct a trial such as SUPPORT under the constraints of preintervention informed consent creates a situation where population bias is a significant issue. We agree with the concerns expressed by Schmidt et al[4] that this circumstance can create a threat to the external validity of the trial. Title 45 of the Code of Federal Regulations allows institutional review boards to waive some or all elements of consent.[6] Our previous observations, combined with the further analysis of this trial, suggest that allowing for the deferral of consent until after birth for trials comparing routinely used interventions can help to ensure that we include the sickest and most at-risk populations, and thus contribute to a more generalizable study population.

What remains unclear is how to deal with trials of greater than minimal risk that require antenatal consent. Current standards for waiver of consent would be the same as those used for "emergency" trials, such as the use of a blood substitute in a prehospital environment. These requirements include high risk balanced with a life-threatening situation, a direct benefit, public disclosure, and the existence of an independent data safety board. Most near-birth trials would not meet the standard of a life-threatening situation, and neonatal trials with prespecified direct benefit are extremely uncommon. In a review of clinical research in critically ill patients, Truog et al concluded that informed consent is required for research interventions that, if they were clinical interventions, would not require specific consent.

TABLE 3 Neonatal Outcomes

Outcome	SUPPORT Enrolled (N = 1316)	Nonenrolled (N = 3053)	Unadjusted P
Death	18.0%	24.1%	<.001
BPD (oxygen at 36 wk)	42.2	47.7	.003
BPD or death by 36 wk	51.4	59.1	<.001
ROP (surgery or retinal detachment)	10.4	12.4	.101
NEC (medical or surgical)	11.3	12.7	.214
IVH grade 3–4	13.0	17.6	<.001
PVL	3.8%	5.1%	.068
IVH 3–4 or PVL	15.1%	19.8%	<.001
Death or IVH 3–4 or PVL	27.4%	35.6%	<.001

NEC, necrotizing enterocolitis.

They suggest that the requirement for consent in a clinical trial be based on 5 criteria: (1) whether all of the treatments in the trial could be offered outside the trial, (2) whether there is minimal additional risk compared with the alternative clinical treatment, (3) whether there is equipoise, (4) whether a reasonable person would have a preference between the 2 treatments, and (5) that the subject be informed that the previous 4 criteria are the basis for determining the need for specific rather than general consent in the institution involved.[7] Based on these characteristics, one could make the argument that the SUPPORT trial could have been carried out under waiver. Luce countered this argument with the statement that informed consent in critically ill subjects is necessary to promote respect for patients and their right of self-determination, and because investigator self-regulation is inadequate.[8]

In trials that compare currently used interventions and afford minimal risk, it is suggested that a waiver of consent and a postnatal written consent to use the infant's information be sought. This stipulation allows parents to decide whether they want their infant's information included in the study. This type of delayed consent has been successfully applied in non-US clinical trials requiring near-birth interventions. However, more complex trials requiring antenatal consent are still at risk for the lack of generalizability seen in our results. Additional dialogue with regulatory agencies needs to be conducted to determine the best method of balancing the safety and security of subjects with the need for the evidence that can be properly obtained from large trials that are generalizable to the intended population or population at risk.

CONCLUSIONS

The results of this analysis demonstrate significant outcome differences between enrolled and nonenrolled infants in the eligible population of a trial using antenatal consent; these differences were likely due to enrollment bias resulting from the antenatal consent process. A waiver or delay of parental consent should be considered to promote the generalizability of minimal-risk trials of interventions in the delivery room or shortly after birth. Additional research and regulatory review need to be carried out to ensure that large moderate-risk trials that currently require antenatal consent can be conducted in such a way as to ensure the generalizability of results.

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