Retrospective Consent in a Neonatal Randomized Controlled Trial

Nils T. Songstad, PhD,a,b Calum T. Roberts, MBChB,a,c,d Brett J. Manley, PhD,a,c,d Louise S. Owen, MD,a,c,d,e Peter G. Davis, MD,a,c,d,e on behalf of the HIPSTER trial investigators

BACKGROUND AND OBJECTIVES: The requirement for prospective consent in clinical trials in acute settings may result in samples unrepresentative of the study population, potentially altering study findings. However, using retrospective consent may raise ethical issues. We assessed whether using retrospective consent affected recruitment, participant characteristics, and outcomes within a randomized controlled trial.

METHODS: We conducted a secondary analysis of a randomized trial, which compared nasal high flow (nHF) with nasal continuous positive airway pressure (CPAP) for primary respiratory support in preterm infants. In Era 1, all infants were consented prospectively; in Era 2, retrospective consent was available. We assessed inclusion rates of eligible infants, demographic data, and primary trial outcome (treatment failure within 72 hours).

RESULTS: In Era 1, recruitment of eligible infants was lower than in Era 2: 111 of 220 (50%) versus 171 of 209 (82%), \( P < .001 \); intrapartum antibiotic administration was lower: 23 of 111 (21%) versus 84 of 165 (51%), \( P < .001 \); full courses of antenatal steroids were higher: 86 of 111 (78%) versus 103 of 170 (61%), \( P = .004 \); and more infants received prerandomization CPAP: 77 of 111 (69%) versus 48 of 171 (28%), \( P < .001 \). In Era 1, nHF failure (15 of 56, 27%) and CPAP failure (14 of 55, 26%) rates were similar, \( P = .9 \). In Era 2, failure rates differed: 24 of 85 (28%) nHF infants versus 13 of 86 (15%) CPAP infants, \( P = .04 \). The \( \chi^2 \) interaction test was nonsignificant (\( P = .20 \)).

CONCLUSIONS: The use of retrospective consent resulted in greater recruitment and differences in risk factors between eras. Using retrospective consent altered the study sample, which may be more representative of the whole population. This may improve scientific validity but requires further ethical evaluation.

WHAT'S KNOWN ON THIS SUBJECT: Obtaining prospective parental consent may be difficult or inappropriate for some families before, or shortly after, preterm birth. This may result in trials that do not adequately represent the populations that the trial authors intend to study.

WHAT THIS STUDY ADDS: Use of retrospective parental consent in a neonatal randomized controlled trial improved recruitment and altered the demographics of the study population in comparison with recruitment using only prospective consent, potentially affecting outcomes and their applicability to clinical practice.

To cite: Songstad NT, Roberts CT, Manley BJ, et al. Retrospective Consent in a Neonatal Randomized Controlled Trial. Pediatrics. 2018;141(1):e20172092
Randomized controlled trials (RCTs) are considered the gold standard for evaluating the safety and efficacy of interventions in clinical care. However, RCTs remain challenging to perform for interventions in emergency settings, particularly in vulnerable populations such as newborns.

According to the Declaration of Helsinki, all human subjects participating in clinical trials must provide informed consent. For infants incapable of giving consent, a legally authorized representativeconsents on their behalf. However, identifying the at-risk population, and obtaining ethically appropriate consent, is challenging in the setting of preterm birth. Difficulty in obtaining prospective parental consent is an important reason for the lack of large clinical studies of the early management of very preterm newborns. In the hours preceding preterm birth, parents may be emotionally distressed, and the mother may be in physical pain from labor, or receiving medication that affects concentration and capacity. Truly informed consent may not be possible or appropriate in this situation, meaning that trial participants may come from a biased selection of parents who can be approached for consent. As a result, trials may not adequately represent the populations that their authors intend to study. Secondary analysis of the Surfactant, Positive Pressure, and Oxygenation Randomized Trial, which required prospective, antenatal parental consent, revealed significant differences in outcomes between the enrolled population and the eligible but unenrolled population. Options to overcome this include the use of retrospective consent (also known as deferred consent), a waiver of consent, or an opt-out consent process. These options have the potential to increase enrolment and provide a more representative sample of infants, but they raise ethical dilemmas for researchers and clinicians delivering newborn care.

The aim of this study was to compare recruitment rates, participant characteristics, and outcomes before and after the introduction of retrospective consent during an RCT comparing 2 modes of noninvasive respiratory support for preterm infants. We hypothesized that the addition of retrospective consent would increase the inclusion rate of eligible infants, alter the demographic composition of included infants, and affect the primary outcome of the trial.

**METHODS**

The High Flow Nasal Cannulae as Primary Support in the Treatment of Early Respiratory Distress (HIPSTER) trial was an unblinded, international, multicenter, randomized noninferiority trial comparing nasal high flow (nHF) therapy with nasal continuous positive airway pressure (CPAP) as primary respiratory support for preterm infants. Preterm infants born at 28 weeks’ gestation to 36 weeks and 6 days’ gestation who required primary noninvasive respiratory support for respiratory distress within 24 hours of birth were eligible for inclusion. Infants were ineligible if they did not require noninvasive respiratory support, had previously been intubated, had already met the trial treatment failure criteria while receiving CPAP with 8 cm of water, had an air leak or major congenital anomaly, or had already received 4 hours or longer of CPAP treatment. The primary outcome was treatment failure within 72 hours after randomization.

At the initial ethics committee submission at the lead HIPSTER study center (The Royal Women’s Hospital [RWH], Melbourne, Australia), the RWH Ethics Committee (institutional review board equivalent) was asked to consider whether a retrospective consent process would be acceptable. Australian national guidelines at this time stated that for a waiver of previous consent to be acceptable for persons highly dependent on medical care who may be unable to give consent, specific conditions must be met, including that “involvement in the research carries no more than low risk,” “the benefits from the research justify any risks of harm associated with not seeking consent,” “it is impracticable to obtain consent,” and “the research supports a reasonable possibility of benefit over standard care.” HIPSTER was judged to meet these conditions; at the time, there were reasonable grounds to believe that nHF could be noninferior to CPAP (primary nHF was in use as standard care in some units), that using “rescue” CPAP (the standard active treatment) after nHF failure would help avoid any increased risk of intubation, and that nHF’s potential advantages over CPAP were well described. The timing of preterm birth is unpredictable, and the trial protocol allowed only 4 hours between CPAP commencement and randomization, giving parents little time in which to consider their consent decision. It was anticipated that this would, in many cases, be impractical, resulting in exclusion of a large proportion of eligible infants. The RWH Ethics Committee initially approved the study for use of prospective consent but requested an audit of eligibility and recruitment, with the audit results to be reported to the committee.

The audit, conducted during the first 3 months of trial recruitment (C.T.R., unpublished observations), revealed that many parents were open to study participation but felt unable to consent within the short time frame permitted. Several reasons were cited by parents for declining participation: (1) the short decision time available within the 4-hour
time limit for CPAP treatment; (2) their preference to discuss the trial at a later time; (3) their observation that their infant was settled on CPAP and a desire to avoid the possibility that their infant would be disturbed by changing to nHF. In other cases, mothers were not medically fit to be approached within the 4-hour window and a second parent was unavailable. A concern raised at this time was that these factors could affect the characteristics of families approached for consent, and adversely affect the consent rate, both of which could compromise the validity and generalizability of the eventual trial results.

We analyzed data obtained from HIPSTER trial participants recruited at the RWH. We compared the initial era when all infants were enrolled after prospective (antenatal or early postnatal) parental consent (Era 1) with the later era when either prospective or retrospective consent could be used (Era 2). Era 1 was from study commencement in May 2013 until May 2014; Era 2 was from June 2014 until study cessation in June 2015. During Era 2, parents were approached for consent in the first few days after birth, at a time judged to be appropriate by both the clinical and research teams. The approach always came after an initial update on the infant’s clinical status by a member of the clinical team (who was not a study researcher) at a time when the infant was stable and when the mother had recovered from any medications and procedures. During this discussion, parents were specifically informed that if they chose for their infant not to remain in the study, then there would be no adverse effect on their care and primary respiratory support would be provided according to standard RWH guidelines (ie, their infant would receive CPAP). The time of first approach for consent was not routinely documented. After initial approach by the research team, parents were offered time to consider whether they wished to provide consent for their infant(s) to remain in the trial, to read the consent form in detail, and to discuss the study with their partner (if applicable). In most cases, parents chose to take this time and were then reapproached for their decision, typically the next day. The day on which written consent was ultimately provided was the reported time of consent.

Data were analyzed by using Stata/IC software, version 12.0 (StataCorp, College Station, TX). A Fisher’s exact test or \( \chi^2 \) test was used to analyze categorical outcome variables. Significance was set at \( P < .05 \). Review Manager version 5.3 (Cochrane Collaboration, Copenhagen, Denmark) was used to calculate heterogeneity between groups when comparing the incidence of treatment failure.

### RESULTS

#### Enrollment of Eligible Infants

Inclusion rates and reasons for noninclusion of eligible infants in the 2 eras are presented in Table 1. Era 2 had a significantly higher consent rate, and fewer infants were excluded because of declined consent, or other reasons. During Era 1, 18 of 111 (16%) included infants had consent obtained antenatally and 84% had consent obtained postnatally. During Era 2, consent was obtained retrospectively for 166 of 171 (97%) infants, and consent was ultimately obtained at a median of 3 days (interquartile range: 2–6 days) after randomization. No concerns were raised by parents regarding the retrospective consent process, either formally or informally. However, they were not routinely asked about their experience of this process.

### Characteristics of Included Mothers and Infants

Infants’ birth weight, gestational age, sex, and mode of delivery and the incidence of preterm rupture of membranes, chorioamnionitis, and exposure to intrapartum magnesium sulfate did not differ between eras (Table 2). In Era 2, fewer mothers had received a complete course of antenatal corticosteroids and more had received intrapartum antibiotics. During Era 2, fewer infants received prerandomization CPAP (28% vs 69%, \( P < .001 \)).

### Effect of Mode of Consent on the Rate of the HIPSTER Primary Outcome

In Era 1, the rate of nHF failure was 27%, compared with 26% in the CPAP group (\( P = .9 \)). In Era 2, the rate of nHF failure was 28%, compared with 15% in the CPAP group (\( P = .04 \)). A test for interaction between eras was not significant: \( \chi^2 \) interaction \( P = .20 \) (Fig 1).

### DISCUSSION

To our knowledge, this is the first study in which the use of prospective and retrospective consent processes

---

**Table 1. Inclusion Rate and Reasons for Noninclusion of Eligible Infants**

<table>
<thead>
<tr>
<th>Reason for Noninclusion</th>
<th>Era 1</th>
<th>Era 2</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible infants, n</td>
<td>220</td>
<td>209</td>
<td>—</td>
</tr>
<tr>
<td>Included infants, n (%)</td>
<td>111 (50)</td>
<td>171 (82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Declined consent, n (%)</td>
<td>43 (20)</td>
<td>10 (5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Research team not notified, n (%)</td>
<td>31 (14)</td>
<td>11 (5)</td>
<td>.003</td>
</tr>
<tr>
<td>Enrolled in other study, n (%)</td>
<td>10 (5)</td>
<td>7 (3)</td>
<td>.6</td>
</tr>
<tr>
<td>Unable to consent for social reasons or language, n (%)</td>
<td>13 (6)</td>
<td>3 (1)</td>
<td>.02</td>
</tr>
<tr>
<td>Transfer to other site, n (%)</td>
<td>10 (5)</td>
<td>1 (0)</td>
<td>.01</td>
</tr>
<tr>
<td>CPAP &gt;4 h before randomization, n (%)</td>
<td>1 (0)</td>
<td>6 (3)</td>
<td>.06</td>
</tr>
<tr>
<td>Research team not available, n (%)</td>
<td>1 (0)</td>
<td>0 (0)</td>
<td>&gt;.8</td>
</tr>
</tbody>
</table>

---

—, not applicable.
are compared within a neonatal clinical trial. The use of retrospective consent was associated with an increase in the proportion of eligible infants recruited, as well as with some important differences in the demographics of mothers and infants. The primary outcome of the HIPSTER trial was not significantly altered by the use of retrospective consent. The increased enrollment of eligible infants during the retrospective consent era could be attributed to more parents of eligible infants being approached, fewer infants not being enrolled for social or language reasons, and fewer parents declining consent.

When approached prospectively, some parents felt uncomfortable with the short decision time frame or the possibility of a change of treatment. In some cases, consent was impossible because of the mother’s medical condition or because a parent was unavailable. Although the median time at which consent was given in this study (3 days after randomization) might be regarded as relatively late, this is, in part, a reflection that the factors identified in the audit of prospective consent were taken into account in the approach to retrospective consent. The consent delay is also a reflection of parents taking time after the initial approach by the research team to consider their decision and of time being taken for both parents (if applicable) to be involved in the consent process. These aspects may be considered desirable in ensuring that an informed consent decision has been made.

Social and language barriers could more often be overcome by using retrospective consent, mostly because more time was available.

For example, when the mother was unable to consent for medical reasons, consent could be obtained after her recovery, or after the arrival of her partner, or an interpreter could be arranged for non-English speaking parents.

Retrospective consent facilitated the early random assignment of infants and reduced “contamination” between the treatment arms of the trial; infants randomly assigned to nHF had less CPAP exposure before inclusion. In this particular trial, this effect had the potential to alter the primary trial outcome. As the trial revealed that CPAP was more effective in preventing treatment failure, it is possible that early CPAP exposure in fact reduced the difference in treatment efficacy between groups. Retrospective consent allowed clinical staff to randomly assign infants immediately on their arrival to the neonatal unit, and the research team could then approach parents to discuss consent.

This study did not demonstrate a statistically significant effect of the mode of consent on the rates of the primary outcome. However, 2 important risk factors known to influence the severity of preterm lung disease were significantly affected by the mode of consent.
Mothers of infants enrolled by using retrospective consent were less likely to have received a full course of antenatal corticosteroids, likely because of the inclusion of more infants born unexpectedly. Mothers in Era 2 were also more likely to have received intrapartum antibiotics, implying that more infants suspected of infection exposure in utero were included. It was not unexpected that demographic differences were observed with contrasting consent processes in HIPSTER; this effect has been reported in previous trials and is well described in the literature. Junghans and Jones have discussed how consent requirements create “consent bias,” which can exclude participants most likely to benefit from study interventions, leading to biased research and ultimately to poorer patient care. They noted that active consent processes are more likely to cause this bias and that greater understanding is needed to be able to balance individual autonomy with the societal benefits of research.

There are some important limitations of this study. This was a secondary analysis of 50% of the 564 infants included in HIPSTER, and it was therefore underpowered to detect differences in treatment failure rates. As we compared subsequent eras, changes in population demographics or clinical practice could have affected outcomes, although we are not aware of any such changes.

The use of retrospective consent may be considered ethically challenging; it has sparked much debate, with some researchers suggesting the use of “less powerful alternative design” methods, rather than pursuing RCTs reliant on retrospective consent. Experienced delivery room investigators are divided in their acceptance of using retrospective consent for studying emergency interventions immediately after delivery. Gale et al. reported that research ethics committees in the United Kingdom have different reactions to proposed consent procedures; 1 committee stated that nonprospective consent, specifically opt-out consent, is not a “recognized concept.” National research bodies have developed guidelines for the use of retrospective consent that require the researcher to demonstrate “minimal risk” to participants, but what review boards, researchers, and families consider to be minimal risk varies. Current regulations protect patients from the potential risks of research but consequently discourage proper testing and thereby encourage the use of unproven therapies.

Consideration as to whether there is any ethically meaningful difference between comparative effectiveness research without prospective consent and the unregulated clinical application of unproven therapies is warranted.

There are few examples of the use of retrospective consent in neonatal resuscitation research, and to our knowledge, only 1 study other than HIPSTER in which it has been used beyond the delivery room. The authors of all of these trials reported high rates of consent (≥94%) with a retrospective consent process. Retrospective consent may be interpreted as being well received in the HIPSTER population, given the high consent rate. Conversely, the higher rate of consent during Era 2 could be attributed to parents feeling that they ought to give consent because it was a fait accompli, because opting to withdraw from the study would potentially require their child to change respiratory support, or because they felt they had no choice. Although we did not formally record feedback from parents, there were no instances in which parents indicated that they were upset or distressed by the retrospective consent process. However, we acknowledge that some parents may have had such concerns but felt unable to raise them, or felt that there would have been no benefit in doing so. In this study, aside from the initial allocation of respiratory support, there were no major differences in the control and intervention treatment protocols; in studies in which greater differences exist, retrospective consent might be less acceptable to parents.

The experience of families whose newborns have been enrolled into studies by using retrospective consent is poorly reported. The single published survey in this area assessed parents of very preterm infants included in a delivery room trial, comparing umbilical cord milking with delayed cord clamping. The authors reported that 71% of parents felt positively or very positively about their infant’s participation in the study, that 29% were neutral, and that none felt negatively toward it. Previously, Woolfall et al. reported that some parents of acutely ill children randomly assigned to the Catheter Infections in Children trial (none of whom were preterm infants) felt shock or anger when they were first informed of their child’s entry without previous consent into a study comparing central venous catheters in critically ill children. However, they also reported that initial parental concerns were allayed after the reasons for deferral of consent were explained. Colbert and Davis surveyed new parents and parents-to-be about hypothetical resuscitation research scenarios and reported that parents fell into 2 groups regarding retrospective consent; a larger proportion (43%) felt uncomfortable with the theoretical process. Stenson et al. showed that 18 months after prospectively consenting to a study conducted during ventilation after birth, 27% of parents reported understanding what they had consented to, and a majority (83%) were uncomfortable with the
hypothetical use of retrospective consent instead.

Culbert and Davis went on to report that parents regarded their perception of fully understanding the study, with sufficient time to consider participation, was very important. Parents reported being uncomfortable consenting prospectively to something that had not yet happened, feeling unable to make a decision until the situation applied directly to them and feeling that prospective consent provoked unnecessary anxiety. Importantly, parents did not wish to be approached for consent once labor had started. Researchers must be careful not to erode the delicate trust between professionals and families by applying unacceptable consent processes. Some would argue that any discussion of research is better than none, even if that discussion occurs at a time of physical and emotional stress. Others argue that discussing enrollment in a trial during labor, for an outcome yet to occur, which is well known to increase fetal transpire, increases maternal anxiety, provoking unnecessary anxiety. However, in this study, the primary outcome was not significantly affected. The use of retrospective consent may increase generalizability in trials investigating sick or preterm newborns, but it must be carefully weighed against ethical concerns about including infants without previous parental consent.

**CONCLUSIONS**

In an RCT comparing 2 modes of noninvasive respiratory support in preterm infants, the use of retrospective consent resulted in a different sample population from that achieved by using only prospective consent; this has the potential to alter outcomes. However, in this study, the primary outcome was not significantly affected. The use of retrospective consent may increase generalizability in trials investigating sick or preterm newborns, but it must be carefully weighed against ethical concerns about including infants without previous parental consent.

**HIPSTER STUDY GROUP**


**ABBREVIATIONS**

CPAP: continuous positive airway pressure

HIPSTER: High Flow Nasal Cannulae as Primary Support in the Treatment of Early Respiratory Distress

nHF: nasal high flow

RCT: randomized controlled trial

RWH: Royal Women’s Hospital


10. Roberts CT, Owen LS, Manley BJ, Donath SM, Davis PG. A multicentre, randomised controlled, non-inferiority trial, comparing high flow therapy with nasal continuous positive airway pressure as primary support for preterm infants with respiratory distress (the HIPSTER trial): study protocol. BMJ Open. 2015;5(6):e008483


Retrospective Consent in a Neonatal Randomized Controlled Trial
Nils T. Songstad, Calum T. Roberts, Brett J. Manley, Louise S. Owen, Peter G. Davis
and on behalf of the HIPSTER trial investigators

Pediatrics 2018;141;
DOI: 10.1542/peds.2017-2092 originally published online December 29, 2017;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/141/1/e20172092

References
This article cites 24 articles, 16 of which you can access for free at:
http://pediatrics.aappublications.org/content/141/1/e20172092#BIBL

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Medical Education
http://www.aappublications.org/cgi/collection/medical_education_sub
Research Methods & Statistics
http://www.aappublications.org/cgi/collection/research_methods_-_statistics_sub
Fetus/Newborn Infant
http://www.aappublications.org/cgi/collection/fetus:newborn_infant_sub
Neonatology
http://www.aappublications.org/cgi/collection/neonatology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml
Retrospective Consent in a Neonatal Randomized Controlled Trial
Nils T. Songstad, Calum T. Roberts, Brett J. Manley, Louise S. Owen, Peter G. Davis
and on behalf of the HIPSTER trial investigators

Pediatrics 2018;141;
DOI: 10.1542/peds.2017-2092 originally published online December 29, 2017;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/141/1/e20172092