Determinants of Parental Authorization for Involvement of Newborn Infants in Clinical Trials

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ABSTRACT. Objective. Parents have the right to decide on behalf of their infants whether to enroll them in controlled clinical trials. We determined the degree to which such parental decisions are influenced by risk and benefit considerations compared with other factors.


Participants. Parents who had recently given or declined consent to one of three controlled trials in the neonatal intensive care unit.

Intervention. Parents were asked to complete a questionnaire that consisted of 15 sociodemographic items and 13 scaled responses to statements assessing the probability and magnitude of risk and benefit as well as perceived illness severity, attitudes toward research, and the consent process.

Analysis. Responses were subjected to factor analysis to identify underlying constructs. The sample was then randomly split, and multiple regression was performed on each half.

Results. The response rate was 83% (103 of 124) for those who had consented and 86% (37 of 43) for those who had declined. Factor analysis yielded three factors: (1) illness severity, (2) perceptions of risk or benefit and attitudes to research, and (3) sociodemographic characteristics. Multiple linear regression showed a significant multiple correlation of consent decision ($r = .502$), but only the second factor contributed. The analyses on split halves of the sample were comparable. Thirty-two percent of all parents agreed with the statement, “I would prefer to have the doctors advise me whether my baby should be in the study, rather than asking me to decide.”

Conclusions. In making consent decisions on behalf of their newborn infants, parents are influenced by risk and benefit assessments, attitudes toward research, and the integrity of the consent process. Illness severity or sociodemographic characteristics do not seem to be of similar importance. Rather than making the decision alone, a significant minority of parents would prefer to have the physicians advise them whether to volunteer their infants for a clinical trial. Pediatrics 1997;99(1). URL: http://www.pediatrics.org/cgi/content/full/99/1/e6; medical ethics, informed consent, newborn infant, clinical trial.

ABBREVIATIONS. NICU, neonatal intensive care unit; SNAP, Score for Neonatal Acute Physiology.

In 1964, the World Medical Association recommended in its Declaration of Helsinki that informed consent be obtained from all human subjects before their involvement in biomedical research. The acceptance of the doctrine of informed consent has accompanied an important shift from paternalism in clinical medicine to patient autonomy. Legal precedents and reports of research excesses led to political regulation of consent for clinical research along similar lines to consent for therapeutic procedures. However, one assumption underlying the principle of autonomy—that a competent person who understands disclosed information decides to give or to refuse consent after considering potential risks and benefits—remains more or less untested.

A paucity of empirical data is particularly evident for parental authorization of neonatal research involvement. Despite the intense clinical research activity in many neonatal intensive care units (NICUs), few, if any, studies have so far examined the process of proxy consent for the newborn. An exploration of this process is particularly important, because decisions on behalf of children are expected to be made in their best interests. This implies that parents have less latitude to be as idiosyncratic or unconventional as they may be in making decisions for themselves. Instead, they have a greater responsibility to weigh risks and benefits.

The present study was designed to determine the degree to which parental authorization of neonatal involvement in clinical trials is influenced by risk and benefit considerations compared with other factors such as the infant’s severity of illness at the time of the consent decision or parental sociodemographic characteristics and attitudes to research and the consent process.

METHODS

Instruments

A 29-item questionnaire was developed specifically for the study. The instrument included four items in which the parents were asked to estimate the probability as well as the magnitude of benefit and harm that they expected for their infants from participation in the “feeder” trial. Responses were entered on a seven-point Likert scale, anchored at “definitely would not” (benefit or be harmed) and “definitely would” (benefit or be harmed). Nine additional questions assessed factors that have been suggested to affect consent rate; these included a parental rating of illness.
severity, perceived coercion, and perceived complexity of the consent process, as well as altruism, the desire to delegate decision making to physicians, and general attitudes toward research. For each, the parents were asked to what extent they agreed or disagreed with the statement, again using a seven-point scale. One open-ended question, used to check content validity, asked for the single most important reason for the parental decision. The remaining 72 items of the questionnaire assessed sociodemographic factors.

The instrument was pretested for readability and comprehensibility on a sample of 10 parents in the NICU who were not included in the main study. Face validity was good, and any misunderstood or ambiguous items were rewritten. All responses to the open-ended question were addressed by one of the scaled items.

The first 10 parents enrolled were asked to complete the questionnaire again 2 weeks after their initial response. The intraclass correlation coefficients for the individual scaled responses ranged from $r = .77$ to .97, indicating very good test-retest reliability. The response distribution on scaled questions was good, with frequency of endorsement for at least three of seven response alternatives of greater than 5% on all items.

Objective scores for illness severity were assigned using the previously validated Score for Neonatal Acute Physiology (SNAP). The SNAP was calculated for the calendar day on which the parents had been approached for consent to one of the three feeder trials. The Hollingshead index of social status was calculated to condense sociodemographic information.

**Study Population and Setting**

The study took place in the NICU at McMaster University Medical Centre from February 1993 to March 1995. This 33-bed tertiary referral unit serves a regional population of 1.8 million people. Approximately 1000 neonates are admitted annually, of whom 80% are born in the center; the remainder are referred from surrounding hospitals.

The subjects were parents who had recently been approached for enrollment of their newborns in one of the three independently funded randomized, controlled trials taking place concurrently in the NICU. The first of these was a multicenter controlled trial of the effect of vitamin C supplementation on hemolysis. It involved stable, premature infants with birth weights 1000 to 1500 g who were enrolled between days 2 and 5 of life. Infants received a study medication such that their total vitamin C intake was equivalent to the low amount found in breast milk or to the high amount that is contained in some commercially available formulas. The intervention continued for 14 days, during which three small blood samples were drawn at the time of routine blood work. The second study was a placebo-controlled trial of the protease inhibitor antithrombin. Participants were mechanically ventilated infants with birth weights of 750 to 1500 g who had respiratory distress syndrome. Infants were enrolled in the first few hours after birth and remained in the trial for 48 hours, during which several small blood samples were drawn from an indwelling catheter. The third investigation was a randomized comparison of continuous infusioan to maintain the patency of intravenous lines with a saline lock device in stable infants of any birth weight who needed intravenous access only for medications. No additional testing was required.

Informed consent for each of the three trials was obtained by a variety of staff, including a research nurse, neonatal fellows, and neonatologists. In each case, parents received a one-page information sheet, which summarized the objective and design of the trial.

**Maneuver**

Shortly after authorizing or declining enrollment of their infants in one of the trials, parents were informed by letter of the questionnaire study. They were then approached by a research nurse a few days after the initial consent decision; this timing represented a compromise between further interference with the parents at a time of stress and the need to assess attitudes as closely as possible to the actual consent decision. The purpose of the study was again outlined, and a copy of the confidential questionnaire was given to the parents to be returned in a sealed envelope. Assistance with any reading difficulties was offered, but no parents availed themselves of this opportunity. In contrast to some consent discussions at entry into a feeder trial, interpreter services were not offered for completion of the questionnaire.

The option to decline participation or to leave some questions unanswered was emphasized. The study was approved by the Research Advisory Group at McMaster University.

**Data Analysis**

Responses and data for SNAP scores were entered into a spreadsheet program. SNAP scores were calculated using the Excel 4.0 computer program (Microsoft Corp, Redmond, WA, 1992), and statistical analysis of questionnaire responses was completed with the Statview 4.1 computer program (Abacus Concepts, Inc, Berkeley, CA, 1994). All scaled responses were treated as interval data. Responses were subjected to factor analysis, using principal components analysis and varimax rotation. Three factors were retained using Cattell’s Scree test. This reduction in the number of variables allowed the original sample to be randomly split; the first half was used to generate a multiple regression model, and validation of the model was performed on the second half. Demographic data not included in this analysis were compared using Student’s $t$ test and the $\chi^2$ test for continuous and nominal data, respectively.

**RESULTS**

**Study Participants**

During the study period, the parents of 186 patients were asked for permission to enroll their infants in one of the three feeder trials (vitamin C, $n = 12$; antithrombin, $n = 96$; and saline lock, $n = 78$). Consent rates were 42% for the vitamin C study, 80% for the antithrombin trial, and 76% for the saline lock study. One hundred sixty-seven sets of parents were approached for participation in the questionnaire study. Of the 19 families excluded, 3 had limited English skills, 5 were not approached for compassionate reasons, 6 could not be contacted in due time, and in 5 pairs of twins the questionnaire was requested only for the second twin, according to study protocol. Of the 167 sets of parents who received the questionnaire, 140 (84%) responded. Among parents who consented to a feeder trial, 103 (83%) of 124 responded, compared with 37 (86%) of 43 parents who did not consent to a feeder trial.

**Sociodemographic Data**

Infant characteristics and family sociodemographic data are given in Tables 1 and 2, respectively. There were no significant differences between consenters and nonconsenters for any of these variables.

<table>
<thead>
<tr>
<th>TABLE 1. Infant Characteristics</th>
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<tr>
<td><strong>Characteristic</strong></td>
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<tr>
<td><strong>(n = 103)</strong></td>
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<tr>
<td>Birth weight, g</td>
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<td>Gestation, wk</td>
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<td>Sex, % male</td>
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<td>Apgar score</td>
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<td>Inborn, %</td>
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<tr>
<td>Score for Neonatal Acute Physiology</td>
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<td>Postnatal age, d, median</td>
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<td>Time to questionnaire, d, median</td>
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* All values are given as mean (SD), percentage, or median as indicated.
Parental Responses to Scaled Items

Responses to the 13 scaled items are shown in Figs 1 through 4. The differences between consenters and nonconsenters were most marked for estimates of risks and benefits (Fig 1). In contrast, parental perceptions of illness severity were similar between consenters and nonconsenters (Fig 2). Ninety-four percent of all parents (98% of consenters and 84% of nonconsenters) endorsed altruistic motives as important considerations in making the decision (Fig 3). Thirteen percent of parents (10% of consenters and 22% of nonconsenters) agreed or strongly agreed that the process was too complex, whereas only 3% (3% of consenters and 6% of nonconsenters) reported feeling pressure to consent. Four percent of parents were concerned that there might be reprisals for not participating in a trial (Fig 4).

Thirty-two percent of parents (33% of consenters and 30% of nonconsenters) agreed or strongly agreed with the statement, “I would prefer to have the doctors advise me whether my baby should be in the study, rather than asking me to decide” (Fig 3).

Factor Analysis and Regression Model

Factor analysis yielded three factors. The first corresponded to “illness severity” and comprised birth weight, SNAP, and parental rating of illness severity. The second factor, “risk, benefit, and attitudes,” included the probability and magnitude of risk and benefit, altruism, general attitude to research, perceived complexity of decisions, freedom to make decisions, and concerns about reprisal. Items loading on the third factor, “sociodemographics,” included parental age and the Hollingshead index of social status.

Multiple linear regression showed a significant multiple correlation of consent decision ($r = .502; P < .0001$), but only factor 2, risk, benefit, and attitudes, contributed. The analyses on split halves of the sample were comparable (sample 1, $r = .577; P < .0001$; sample 2, $r = .438; P = .0015$). There was no correlation between the desire to have physicians advise on the consent decision, other attitudes to research, the estimate of risk and benefit, illness severity, or sociodemographic variables ($r = .176; P = .2319$).

DISCUSSION

In this study, authorization of neonatal involvement in controlled clinical trials was correlated with lower parental estimates of risk and higher estimates of benefit. The analyses on split halves of the sample were comparable (sample 1, $r = .577; P < .0001$; sample 2, $r = .438; P = .0015$). There was no correlation between the desire to have physicians advise on the consent decision, other attitudes to research, the estimate of risk and benefit, illness severity, or sociodemographic variables ($r = .176; P = .2319$).

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of benefit. Consenting parents were also more likely to report altruistic motivation, freedom to make the decision independently, and positive attitudes toward research and the consent process. Sociodemographic characteristics and the infant’s severity of illness at the time of the consent decision seemed of lesser importance.

This study is the first to correlate the determinants of parental decision making for the involvement of newborn infants in clinical trials with the direction of the consent decision and the first to test the assumption that parents weigh risks and benefits of a proposed research protocol. Several limitations of previous studies in older children and adults have been avoided. The instrument was pretested and had good reliability, face validity, and response distribution. Real rather than hypothetical consent decisions were examined, thus ensuring that the emotional influences associated with the stress of personal involvement would be assessed. Parents who consented were compared with those who refused, allowing a meaningful control for trends in responses. The response rate was good, even among parents who had refused participation in the feeder study. Generalizability was enhanced by the sampling of parents involved in consent decisions for three trials with very different risks and inclusion criteria.

Concern has been expressed that, among those consenting to research involvement, there may be a disproportionate representation of individuals who are unable to understand the information or who, by virtue of social disadvantage, are too intimidated to refuse. Our results are reassuring. Parents who consented showed no differences in education or social class index. More importantly, parents who reported less freedom to make the decision and who thought that the consent process was too complicated were actually less likely to permit involvement of their children in a clinical trial. It is possible that the parents who are most vulnerable to deficits in the integrity of the research process may recognize this and may decline any involvement. In contrast, con-
senting parents in an Australian trial of a drug to treat asthma had a lower level of postsecondary education and professional occupation than parents who had not volunteered their children for this trial.\textsuperscript{10}

One third of the parents in this study agreed or strongly agreed with the statement, “I would prefer to have the doctors advise me whether my baby should be in the study, rather than asking me to decide.” In the Australian survey of parents who volunteered their children for a trial of a new asthma drug, 15\% of the parents were of the opinion that the informed consent procedure was unnecessary because of their faith in their physicians' advice.\textsuperscript{11} Attempts to define this group of parents further in our study with respect to direction of consent, attitudes, sociodemographic factors, risk and benefit considerations, or illness severity showed no differences from those who would prefer to make the decision themselves.

Because genuine respect for parental autonomy would require that families be allowed the option to solicit their physician’s advice before making a consent decision, future research is needed to confirm our findings and to explore the feasibility of more individualized consent policies, which do justice to the different levels of independence that parents may desire.

Several limitations of the present study must be acknowledged. Any questionnaire-based evaluation is only an approximation of actual motivations. The validity of the responses will also be affected by the time lag between the decision and questionnaire completion, because parents’ interpretation of risks may be altered by the infant’s subsequent course, and their attitudes may be affected by later experiences in the NICU. We did not find it acceptable to approach parents immediately after the consent decision. The proven reliability of the questionnaire may provide some reassurance that experiences in the NICU did not change the responses substantially.

Although the study population is fairly typical for a Canadian tertiary-level NICU, the proportion of socially disadvantaged parents may be much higher in other countries. This may affect the conclusions regarding sociodemographic influences on consent, because we would be less likely to detect these in our more homogeneous population. Similarly, the power of the study to detect influences of illness severity or sociodemographic factors on the consent decision may have been weakened by the smaller numbers of nonconsenters compared with consenters. Moreover, we were not able to determine the relative priority of parental weighing of risks and benefits and their attitudes to research, because both loaded onto the same factor in the analysis. Separation of the two would require a much larger sample. Finally, psychologic profiles of the parents were not determined. Parental anxiety has been correlated with consent for research involvement of asthmatic children in Australia.\textsuperscript{12}

Despite these caveats, we conclude that parents approached for permission to enroll their infants in clinical trials do seem to weigh risks and benefits, and those who are most uncomfortable with the informed consent process are least likely to consent.

Future research should attempt to test in a controlled fashion methods of obtaining authorization, which would increase the degree to which parents use risk and benefit considerations, and decrease further the perceptions of complexity and coercion.

**ACKNOWLEDGMENTS**

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