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Recruitment and Retention in a Clinical Trial for Low Birth Weight, Premature Infants

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ABSTRACT. We report on recruiting and retaining a sample of low birth weight, premature infants for a clinical trial as well as results of tests evaluating sampling and retention biases. A total of 4551 infants were screened, and 1302 were found eligible. Consent was obtained for 1028 infants. After randomization and the presentation of group assignment, the number of infants enrolled was 985 (75.7% of those eligible). Of these, 92.7% completed the 3-year study. Tests to evaluate recruitment bias revealed significant relationships between nonenrollment and site, maternal race, and infant birth weight. Tests to evaluate retention bias revealed a significant relationship between dropout and maternal education. Additionally, infant birth weight and maternal age interacted with treatment in predicting dropout. Despite these statistically significant recruitment and retention biases, there was no evidence of problems with sample representativeness to the population of interest or of treatment group differences on study-relevant background variables. *J Dev Behav Pediatr* 14:1-7, 1993. Index terms: *bias, infant, recruitment, retention, sample.*

Recruitment planning is a critical step in conducting a successful randomized clinical trial.¹⁻⁵ Methods must be defined for recruiting a sample large enough to provide power to detect treatment effects and sufficiently representative of a well-specified and relevant population to allow results to be generalized. During planning, projecting probable ineligibility rates (because of prespecified exclusion criteria) allows better determination of the number of subjects to screen to obtain a sufficiently large sample size. Furthermore, projecting likely losses of eligible subjects owing to consent refusal during the enrollment period and dropout over the course of the study allows better prediction of whether the eventual retained sample will be representative of the population sampled as well as large enough to maintain sufficient statistical power.

Although recruitment bias and subject loss are critical issues in determining the statistical power and the generalizability of findings of research studies of various types, few examples in the literature have addressed these topics. Within the area of infancy research, several authors have noted serious problems in interpreting research findings because of inadequacies in reporting about recruitment and retention issues. For example, Ottenbacher⁶ and Simeonsson et al,⁷ in their recent reviews of early intervention evaluation studies, have pointed out that the sample sizes of many studies have inadequate statistical power to test the hypothesized effects. Simeonsson et al⁷ noted that incomplete specification of inclusion criteria is an additional problem with these studies.

Richardson and McCluskey⁸ and Kiely and Paneth⁹ have discussed the need for better reporting of the descriptive characteristics of samples recruited and retained in basic research on infants and in follow-up studies of low birth weight infants. In studies of infant visual perception, for

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example, subject losses typically range from 25% to 70%. Richardson and McCluskey⁸ demonstrated that there can be biases in the retained sample that affect the results obtained and hence their interpretation.

For follow-up studies with high-risk infants, there is a paucity of available data about the characteristics of subjects who drop out, although several investigators have speculated that parents who are worried about the health and developmental status of their infants are less likely to drop out whereas those who do not want to be seen by professionals (as in cases of child abuse) would be more likely to drop out or refuse consent to participate.^{9,10}

One of the few studies to directly examine the characteristics of dropouts was a collaborative clinical trial of the effects of antenatal dexamethasone treatment on the prevention of respiratory distress syndrome in high-risk infants.¹¹ In a cohort of 645 infants and their families, the investigators examined a variety of characteristics that distinguished those who withdrew from those who remained in the study through 36 months of age. Environmental factors were major predictors of who dropped out, although dropout rates also were greater for infants with higher gestational ages. In addition, analyses of data on infant developmental status did not support the common belief that impaired infants are more likely to remain in follow-up programs. As the authors note, this has important implications for interpreting the rates of neuromotor handicap and developmental delays reported in high-risk infant follow-up studies.

These reports illustrate the limited data available about subject recruitment and retention characteristics and practices as well as the effects such limitations have on interpretations of existing research studies. Our article reports for the Infant Health and Development Program¹² the strategies used in three areas: screening for eligibility, obtaining informed consent, and maintaining the sample. A comparison of background characteristics of those who were eligible with those who enrolled is provided. Comparisons also are reported of those who enrolled with those who completed the 3-year clinical trial. We present the reasons subjects gave for refusing consent or for dropping out during the trial. Finally, we consider whether consent refusal or dropout was related to sociodemographic characteristics.

METHODS

The Infant Health and Development Program

The Infant Health and Development Program (IHDP) was a multisite, randomized clinical trial to test the efficacy of a comprehensive early intervention program in reducing the health and developmental problems of low birth weight (≤ 2500 g), premature (gestational age ≤ 37 weeks) infants.¹² The sample was stratified by eight sites (medical institutions) and two birth weight groups (≤ 2000 g, and 2001 to 2500 g). The medical institutions were predominantly large, urban, tertiary care centers serving mainly low socioeconomic status (SES), high-risk neighborhoods. By design, two thirds of the sample were from the lighter-born group and one third from the heavier-born group. Furthermore, within each weight group, one third were randomized to an Intervention Group and two thirds to a Follow-up Group

(comparison group). Both study groups received the same high-quality 3-year pediatric follow-up, but only the Intervention Group received a comprehensive, 3-year, early intervention program. (See Ramey et al¹³ for a complete description of the Intervention Program.)

The projected overall sample size was designed to have at least 99% power, with a 5% two-tailed test, to detect an effect size of 0.5 in both the total group and the lighter group alone. The targeted number of subjects at each of the eight sites was 135, for a total across sites of 1080.

Screening for Eligibility

During the recruitment period, the birth of each inborn infant weighing less than or equal to 2500 g was recorded in a log, and the infant was screened for eligibility. An inclusion/exclusion form was completed for each infant with documentation of either the reason for exclusion or the date of enrollment into the study. A weekly monitoring system was used whereby the sites were required to report to the national coordinating center the status of each infant by either the submission of an inclusion/exclusion form or a report on progress in enrollment.

Of the 4551 infants screened across the eight sites, 1302 (28.6%) were found eligible. Using a list of enrollment criteria, exclusions were made after the first exclusion criterion on the list was detected; had further screening occurred, additional exclusion criteria might have been found in some cases. All entry criteria were defined to exclude as few infants as possible so the sample would best represent the population of premature, low birth weight infants at each site. The primary reasons for exclusion are shown in Table 1.

A total of 61 infants were excluded because it was believed their medical impairments would be so severe they would not be able to benefit from the intervention. An additional 108 infants were excluded because their mothers were unable to communicate in English; similarly, these mothers would not be able to benefit from the intervention. (Mothers with limited ability to communicate in English were enrolled, however.) Finally, infants whose mothers reported drug and/or alcohol abuse or previous psychiatric hospitalizations were excluded during recruitment. During the course of the study it became evident, however, that some enrolled mothers had these kinds of problems.¹⁴

Recruitment: Informed Consent and Randomization

The 1302 infants who were found eligible made up the study's recruitment group. Mothers of each of these infants were given full information about the program and approached for written consent to be randomized into either the Intervention or Follow-up Group while the infants were still in the hospital nursery. After discharge, the infants were randomly assigned at the national coordinating center to one of the two groups using a procedure that monitored the balance between them. (See Kraemer and Fendt¹⁵ for a complete description of the randomization procedures.) Program staff members met with each family at home to present the group assignment and confirm the mother's commitment to participating in the study.

TABLE 1. Reasons for Exclusion from Eligibility, or for Not Enrolling

	N	(%)
Total screened	4551	
Total excluded	3249	71% of total screened
Initial exclusions	2790	(86% of total excluded)
Residence outside catchment area	1524	
Gestational age >37 weeks	604	
Hospital discharge outside recruitment period	431	
Sibling of eligible twin	140	
Other initial exclusion	91	
Infant exclusions	294	(9% of total excluded)
Death	233	
Chromosome/multiple anomaly syndrome	25	
Recipient of oxygen for >90 days	19	
Extended hospitalization for ≥ 60 days after 40 weeks corrected age or severe neurological or sensory defect	17	
Maternal exclusions	165	(5% of total excluded)
Unable to participate in the program in English	108	
Maternal report of drug/alcohol abuse or psychiatric hospitalization	57	
Total eligible	1302	29% of total screened
Not enrolled	317	(24% of total eligible)
Family refused consent	274	
Group assignment could not be presented	26	
Family rejected treatment group assignment	17	
Enrolled	985	(76% of total eligible)

Table 1 also shows the reasons for which eligible infants were not enrolled in the study. Of the 1302 eligible infants, consent was refused for 274 infants (21.0%). Reasons for refusal included family not wanting day care ($n = 73$), program too much of a time commitment ($n = 53$), program not needed, no special needs perceived ($n = 45$), family not wanting to participate in research or had concerns regarding privacy invasion ($n = 32$), and staff not able to locate the family to request consent ($n = 8$). Additionally, some families were not interested but gave no reason for refusing consent ($n = 63$).

After consent was granted and random assignment to treatment group was conducted, 26 (2.0%) were not enrolled because group assignment could not be presented for a variety of reasons. Another 17 (1.3%) were not enrolled because of the family's rejection of group assignment. The remaining 985 infants (75.7% of those eligible) became the primary analysis group for the study. Thus 21.6% of the total of 4551 infants initially screened for eligibility were enrolled in the study. Although the final sample of 985 infants was slightly smaller than planned (1080), and the number enrolled per site ranged from 100 to 138 (versus 135 planned), the final sample did provide the specified statistical power.

Retention: Maintaining the Sample

Each enrolled infant was seen at the study clinic at 40 weeks' gestational age (0 months corrected age or the date at which infant would have been full-term), and at 4, 8, 12, 18, 24, 30, and 36 months corrected age (corrected for prematurity). The duration of a clinic visit was anywhere from 1½ to 3 hours, depending on the planned assessments.

To minimize attrition and maintain compliance with the clinic appointments, extensive tracking procedures and incentives were employed. The tracking procedures included

mandated contacts between visits as well as written protocols for locating lost families. Incentives to improve compliance included transportation to clinic visits, remuneration for completed assessments, photos of the children, T-shirts, books and toys, and birthday, holiday, and mother's day cards.

When families moved outside the original catchment area to a known address, they were encouraged to return to the clinic for their regular assessments with reimbursement given for travel expenses. If the family could not return to the site, partial assessments were conducted via telephone interviews.

Because the final 36-month assessment involved many of the study's primary outcome measures, extra efforts were made to conduct the 36-month assessments with all families who had moved away from the sites. In addition to the usual offer of travel reimbursements and increased monetary incentives, satellite clinics were established for those families who could not return to the site.

Bias Associated with Recruitment and Retention: Statistical Methods

To address the question of recruitment bias, multiple logistic regression was used. This technique is similar to the more common multiple linear regression. The difference is that the relationship between a dichotomous dependent variable and a set of independent variables is modeled by a logistic function, rather than the relationship between a continuous dependent variable and the independent variables being modeled by a straight line. Enrollment (versus nonenrollment) was the dependent variable; site, birth weight, gender, single versus multiple birth, maternal age, and maternal race were the independent variables. The set of site variables was entered first, then the other independent

variables were stepped-in in order of significance level.

To address the question of retention bias, the Cox Proportional Hazards Model was used. This is a regression model formulated in terms of the effects of the independent variables on dropout rates over time. No assumptions about the shape of the survival (regression) curve are made. Time of dropout was employed as the dependent variable. A dropout was defined as a subject for whom the 36-month data used in the major outcome article¹² were missing. The time of dropout was the last assessment point at which data used in the major outcome article were collected. Included in this analysis were the main effects of the independent variables as well as the interaction effects for treatment crossed with the independent variables. The independent variables evaluated were treatment group, birth weight, gender, single versus multiple birth, maternal age, maternal race, and maternal education. Treatment group was entered first, then all independent variables were stepped in, and finally all treatment by independent variable interactions were stepped in. (The site variables were dropped after being initially tested alone and found to have no significant overall effect on the time of dropout.)

RESULTS

Analyses of Recruitment Bias

As shown in Table 2, 75.7% of all eligible infants were enrolled in the study. Of the independent variables tested, nonenrollment (because of family consent refusal, group assignment not presented, or family rejection of group assignment) was significantly related to four: site (model $\chi^2 = 74.67$, $df = 7$, $p < .01$), maternal race black ($\chi^2 = 21.10$, $df = 1$, $p < .01$), infant birth weight ($\chi^2 = 12.05$, $df = 1$, $p < .01$), and maternal race Hispanic ($\chi^2 = 7.39$, $df = 1$, $p < .01$). These four variables entered in the order listed and statistics for each variable were calculated adjusting for preceding variables only. Enrollment rates were significantly different across sites. Mothers of lighter-weight infants were more likely to enroll than were mothers of heavier-weight infants, and blacks and Hispanics were more likely to enroll than were whites and others. The final column of this table shows that the percentages of those eligible who actually were enrolled was high at all sites except for Harvard.

Analyses of Retention Bias

Retention was very high, with 93% of the sample participating in the final 36-month assessment. Of the 72 subjects who dropped out, 30 did so early in the study, i.e., at or before the 4-month assessment. After this point had passed, dropout occurred at a low and fairly consistent rate over the course of the study. By 12 months, 53 of the 72 infants who were to drop out had done so. The reasons for dropout were: whereabouts unknown ($n = 25$); refused further participation ($n = 16$); infant deceased ($n = 12$); moved out of state and unable to contact ($n = 10$); and moved out of the country ($n = 9$).

The results of the analysis relating baseline characteristics to dropout status (including time of dropout) are shown in Table 3. Of the seven independent variables tested, only

TABLE 2. Baseline Characteristics Significantly Associated with Enrollment Status

	Number Eligible ^a	Number Enrolled ^b	Percent Enrolled ^c
All sites	1302	985	75.7
Site			
Arkansas	152	128	84.2
Einstein	178	138	77.5
Harvard	245	138	56.3
Miami	116	100	86.2
Pennsylvania	135	101	74.8
Texas	156	137	87.8
Washington	175	131	74.9
Yale	145	112	77.2
Birth weight			
Less than 1501 g	316	256	81.0
1501-2000 g	474	367	77.4
2001 g and above	512	362	70.7
Maternal race			
Black	617	517	83.8
Hispanic	130	105	80.8
Caucasian, other	554	363	65.5

^aColumn does not add to 1302 because of missing data for one subject.

^bEnrolled = consented and accepted group assignment.

^cPercent enrolled = number enrolled/number eligible \times 100. In absence of any bias, expected value of "enrolled" would be 75.7%.

maternal education was significant ($\chi^2 = 6.36$, $df = 1$, $p = .01$). (It is noted, however, that the success in retention resulting in only 72 subjects dropping out has the repercussion of limiting the power of tests to detect the correlates of retention.) Mothers with lower levels of education were more likely to drop out of the study than were mothers with more education. (Maternal education was not examined in analysis of recruitment bias because education level data were not available for mothers who refused.) Treatment group had no significant effect on retention: 92.8% of the Intervention Group was retained versus 92.6% of the Follow-up Group. Furthermore, the survival curves for time of dropout reveal little difference between the two study groups (Fig. 1). However, two variables were found to interact significantly with treatment in predicting retention: birth weight ($\chi^2 = 5.00$, $df = 1$, $p = .03$) and maternal age ($\chi^2 = 4.95$, $df = 1$, $p = .03$). Table 3 also shows the treatment group differences in retention for each level of these two independent variables. For the lightest infants (less than 1501 g), those in the Intervention Group were more likely to be retained relative to infants in the Follow-up Group. For the heaviest infants (2001 to 2500 g), the effect was the opposite: those in the Follow-up Group were more likely to be retained than were those in the Intervention Group. Regarding maternal age, infants of the youngest mothers (younger than 18 years) were more likely to be retained in the Intervention Group than those in the Follow-up Group. For the oldest mothers (older than 30 years), the effect was opposite: those in the Follow-up Group were more likely to be retained than were those in the Intervention Group. No other differential effects by treatment group on retention were found.

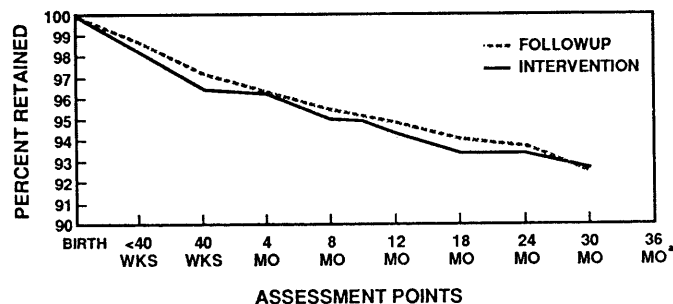
TABLE 3. Significant Baseline Characteristic and Treatment × Independent Variable Interaction of Enrolled Infants (n = 985) by Retention Status

	Total Enrolled	Number Completed Study	Percent Completed Study ^a
All enrolled infants	985	913	92.7
Significant baseline characteristic			
Maternal education at birth			
Not a high school graduate	394	355	90.1
High school graduate	270	255	94.4
Some college or more	321	303	94.4
Significant treatment × independent variable interaction			
Birth weight			
Less than 1501 g			
Follow-up	169	150	88.8
Intervention	87	82	94.3
1501–2000 g			
Follow-up	219	209	95.4
Intervention	148	142	95.9
2001 and above			
Follow-up	220	204	92.7
Intervention	142	126	88.7
Maternal age at birth			
Younger than 18 yrs			
Follow-up	59	52	88.1
Intervention	44	41	93.2
18–19 yr			
Follow-up	81	74	91.4
Intervention	44	40	90.9
20–30 yr			
Follow-up	350	325	92.9
Intervention	218	206	94.5
Older than 30 yr			
Follow-up	118	112	94.9
Intervention	71	63	88.7

^aPercent completed study = number completed study/total enrolled × 100. In absence of any bias, expected value for “completed study” would be 92.7%.

DISCUSSION

The findings reported above show that all potentially eligible infants were screened for eligibility, and 28.6% (n = 1302) were found eligible. Of those 1302 eligible infants, 75.7% (n = 985) were enrolled. At the final study assess-



*CENSORED OBSERVATION
FIGURE 1. Kaplan-Meier survival curves for retention within the Intervention and Follow-up groups.

ment conducted at 36 months, 92.7% of the enrolled sample participated.

Screening for Eligibility

Every potentially eligible infant was screened, and, when appropriate, approached for consent. These findings support our belief that the system where each site accounted weekly to the national coordinating center on their enrollment progress was effective. This system facilitated the early detection of a potential shortfall in enrollment, providing sufficient time to design and implement adjustments to the enrollment criteria and timeline when necessary.

Recruitment: Informed Consent and Randomization

Given the time commitment required for study participation, the low consent-refusal rate of 21.0% is encouraging. Factors accounting for this probably include the detail in which the consent protocol was delineated for program staff in the manual of operations, the care taken to ensure that the consent form was understandable to mothers from a variety of educational backgrounds, and having project staff approach the mother before the infant was discharged home.

Two of the three most common reasons for refusing consent were “do not want day care” (a component of the intervention program), and “program not needed; no special needs perceived.” The protocol required recruiters to stress the potential benefits of involvement in the program, including the benefits of high-quality day care, but perhaps these issues could have been covered more effectively.

Although the services offered to the two treatment groups differed greatly, group assignment was rejected for only 17 (1.7%) of the 1028 infants for whom consent was obtained. We speculate that having a project staff member present group assignment in the subject’s home helped minimize rejection of group assignment. Of these 17 rejections, however, 14 had been randomly assigned to the Intervention Group and 3 to the Follow-up Group. It appears that the Intervention Group was viewed as the less attractive assignment, perhaps because of the heavy commitment it required. Because the number of mothers rejecting group assignment was so low, the representativeness of the sample was not significantly affected.

In the analysis of recruitment bias, we found that those more likely to enroll included mothers who were black or Hispanic and mothers of lower birth weight infants. The higher rate of enrollment among blacks and Hispanics may have occurred because more members of this group felt need for the program’s services, e.g., long-term medical follow-up and the chance of being assigned to the Intervention Group that would provide 2 years of free, high-quality day care. Similarly, higher enrollment for the lighter-born infants (less than or equal to 2000 g) was possibly owing to a greater perceived value of the program’s services to this group, as they were at greater risk for medical and developmental problems than heavier-born infants (those more than 2000 g).

Enrollment also was less likely at one of the sites. Given the care taken to design a common recruitment protocol, it is probable that the marked differences in the sociodemo-

graphic characteristics of that site were the major influence. Because site differences in recruitment so often occur, it becomes especially important to randomize subjects to treatment groups after informed consent is obtained and to randomize within each site. Such procedures ensure the comparability of the two treatment groups at each site.

Retention: Maintaining the Sample

The 92.7% retention rate after 3 years in such an intensive program can be attributed to the wide variety of techniques used to maintain the sample. Of the many mandated procedures used, a few stand out anecdotally. These include contacting families to reschedule appointments after repeated no-shows, providing transportation to the assessment site, placing two telephone calls to the families between assessment points (or home visiting those families with no telephones), family remuneration, and aggressive tracking of subjects who had moved. Additionally, staff traveled to local communities to conduct the final assessment for families living too far to return to the site ($n = 37$). These procedures required extensive fiscal resources, particularly to support high staffing levels.

Of the 72 infants who dropped out of the study, 30 were lost to the study either before the first assessment visit at 40 weeks gestational age or at or before the second visit at 4 months. Of these 30 infants, more than half were lost for the reasons "whereabouts unknown" and "moved out of state and unable to contact." We note that early in the study the tracking protocol used for much of the trial had not yet been mandated. These findings illustrate the need for an aggressive tracking protocol early in a long-term follow-up study.

In the analysis of retention bias, only low maternal education was independently associated with increased dropout. Assuming education as a proxy for socioeconomic status (SES), these findings are consistent with those found by Aylward et al.¹¹ For their multicenter clinical trial with a similar sample of infants, they reported lower follow-up attendance among lower socioeconomic groups.

There were only two variables with which retention differed by treatment group. First, the findings showed that mothers of the lightest infants (less than 1501 g) in the Intervention Group were more likely to remain in the study than were mothers of the lightest infants in the Follow-up Group. Conversely, mothers of the heaviest infants (2001 g or more) in the Follow-up Group were more likely to remain in the study than were mothers of the heaviest infants in the Intervention Group. It is possible this differential effect of birth weight on retention was because of different perceived needs of the families of the two birth weight groups. Mothers of lighter-born infants may have perceived a greater need for the Intervention program and therefore were willing to persist despite the time commitment required by this program. For mothers of the heavier-born infants, the Intervention program may have been perceived as unnecessary and perhaps even burdensome compared with the Follow-up program.

Finally, the youngest mothers (under 18) were more likely to remain in the Intervention Group compared with the youngest mothers in the Follow-up Group. These young mothers,

with perhaps less social support or resources, may have perceived a greater need for the services offered by the Intervention program.

CONCLUSIONS

There are three chief concerns related to consent refusal and attrition over the course of a clinical trial: (1) the representativeness of the study sample to the population of interest (external validity), (2) the comparability of the treatment groups (internal validity), and (3) the ability to detect treatment effects (power). External validity is threatened when the sample becomes unrepresentative of the population owing to subject loss associated with characteristics related to the treatment or outcomes of the study. Internal validity is threatened by differential subject loss between treatment groups. Power is diminished as the overall size of the sample decreases.

The exceptionally high recruitment and retention rates of 75.7% and 92.7% achieved in the Infant Health and Development Program (IHDP) minimize both external and internal validity concerns and provide the desired power to detect treatment group differences specified at the beginning of the study. The success we had was in large part because the attention and resources allocated to the important study goals of (1) recruiting from the total pool so there would be no losses of eligible subjects owing to not being approached, (2) enrolling a high proportion of eligible subjects, and (3) retaining a high proportion of the enrolled sample. This took intensive effort by the national coordinating center to provide detailed written protocols, training, and monitoring to help the sites recruit and retain subjects. One should not assume that staff knows how to perform these activities. Experienced professionals are needed to write protocols. Relevant literature must be reviewed, especially from fields such as survey research and epidemiology. Other important resources are staff time to approach and follow subjects and money for family remuneration and other incentives. Our findings show that longitudinal studies serving a mainly low SES, high-risk population can succeed in recruitment and retention if they bring adequate resources to bear on these activities.

In the recruitment analyses we found small but statistically significant effects of site, maternal race, and birth weight. These differences between the successfully recruited sample and the refusers were not large enough to have any practical effect on the representativeness of the study sample to the population and had no effect on the comparability of the treatment groups. In the retention analyses, we found small but statistically significant effects of maternal education, maternal age by treatment group, and birth weight by treatment group. Again these differences were not large enough to have any practical effect on internal or external validity, in particular because the treatment groups did not differ significantly or appreciably on any of these characteristics in the retained sample. Because interactions were found between treatment effect and some of these variables in the main study, subgroup-specific treatment effects should be considered as part of the overall interpretation of the IHDP results.

These findings also are important in demonstrating that despite intensive efforts, study-relevant variables can be related to both recruitment and retention. Given that most large studies do not achieve such high rates of recruitment and retention, we recommend that regression analyses such as those employed here be conducted to evaluate threats to internal and external validity. As the rates of successful recruitment and retention go down, the potential threat of these types of effects becomes more serious.

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MEETING ANNOUNCEMENT

The SOCIETY FOR BEHAVIORAL PEDIATRICS will conduct its 11th Annual Scientific Meeting and Workshops on September 9-13, 1993 at the Providence Marriott in Providence, Rhode Island. For further information and registration forms, please contact Ms. Noreen Spota at 215-248-9168.