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Predictors of Study Completion and Withdrawal in a Randomized Clinical Trial of a Pediatric Diabetes Adherence Intervention

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Abstract

Purpose—Loss of participants in randomized clinical trials threatens the validity of study findings. The purpose of this study was to determine pre-randomization predictors of study withdrawal throughout the course of a randomized clinical trial involving young children with type 1 diabetes and their primary caregivers.

Methods—An intervention to improve adherence to the diabetes treatment regimen was delivered as part of the child's regular 3-month diabetes clinic visit. The study protocol involved 7 clinic visits across 18 months for the Immediate Treatment group and 9 clinic visits across 24 months for the Delayed Treatment group. Among those who completed the study and regardless of treatment group, participants were categorized into two groups: On-Time Completers ($n = 41$) and Late Completers ($n = 39$). Demographic, disease, and psychosocial characteristics of children and their primary caregivers measured prior to study randomization were tested for their association with the participants' completion status (i.e., On-Time Completers, Late Completers, or Withdrawals).

Results—Of the 108 participants, 28 (25.9%) withdrew and 80 (74.1%) completed the study. On-Time Completers (i.e., study completed within 4 months of expected date) were more likely to have private insurance and primary caregivers with some college education. Late Completers (i.e., study completion took longer than 4 months) were more likely to be boys and to have primary caregivers who reported mild to moderate levels of depression. Children who subsequently withdrew from the study reported poorer diabetes-related quality of life and poorer school-related quality of life at study inception and were more likely to have primary caregivers who did not work outside the home.

Conclusions—Pre-randomization screening of participants on both demographic and psychological variables may help identify those at greatest risk for study withdrawal or poor study protocol adherence, permitting the investigators to develop retention strategies aimed at this high-risk group.

Keywords

Study Withdrawal; Protocol Compliance; Children; Type 1 Diabetes; Adherence Intervention; Psychological Functioning; Health-Related Quality of Life; Socioeconomic Status

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1. Introduction and background

The loss of participants during a randomized clinical trial reduces the study's statistical power to detect true treatment effects. Nonrandom participant attrition is particularly problematic because it may bias study results and limit the relevance of the study's findings to the target patient population [1,2]. The situation is further complicated in pediatric populations because trial participation is dependent upon parent as well as child behavior.

Historically, attrition rates in pediatric randomized clinical trials have not been consistently reported with only about half of studies providing this information [3]. In their review of attrition rates in pediatric randomized clinical trials, Karlson and Rapoff [3] found that 20% and 32% of participants withdrew prior to the first follow-up session and were lost to extended follow-up, respectively. In pediatric diabetes randomized clinical trials, rates are variable and range from 0-16% for withdrawals prior to the first follow-up and 2-26% for those who were lost to extended follow-up [3].

Findings from the few published studies examining attrition in pediatric randomized clinical trials suggest that child characteristics (e.g., age, sex, health status, cognitive, emotional, behavioral functioning), parent characteristics (e.g., age, education, psychological functioning), and family conflict or cohesion may be important determinants of study protocol adherence or drop-out [4-10]. Unfortunately, interpretation of this literature is sometimes difficult due to the use of different definitions of study attrition. Bender, Zebracki and their colleagues [9,10] suggest that study drop-outs and those with erratic attendance be treated as two separate groups. Consistent with this recommendation, we examined pre-randomization demographic, disease, and psychosocial characteristics of patients and their caregivers enrolled in a randomized clinical trial that predicted the participants' study completion status (i.e., On-Time Completers, Late Completers, or Withdrawals). The overall purpose of the randomized clinical trial was to provide intervention to improve adherence to the type 1 diabetes treatment regimen. Information obtained from this study may help maximize participant retention and protocol adherence in future clinical trials with pediatric populations, which will likely lead to increased internal, external and statistical validity and reduced bias [2] and improved clinical care of children with chronic illnesses.

2. Methods

HANDling Diabetes was a randomized clinical trial, funded by the National Heart, Lung, and Blood Institute, assessing an adherence intervention incorporated into the routine clinical care of children with type 1 diabetes. This study was approved by the Florida State University and University of Florida Institutional Review Boards.

2.1. Study Participants

Between March 2002 and October 2007, 108 children and their primary caregivers from two pediatric diabetes clinics in Florida (Shands Clinics in Gainesville, n = 57; a private pediatric endocrinologist's office in Tallahassee, n = 51) participated in this study. All families with children 12 years of age or older with type 1 diabetes for at least 6 months were invited to participate. Informed parental consent and child assent (for children 5 years of age or older) were obtained.

In Florida, all low-income children with chronic medical conditions are eligible for health care coverage through state and federal programs (i.e., Medicaid, Children's Medical Services). No child who participated in this study was ever denied health care.

2.2. Study Design and Procedures

At the study's inception, primary caregivers and children 5 years of age or older completed a number of pre-randomization questionnaires. Participants were then randomized into an Immediate Treatment or a Delayed Treatment group (i.e., replication design; see Figure 1). This staggered design enabled the investigators to compare the effectiveness of various components of the intervention between those who received Immediate versus Delayed Treatment.

All participants were seen in clinic by their pediatric endocrinologist at 3-month intervals, with the Delayed Treatment group beginning the intervention 9 months following initial enrollment in the study. The study protocol involved 7 clinic visits across 18 months for the Immediate Treatment group and 9 clinic visits across 24 months for the Delayed Treatment group. Although each HANDling Diabetes study visit coincided with the child's routine clinic visit, study participation involved an extra 30 minutes to 1 hour of time per visit. The adherence intervention involved three components delivered during 5 clinic visits: a written prescribed treatment form completed by the physician and given to the family to take home; diabetes knowledge and skills assessments of all components of the child's treatment regimen with reeducation as needed; and three diabetes problem-solving skills intervention sessions tailored to each family's particular difficulties adhering to the diabetes treatment regimen. Between each clinic visit, primary caregivers were contacted by telephone on three separate occasions and asked to recall the child's diet, exercise, and diabetes management activities in the preceding 24 hours. Following completion of the 5-session intervention, a post-intervention session occurred in which re-assessment of study questionnaires and diabetes-care skills occurred (see Figure 1).

Several strategies were used to improve study participation and minimize withdrawal. Study visits always coincided with clinic visits. If families had difficulty affording blood glucose testing meters and strips, they were provided at no cost. Children were given small toys for their participation and primary caregivers were reimbursed with cash or gift cards for completing the 24-hour telephone recalls.

2.3. Classification of Participants as On-Time Completers, Late Completers, and Withdrawals

Of the 108 participants, 28 (25.9%) withdrew and 80 (74.1%) completed the study. Time to study completion in the 80 families who completed the study was examined. Because ideal completion time differed for the Immediate and Delayed Treatment groups, we subtracted ideal time to completion (18 months for the Immediate Treatment group and 24 months for the Delayed Treatment group) from actual time to completion; the distribution was bimodal. More than fifty percent ($n = 41$, 51.3%) completed the study within 4 months of the ideal study completion date ($M = 1.32$ months; $SD = 1.31$) and were labeled On-Time Completers. The remaining participants ($n = 39$, 48.8%) completed the study more than 4 months after the ideal study completion date ($M = 9.79$ months, $SD = 4.29$) and were labeled Late Completers. Those who withdrew from the study left an average of almost 10 months prior to the expected time of study completion ($M = 9.96$ months, $SD = 6.48$); however, there was great variability in time to withdrawal, with 1-3 withdrawals each month throughout the 24 months of the study.

2.4. Measures Collected Pre-randomization

2.4.1. Demographic Information—Prior to randomization, each primary caregiver provided information about the child's sex, race/ethnicity, age, and health insurance, the child's caregivers' age, education, marital status, and employment status, and the age, sex and relationship to the child of all persons living in the household. Based on the primary caregivers' occupation and education level, a Hollingshead score was calculated as an indicator of

socioeconomic status (SES) [11]. In addition, the mileage between the family home and the diabetes clinic was obtained.

2.4.2. Disease Variables—Prior to randomization, the duration of the child's diabetes and the child's hemoglobin A₁C (HA1C), an indicator of the average glucose level during the past 2.5 to 3 months considered as the gold standard of diabetes control [12], was obtained from the medical record.

2.4.3. Primary Caregiver Depressive Symptoms and Diabetes-Specific Stress—Prior to randomization, primary caregivers completed the 20-item Center for Epidemiological Studies–Depression Scale (CES-D), for which large sample normative data are available [13, 14], to assess depressive symptoms. Primary caregivers were categorized into one of three groups: those exhibiting low levels of depressive symptoms (scores of 15 or less), those exhibiting mild to moderate levels of depressive symptoms (16-22), and those with high levels of depressive symptoms (scores of 23 or greater) [14]. In this study, internal consistency (coefficient alpha) for the CES-D was .88.

The 15-item Family Stress Scale (FSS) [15-17], previously developed for cystic fibrosis populations, was adapted for use in this study. The FSS assesses generic (e.g., discipline) and diabetes-specific stress (e.g., doing treatments such as insulin injections and blood glucose testing), with high scores indicating greater family stress. The measure demonstrated good internal consistency in this study (coefficient alpha = .90).

Primary caregivers also completed the 13-item Family Interruption Scale (FIS) [18], a diabetes-specific measure that assesses the degree to which the diabetes treatment regimen negatively impacts family activities (e.g., “Our child's diabetes limits what the family can do with our time and money”). On this measure, low scores indicate greater family disruption. Internal consistency for the FIS was good in this study (coefficient alpha = .82).

2.4.5. Child Health-Related Quality of Life—Primary caregivers provided caregiver-proxy reports and children 5 years of age or older provided self-reports of general and diabetes-specific health-related quality of life. The Pediatric Quality of Life Inventory™, Version 4.0 (PedsQL™ 4.0) [19] consists of 23 items that assess generic quality of life on a variety of domains. Higher scores indicated better quality of life. Coefficient alphas for this study's primary caregiver-proxy reports for the Total score and by domain were: Total = .92, Physical = .91, Emotional = .79, Social = .91, and School Functioning = .82. Coefficient alphas for this study's children's self-reports were: Total = .87; Physical = .74; Emotional = .70, Social = .79, and School Functioning = .65.

The Diabetes Quality of Life (DQOL) [20] is a 46-item inventory assessing diabetes-specific quality of life in three domains: Satisfaction (e.g., How do you feel about the amount of time it takes to do things for diabetes?), Disease Impact (e.g., How often does your diabetes stop you from doing things with your friends?), and Worries (e.g., How often do you worry that you will pass out because of your diabetes?). It has been widely used with adults and has been modified for adolescents [21] and children [22]. The child and primary caregiver-proxy versions of the measure were used in this study. Higher scores indicate poorer quality of life. Coefficient alphas for this measure were good for both primary caregiver-proxy (Total = .94, Satisfaction = .90, Impact = .78, Worry = .89) and child self-reports (Total = .93, Satisfaction = .87, Impact = .82, Worry = .88).

2.5. Reasons for Withdrawal

When participants expressed their intention to withdraw from the study or if they did not return to clinic, whenever possible, reasons for withdrawing from the study were gathered directly

from primary caregivers. Reasons for withdrawal could not be obtained from 39.3% of those who withdrew from the study. Among those who gave a reason, lengthy study visits or not having time for the study (47.1%) were the most frequent reasons for withdrawal. Other reasons included moving out of town (23.5%) or being committed to other research (17.6%).

2.6. Statistical Analyses

Statistical analyses were performed using SPSS Version 15. Because data were collected at two sites, possible site differences were examined for all study variables. Next, tests of association were used to identify variables collected prior to randomization (e.g., demographics, depressive symptoms, health-related quality of life, etc.) that predicted study completion status as On-Time Completers, Late Completers, or Withdrawals. Chi-square tests or analyses of variance (ANOVA) were used depending on the type of variable (i.e., dichotomous or continuous). Multinomial logistic regression was used to examine which predictors identified through univariate tests remained when multiple predictors were retained in the same model.

3. Results

3.1 Site Differences

Because data were collected at two sites, possible site differences were examined for all study variables. Compared to participants at the Gainesville site, Tallahassee participants drove farther distances to clinic ($M_{\text{Tallahassee}} = 60.03 \text{ miles} \pm 56.87$, $M_{\text{Gainesville}} = 41.47 \text{ miles} \pm 33.24$; $t(103) = -2.07$, $p < .001$), were more likely to have a primary caretaker who worked outside of the home (Tallahassee = 88%, Gainesville = 64.9%; $\chi^2 = 7.72$, $df = 1$, $p < .01$), and had greater Hollingshead scores ($M_{\text{Tallahassee}} = 37.29 \pm 11.95$, $M_{\text{Gainesville}} = 32.70 \pm 12.15$; $t(106) = -1.98$, $p < .05$). Therefore, site was included as a variable in the models.

3.2. Predictors of Study Completion Status

Table 1 provides the results of univariate tests of differences based on study completion status (i.e., On-Time Completers, Late Completers, Withdrawals) by site, treatment group and pre-randomization demographic and disease-related variables. Table 2 provides the pre-randomization primary caregiver depressive symptoms, diabetes-specific stress and child health-related quality of life univariate tests between the three study completion status groups. Study withdrawals were more common at the Gainesville site and were characterized by a larger percentage of primary caretakers who did not work outside the home. Reports from children who subsequently withdrew from the study indicated poorer diabetes-related quality of life and poorer school-related quality of life. On-Time Completers were more likely to have a primary caretaker with some college education as well as private insurance. Late Completers were more often male and more likely to have a primary caretaker with mild to moderate levels of depressive symptoms.

3.3. Multivariate Predictors of Study Completion Status

Multinomial logistic regression was used to determine which predictors that were significant ($p < .05$) or near significant ($p < .10$) in the univariate tests remained significant when entered in a multivariate model. In the initial multivariate model, we excluded the child self-report measures so as to include the full sample since only children 5 years of age or older completed these measures. Both site and primary caregiver education were no longer significant when placed in a multivariate model. Primary caregiver working outside the home (yes/no) ($\chi^2 = 8.83$, $df = 2$, $p < .05$); type of insurance (private/public) ($\chi^2 = 14.37$, $df = 2$, $p < .001$); and sex of child ($\chi^2 = 20.73$, $df = 2$, $p < .001$) remained significant predictors of study completion status

in the multivariate analysis. Primary caretaker mild-moderate CES-D scores (yes/no) approached significance ($\chi^2 = 4.83$, $df = 2$, $p = .089$).

Next, we added the child self-report diabetes quality of life scores (i.e., DQOL subscale scores) to the multinomial logistic regression model. This reduced the sample size from 108 to 80, since children less than 5 years of age did not complete this measure. Separate models were run for the child self-report DQOL Impact and Worry subscales and the DQOL Total score. Although all of the DQOL subscales, remained significant, the remainder of the multivariate results reported here include only the DQOL Total score. Thus, in addition to the child self-report DQOL Total score ($\chi^2 = 7.83$, $df = 2$, $p < .02$), sex of the child ($\chi^2 = 16.40$, $df = 2$, $p < .001$), child's insurance status ($\chi^2 = 10.72$, $df = 2$, $p < .01$), and mild to moderate primary caregiver depressive symptoms ($\chi^2 = 6.82$, $df = 2$, $p < .03$) remained significant in the multivariate model; primary caregiver working outside the home ($\chi^2 = .88$, $df = 2$, $p < .64$) was no longer significant.

Finally, we added the PedsQL School subscale score to the multivariate model. In the univariate analysis, the PedsQL School subscale was a near significant predictor of study completion status. In the multivariate model, it became a significant predictor ($\chi^2 = 6.65$, $df = 2$, $p < .04$), along with sex of the child ($\chi^2 = 17.67$, $df = 2$, $p < .001$), and the child's insurance status ($\chi^2 = 11.33$, $df = 2$, $p < .01$). Mild to moderate primary caregiver depressive symptoms ($\chi^2 = 5.10$, $df = 2$, $p < .08$) approached significance. Similar to the child-report DQOL analysis, primary caregiver working outside the home was no longer significant when included in this multivariate analysis.

Child self-report DQOL Total and PedsQL School subscale scores were highly correlated ($r = -.61$, $p < .001$) in this sample. Due to multicollinearity, including both of these child-report measures in the same multivariate analysis yielded a nonsignificant result for both measures.

3.3. Comparison of Univariate and Multivariate Results

Site was a significant predictor in the univariate tests but became nonsignificant in the multivariate model. Sites differed significantly in both the percent of primary caretakers working outside the home and SES. When both primary caretaker working outside the home and SES variables were included in the multivariate model, site was no longer significant.

Primary caregiver education was also a significant predictor in the univariate model but became nonsignificant in the multivariate model. In this sample, primary caregiver education was positively correlated ($r = .42$, $p < .01$), with type of insurance. When both were entered into the same multivariate model, only type of insurance remained significant.

4. Discussion

The 25% withdrawal rate found in this study is comparable to withdrawal rates reported in other long term (1 year or longer) randomized clinical trials with pediatric populations [3-5, 10,23-25], including those involving participants with diabetes [26]. Participants withdrew from the study at a slow but steady rate of 1-3 participants per month during a 24-month period. Although the study intervention was 5 sessions which could have been accomplished in a 1-year interval, study design requirements (possible randomization to a delayed treatment group, pre- and post-treatment assessments) extended the length of the study protocol. The pattern of withdrawals suggests that study interventions delivered during regular clinic visits, that can be accomplished in 1 year or less, may be associated with withdrawal rates closer to 10%, enhancing the validity of study findings. Investigators working with children seen at 3-month intervals may want to carefully design their clinic-based interventions for delivery in three to four visits.

We were able to determine reasons for attrition for nearly 40% of those who withdrew and those reasons were comparable to those reported in other studies [3]. Only approximately half of the pediatric studies using randomized clinical trial design report withdrawal reasons and none of those involving patients with diabetes reported reasons [3]. Greater consideration of reasons for withdrawal in complex clinical trial designs may guide the design of future trials and improve study retention.

Study results also support Bender's, Zebracki's and their colleagues' recommendation that on-time study completers, those with erratic attendance, and study drop-outs be treated as three separate groups [9,10]. We found study completion to be bimodal with approximately half of the sample completing the study close to the expected completion date and the remaining participants taking an average of 10 additional months to complete the study.

In this study, children with college-educated primary caregivers who had private health insurance were more likely to complete the study on-time. Others have reported a similar association between parent education and study completion [5,7,10], although this association is not consistently reported particularly in samples with little variability in the parents' educational level [7,9]. Type of health insurance (public or private) has not been examined as a predictor of study attrition but may be a good indicator of SES, at least in the United States. Poor education and low SES are commonly associated with poor adherence to diabetes clinic visits [27] so it is not surprising that insurance would be associated with timely completion of the study protocol. In this study, primary caregiver education and insurance type were highly correlated, suggesting that they may both be serving as an indicator of the family's SES. When both were considered in the same multivariate model, type of health insurance proved to be the better predictor. It is important to note, that all children in this study were insured by a public or private insurance entity and no child was denied clinical care based on insurance status. In other words, type of insurance was not associated with differences in access to health care, suggesting that it is likely an indicator of SES.

About half of the study completers took a very long time to complete the study protocol, finishing an average of 10 months after their projected date of study completion. Late Completers were characterized by male gender and primary caretakers with mild to moderate symptoms of depression. The mechanisms underlying these associations are unclear. Since boys are more likely to exhibit behavior problems than girls [28,29] it may be more challenging for families to complete demanding protocols with male children. Similarly, a primary caretaker who is experiencing mild to moderate depression may lack the energy to adhere to the study protocol in a timely manner [7,30]. Clearly, more research is needed.

Children who withdrew from the study were more likely to have primary caretakers who did not work outside the home and reported poorer diabetes-related and school-related quality of life at the study's inception. While most of the primary caregivers in this study were employed outside the home, unemployed primary caregivers were more common in the group of children who subsequently withdrew from the study. Few previous studies have examined primary caregiver employment status as a predictor of study completion or withdrawal. Zebracki and colleagues [10] did not find employment status to be linked to study drop-out. In contrast, Moser and colleagues [7] reported results opposite to our own; most caregivers in their study were employed outside of the home but unemployed caregivers were far more common in the study completion group compared to the study withdrawal group. Moser and colleagues' sample – caregivers of newborns at risk for cardiopulmonary arrest – was very different from the current study sample, suggesting that caregiver employment status may be associated with study participation in different ways depending on the child's age, time since diagnosis, health status, and treatment or monitoring demands placed on the caregiver.

While we found poorer child-reported diabetes quality of life and poorer school-related quality of life were associated with study drop-out, previous studies have used traditional measures of psychological functioning, not quality of life indicators, to predict study completion or withdrawal. For example, Bender and colleagues [9] found child anxiety and depression to be associated with erratic study participation and withdrawal while Strunk and colleagues [8] reported that mild anxiety was associated with better study protocol adherence. The relation between the child's disease-specific quality of life and the child's more general psychological functioning is of considerable interest. In this study, poorer diabetes-specific quality of life was associated with poorer child-reported school-related quality of life and both measures were associated with study withdrawal. Examples of items on the school-related quality of life subscale include the degree to which one misses school due to poor health and missing school to attend doctor's appointments, providing a link between these two measures – children who are having difficulty managing their diabetes successfully may miss more school, resulting in poorer disease-specific and school-related quality of life. Taken together, our findings demonstrating an association between quality of life and study completion and prior research demonstrating links between general psychological functioning and study completion [8,9] suggest that both may be beneficial as screening measures to determining risk for drop-out in clinical trials. In addition, inclusion of diabetes-specific and generic measures of quality of life seems warranted [31].

Given the considerable amount of literature showing discrepancies between caregiver-child agreement on measures of health-related quality of life [32], it is not surprising that child-reported quality of life measures predicted study withdrawal, but primary caregiver-proxy measures did not. These findings highlight the importance of collecting information directly from the child participant as primary caregivers' awareness and perceptions of children's health concerns may differ from their children's [32].

We did not find child age, primary caregiver age, or child health status to be predictive of study completion or withdrawal. Both Bender [4] and Strunk [8] and their colleagues found child age to be associated with erratic study compliance, with older children showing poorer attendance. It is interesting to note that the mean child age in our Late Completer group (8.8 years) was almost one year greater than the On-Time Completer group (7.8 years), which is consistent with these earlier studies' findings. Two prior studies documented an association between young caregiver age and study protocol adherence or withdrawal [5,10]. We did not find this to be the case, but our study sample was considerably older than these studies' samples, which may have precluded our ability to detect this effect. Previous studies' findings linking child health status measures to study protocol adherence or withdrawal have been inconsistent. In the pediatric asthma population, Bender and colleagues [9] found mild asthma to be associated with erratic study attendance, whereas, in a different study they reported the opposite results – children with more reactive airways were more likely to withdraw [4]. Zebracki and colleagues [10] reported no association between asthma severity and study drop-out. Our study did not find a link between the child's disease duration or the child's HA1C at study inception with study withdrawal or completion. Riekart and Drotar [6] also found no association between HA1C and study participation in their sample of children with type 1 diabetes. The link between child health status and study participation appears to be complex and likely varies depending on the characteristics of the patient population entered into the trial as well as the nature of the treatment offered.

Limitations of this study include its relatively small sample size and restricted age range, limiting statistical power and generalizability to older patient populations. Nevertheless, the findings reported here have implications for the design and conduct of future clinical trials with pediatric populations. Investigators may wish to screen the target study populations on both demographic and psychological variables to exclude, or provide additional support to those

families most likely to drop out of the study or fail to follow the study protocol. Additional areas to assess include plans to relocate or commitments to other research studies which were reasons cited for withdrawal in our study and other studies as well [3]. The results of this study suggest that when conducting clinical trials in type 1 diabetes important risk-factors to identify include male sex of the child, public health insurance, caregiver education and unemployment status, caregiver depression and child-reported diabetes and school quality of life. Identification of these risk factors may help reduce study attrition by excluding such high risk patients from the study during the recruitment phase of the trial. However, many investigators wish to test a treatment on a representative sample of the target population. This was certainly the case in the HANDling Diabetes Study. Excluding “high-risk” families would prevent us from assessing the adherence intervention’s effectiveness in the patient population we hoped to help. Identifying “high risk” families may permit study investigators to establish procedures to help prevent study withdrawal. The fact that our Late Completers finished the study protocol an average of 10 months after their target completion date suggests that our efforts to work with families to keep them in the study were effective. However, our efforts may have been considerably improved if we had been able to identify such “high-risk” families at study inception. For example, efforts to provide additional support to families or to initiate discussions early in the study to determine participants’ challenges would have allowed us to problem-solve with them to improve the chances that they would complete the study.

5. Conclusion

In this study of an adherence intervention delivered as part of the routine care in a pediatric diabetes clinic, we found that primary caregiver and child demographic and psychological functioning measured prior to study group randomization predicted subsequent study completion and withdrawal. We found that categorizing participants into separate groups based on completion status (on-time completers v. those with erratic study attendance) is a useful data analytic strategy. We conclude that pre-randomization screening of potential study participants on both demographic and psychological variables (e.g., child sex, caregiver employment and educational status, caregiver depression, child quality of life, etc.) may help identify those who are at greatest risk for study withdrawal or poor study protocol adherence. Investigators may want to use this information to exclude those families at “high risk” for study withdrawal from their investigation. Alternatively, in an effort to assure a more representative sample, they may want to use this information to develop retention strategies aimed at this particular “high-risk” population. Strategies useful to investigators wishing to retain these “high-risk” families in the study protocol include: screening patients for drop-out risk prior to randomization and tracking them closely throughout the study, minimizing participant burden, flexible appointment scheduling, providing incentives, social support, and contact between appointments, and providing a detailed orientation session [3,4,33-35]. Although this study focused on predictors of study withdrawal and protocol adherence, it is likely that the same factors predict patient clinic attendance and adherence with the medical regimen. Consequently, identification of these risk factors as part of routine care may help providers better address the particular challenges faced by high risk families caring for a child with a chronic disease.

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References

1. Shadish, WR.; Cook, TD.; Campbell, DT. Experimental and quasi-experimental designs for generalized causal inference. Boston, MA: Houghton Mifflin; 2002.
2. Marcellus L. Are we missing anything? Pursuing research on attrition. *Can J Nurs Res* 2004;36:82–98. [PubMed: 15551664]
3. Karlson CW, Rapoff MA. Attrition in Randomized Controlled Trials for Pediatric Chronic Conditions. *J Pediatr Psychol*. 200810.1093/jpepsy/jsn122
4. Bender BG, Ikke DN, DuHamel T, Tinkleman D. Retention of asthmatic patients in a longitudinal clinical trial. *J Allergy Clin Immunol* 1997;1992:197–203. [PubMed: 9042045]
5. Janus M, Goldberg S. Factors influencing family participation in a longitudinal study: comparison of pediatric and healthy samples. *J Pediatr Psychol* 1997;22:245–62. [PubMed: 9114646]
6. Rieker KA, Drotar D. Who participates in research on adherence to treatment in insulin-dependent diabetes mellitus? Implications and recommendations for research. *J Pediatr Psychol* 1999;24:253–8. [PubMed: 10379140]
7. Moser DK, Dracup K, Doering LV. Factors differentiating dropouts from completers in a longitudinal, multicenter clinical trial. *Nurs Res* 2000;49:109–16. [PubMed: 10768588]
8. Strunk RC, Bender BG, Young DA, et al. Predictors of protocol adherence in a pediatric asthma clinical trial. *J Allergy Clin Immunol* 2002;110:596–602. [PubMed: 12373267]
9. Bender BG, Ellison MC, Gleason M, et al. Minimizing attrition in a long-term clinical trial of pediatric asthma. *Ann Allergy Asthma Immunol* 2003;91:168–76. [PubMed: 12952111]
10. Zebracki K, Drotar D, Kirchner HL, et al. Predicting attrition in a pediatric asthma intervention study. *J Pediatr Psychol* 2003;28:519–28. [PubMed: 14602842]
11. Hollingshead, AB. Four Factor Index of Social Status. New Haven: Author; 1975.
12. Blanc MH, Barnett DM, Gleason RE, Dunn PJ, Soeldner JS. Hemoglobin A1c compared with three conventional measures of diabetes control. *Diabetes Care* 1981;43:349–53. [PubMed: 7344883]
13. Radloff L. The CES-D Scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement* 1977;1:385–401.
14. McLennan JD, Kotelchuck M, Cho H. Prevalence, persistence, and correlates of depressive symptoms in a national sample of mothers of toddlers. *J Am Acad Child Adolesc Psychiatry* 2001;40:1316–23. [PubMed: 11699806]
15. Quittner AL, Glueckauf RL, Jackson DN. Chronic parenting stress: Moderating versus mediating effects of social support. *Journal of Personality and Social Psychology* 1990;59:1266–1278. [PubMed: 2283593]
16. Quittner AL, Opipari LC, Regoli MJ, Jacobsen J, Eigen H. The impact of caregiving and role strain on family life: Comparisons between mothers of children with cystic fibrosis and matched controls. *Rehabilitation Psychology* 1992;37:289–304.
17. Quittner AL, Espalage DL, Opipari LC, Carter BD, Eigen H. Role strain in couples with and without a chronically ill child: Associations with marital satisfaction, intimacy, and daily mood. *Health Psychol* 1998;17:112–124. [PubMed: 9548702]
18. Johnson SB, Meltzer L. Disentangling the effects of current age, onset age, and disease duration: Parent and child attitudes toward diabetes as an exemplar. *J Pediatr Psychol* 2002;27:77–86. [PubMed: 11726682]
19. Varni, JW. PedsQL 4.0. Mapi Research Trust; Lyon, France: 1998.
20. Diabetes Control and Complications Trial Group. Reliability and validity of a diabetes quality-of-life measure for the Diabetes Control and Complication Trial (DCCT). *Diabetes Care* 1988;11:725–732. [PubMed: 3066604]
21. Ingersoll GM, Hibbard RA, Kronz KK. Pediatrics residents' attitudes about insulin-dependent diabetes mellitus and children with diabetes. *Acad Med* 1990;65:643–5. [PubMed: 2261041]
22. Perwien, AL.; Gallo, L.; Johnson, SB. Quality of life in children with insulin dependent diabetes mellitus. Poster presented at the 106th Annual Convention of the American Psychological Association; San Francisco, CA. 1998.

23. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, et al. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. The Dutch Chronic Non-specific Lung Disease Study Group. *Am Rev Respir Dis* 1992;146:547–54. [PubMed: 1355640]
24. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92:64–77. [PubMed: 8516087]
25. Waalkens HJ, Van Essen-Zandvliet EE, Hughes MD, et al. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. The Dutch CNSLD Study Group. *Am Rev Respir Dis* 1993;148:1252–7. [PubMed: 8239161]
26. Ellis DA, Naar-King S, Frey M, et al. Multisystemic treatment of poorly controlled type 1 diabetes: effects on medical resource utilization. *J Pediatr Psychol* 2005;30:656–66. [PubMed: 16260435]
27. Griffin SJ. Lost to follow-up: the problem of defaulters from diabetes clinics. *Diabet Med* 1998;15 (Suppl 3):S14–24. [PubMed: 9829764]
28. Coie, JD.; Dodge, KA. Aggression and antisocial behavior. In: Eisenberg, N., editor. *Handbook of child psychology: Social, emotional, and personality development*. Wiley; New York: 1998. p. 779-862.
29. Hinshaw, SP.; Lee, SS. Conduct and Oppositional Defiant Disorders, in *Child psychopathology*. 2. Mash, EJ.; Barkley, RA., editors. The Guilford Press; New York, NY: 2003. p. 182-183.
30. Bartlett SJ, Krishnan JA, Riekert KA, et al. Maternal depressive symptoms and adherence to therapy in inner-city children with asthma. *Pediatrics* 2004;113:229–237. [PubMed: 14754931]
31. Nansel TR, Weisberg-Benchell J, Wysocki T, et al. Quality of life in children with Type 1 diabetes: a comparison of general and diabetes-specific measures and support for a unitary diabetes quality-of-life construct. *Diabet Med* 2008;25:1316–23. [PubMed: 19046222]
32. Upton P, Lawford J, Eiser C. Parent-child agreement across child health-related quality of life instruments: a review of the literature. *Qual Life Res* 2008;17:895–913. [PubMed: 18521721]
33. Senturia YD, Mortimer KM, Baker D, et al. Successful techniques for retention of study participants in an inner-city population. *Control Clin Trials* 1998;19:544–554. [PubMed: 9875834]
34. Coday M, Boutin-Foster C, Sher TG, et al. Strategies for retaining study participants in behavioral intervention trials: Retention experiences of the NIH behavior change consortium. *Annals of Behavioral Medicine* 2005;29(Suppl):55–65. [PubMed: 15921490]
35. Germann JN, Kirschenbaum DS, Rich BH. Use of an orientation session may help decrease attrition in a pediatric weight management program for low-income minority adolescents. *Journal of Clinical Psychology in Medical Settings* 2006;13:177–187.

Figure 1. HANDling Diabetes Study Design

Note. 3 months elapsed between each clinic visit. In addition, between each clinic visit, three telephone recall interviews were completed. For the Delayed Treatment Group, Intervention sessions started 9 months following enrollment in the study.

Table 1
Study-Related, Demographic, and Disease-Related Variables by Completion Status

Variable	Total N(%) or M(SD)	On-Time Completers N(%) or M(SD)	Late Completers N(%) or M(SD)	Withdrawals N(%) or M(SD)	Test Statistic
Study-Related					
Site					
<i>Tallahassee</i>	51 (47.2%)	24 (58.5%)	19 (48.7%)	8 (28.6%)	$\chi^2 = 6.049^a$
<i>Gainesville</i>	57 (52.8%)	17 (41.5%)	20 (51.3%)	20 (71.4%)	
Intervention Group					
<i>Delayed</i>	53 (49.1%)	17 (41.5%)	21 (53.8%)	15 (53.6%)	$\chi^2 = 1.532$
<i>Immediate</i>	55 (50.9%)	24 (58.5%)	18 (46.2%)	13 (46.4%)	
Demographics					
Child Age (years)	8.1 (2.5)	7.8 (2.4)	8.8 (2.1)	7.8 (2.9)	F=2.392
Primary Caregiver Age (years)	37.6 (8.3)	38.0 (8.2)	37.8 (8.9)	36.8 (8.1)	F=0.182
Hollingshead	34.9 (12.2)	36.0 (9.8)	34.3 (11.9)	33.9 (15.7)	F=0.303
Miles to Clinic	50.3 (46.7)	54.0 (55.1)	44.5 (36.2)	52.6 (46.9)	F=0.439
# of Parents in Home	1.7 (0.5)	1.7 (0.5)	1.7 (0.4)	1.7 (0.5)	F=0.355
# of People in Home	4.0 (1.1)	3.8 (1.0)	4.1 (1.3)	4.0 (0.9)	F=0.893
# of Children in Home	2.1 (0.9)	2.0 (0.9)	2.2 (1.2)	2.1 (0.7)	F=0.596
Child's Sex					
<i>Female</i>	58 (53.7%)	28 (68.3%)	13 (33.3%)	17 (60.7%)	$\chi^2 = 10.572^b$
<i>Male</i>	50 (46.3%)	13 (31.7%)	26 (66.7%)	11 (39.3%)	
Primary Caregiver's Sex					
<i>Female</i>	90 (83.3%)	34 (84.8%)	32 (80.0%)	24 (85.2%)	$\chi^2 = 0.165$
<i>Male</i>	18 (16.7%)	7 (15.2%)	7 (20.0%)	4 (14.8%)	
Primary Caregiver Ethnicity					
<i>Caucasian</i>	92 (85.2%)	33 (80.5%)	35 (89.7%)	24 (85.7%)	$\chi^2 = 0.505$
<i>Non-Caucasian</i>	16 (14.8%)	8 (19.5%)	4 (10.3%)	4 (14.3%)	
Primary Caregiver Marital Status					
<i>Not Married</i>	29 (26.9%)	9 (22.0%)	10 (25.6%)	10 (35.7%)	$\chi^2 = 1.650$
<i>Married</i>	79 (73.1%)	32 (78.0%)	29 (74.4%)	18 (64.3%)	
Primary Caregiver Work Outside of Home					

Variable	Total N(%) or M(SD)	On-Time Completers N(%) or M(SD)	Late Completers N(%) or M(SD)	Withdrawals N(%) or M(SD)	Test Statistic
No	26 (24.3%)	10 (24.4%)	5 (13.2%)	11 (39.3%)	$\chi^2 = 5.983^a$
Yes	81 (75.7%)	31 (75.6%)	33 (86.8%)	17 (60.7%)	
Primary Caregiver Education					
≤High school	33 (30.6%)	7 (17.1%)	17 (43.6%)	9 (32.1%)	$\chi^2 = 6.668^a$
≥Some college	75 (69.4%)	34 (82.9%)	22 (56.4%)	19 (67.9%)	
Health Insurance					
Public	42 (38.9%)	9 (23.9%)	21 (57.1%)	12 (40.7%)	$\chi^2 = 8.806^a$
Private	66 (61.1%)	32 (76.1%)	18 (42.9%)	16 (59.3%)	
Disease-Related					
Disease Duration (years)	3.9 (2.61)	3.44 (2.16)	3.85 (2.72)	4.62 (2.98)	F=1.690
HAIC	8.3 (1.1)	8.2 (1.2)	8.3 (1.2)	8.4 (1.1)	F=0.238

^a $p < .05$,
^b $p < .01$.

Table 2
Primary Caregiver Psychological and Child Quality of Life Variables by Completion Status

Variable	All Participants N(%) or M(SD)	On-Time Completers N(%) or M(SD)	Late Completers N(%) or M(SD)	Withdrawals N(%) or M(SD)	Test Statistic
Primary Caregiver Psychological					
CES-D					
CES-D ≤ 15	71 (67.6%)	28 (73.7%)	21 (53.8%)	22 (78.6%)	$\chi^2 = 8.65^d$
CES-D = 16-22	18 (17.1%)	4 (10.5%)	12 (30.8%)	2 (7.1%)	
CES-D ≥ 23	16 (15.2%)	6 (15.8%)	6 (15.4%)	4 (14.3%)	
CES-D Total Score ^a	12.4 (9.6)	9.9 (10.4)	14.8 (9.2)	12.4 (8.3)	F=2.611 ^d
Family Stress Scale ^a	30.3 (10.4)	29.0 (10.3)	30.2 (10.4)	32.4 (10.5)	F=0.895
Family Interruption Scale ^b	47.5 (9.9)	48.7 (8.6)	47.2 (10.0)	46.2 (11.5)	F=0.524
Child Quality of Life					
DQOL Primary Caregiver-Proxy ^a					
Total	95.6 (19.7)	92.8 (18.9)	94.8 (18.6)	100.5 (22.2)	F=1.233
Satisfaction	36.1 (9.5)	35.4 (9.7)	35.4 (8.2)	38.3 (10.9)	F=0.933
Impact	45.2 (7.9)	43.6 (7.3)	45.6 (7.5)	46.7 (9.1)	F=1.372
Worry	14.6 (5.6)	14.2 (4.7)	14.3 (5.6)	15.6 (6.8)	F=0.578
DQOL Child Self-Report ^a					
Total	99.0 (27.5)	96.1 (24.8)	92.7 (24.8)	112.9 (31.2)	F=3.959 ^c
Satisfaction	32.5 (11.5)	32.1 (10.3)	30.3 (10.9)	36.5 (13.6)	F=1.943
Impact	49.2 (11.8)	48.0 (12.0)	46.7 (10.7)	54.7 (11.7)	F=3.352 ^c
Worry	17.5 (8.1)	16.6 (7.7)	15.7 (6.6)	21.7 (9.6)	F=4.051 ^c
PedsQL Primary Caregiver-Proxy ^b					
Total	0.77 (0.16)	0.79 (0.15)	0.77 (0.18)	0.75 (0.14)	F=0.549
Physical	0.84 (0.16)	0.84 (0.15)	0.83 (0.19)	0.85 (0.14)	F=0.040
Emotional	0.72 (0.18)	0.74 (0.18)	0.76 (0.17)	0.66 (0.18)	F=2.200
Social	0.82 (0.19)	0.83 (0.17)	0.84 (0.18)	0.80 (0.22)	F=0.256
School	0.73 (0.22)	0.76 (0.20)	0.71 (0.22)	0.70 (0.25)	F=0.599
PedsQL Child Self-Report ^b					
Total	0.72 (0.16)	0.72 (0.16)	0.74 (0.17)	0.69 (0.16)	F=0.594

Variable	All Participants N(%) or M(SD)	On-Time Completers N(%) or M(SD)	Late Completers N(%) or M(SD)	Withdrawals N(%) or M(SD)	Test Statistic
Physical	0.77 (0.18)	0.80 (0.16)	0.78 (0.17)	0.72 (0.21)	F=1.287
Emotional	0.68 (0.23)	0.65 (0.25)	0.74 (0.19)	0.66 (0.24)	F=1.461
Social	0.78 (0.22)	0.78 (0.20)	0.77 (0.23)	0.78 (0.22)	F=0.009
School	0.67 (0.18)	0.69 (0.15)	0.70 (0.18)	0.59 (0.21)	F=3.057 ^d

^aHigher scores indicate increased stress, depression, and worse quality of life

^bHigher scores indicate better quality of life and less family disruption

^c $p < .05$;

^d $p < .10$