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RECRUITMENT AND RETENTION STRATEGIES IN A CLINICAL TRIAL FOR CHILDREN WITH CHRONIC HEPATITIS C INFECTION

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Abstract

Successful strategies for recruitment and retention (R & R) in pediatric trials are needed. The purpose of our study was to analyze the effectiveness of R&R in a trial for children with hepatitis C. Recruitment strategies were 1) Initial (months 0 – 12) and 2) Extra effort (months 13 – 18). Initial strategies enrolled 70/114 (61%) of patients. Extra effort strategies included: 1) radio broadcasts, 2) contact with adult hepatologists, 3) dissemination of study material and 4) modification of the exclusion criteria. The overall retention rate was 84% at two years. Lessons learned will be valuable in designing future pediatric trials.

INTRODUCTION

There are about 23 – 42,000 children with chronic hepatitis C (CHC) infection in the United States. At least some of these children are at risk for adverse medical outcomes including hepatocellular carcinoma and end stage liver failure, eventually requiring transplant and most are at the risk of social stigmatization. There have been a number of clinical antiviral trials in children with CHC. Most studies have been retrospective and have involved small sample sizes, frequently with no comparison group because of small numbers of pediatric patients with CHC. Thus, strategies to recruit and retain children with CHC in a clinical trial have not been described. Effective recruitment and retention of participants is an essential component of the workload in conducting a prospective large-scale multi-center clinical trial and presents a methodological challenge. Investigators have to contend with the usual difficulties encountered when recruiting adults with CHC into an interferon based treatment

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trial, including, the lengthy 6 – 12 month treatment, the numerous side effects, and the negative impact of the treatment on usual activities. In addition, investigators involved with trials in children need to take into consideration the factors specific to the pediatric population, including the need for both children and caregivers to comply with treatment, the child's resistance to injections, and age-related differences in understanding the need for treatment (Murray, et. al., 2007). The diverse backgrounds and needs of children affected by CHC have to be considered along with the common reluctance of families to enroll their children in a clinical trial.

Retention of participants requires considerable effort on the part of the children and their families due to absence from school and work, respectively. Studies have shown that it is difficult to recruit and retain children in treatment trials. Parents are furthermore often unwilling to keep their children on treatment regimens which include significant side effects. In discussing the difficulties of conducting clinical trials in children infected with human immunodeficiency virus, Cohen et al (1997) mentioned family stressors, difficulties in coordinating different investigators from different departments, as well as ethical issues. Strunk et al (2002) analyzed factors affecting compliance to pediatric asthma treatment protocols 20 to 40 months in duration and found that 44% of the children had difficulty adhering to the patient diary, appointments, and/or commitment to the study protocol.

Factors having a negative effect on compliance included the older age of the child and the long duration of the study. In describing attrition rates in 40 different pediatric cognitive therapy trials for chronic illnesses including asthma, diabetes, sickle cell anemia, cystic fibrosis, Karlson and Rapott (2009) noted that the mean attrition rate was 20% (range 0-54%) for initial follow-up and 32% (range 0-59%) for extended follow-up. They recommended strategies to improve retention including tailoring recruitment to the study population, providing personalized feedback, maintaining consistent study procedures, providing incentives, and using intensive tracking measures.

The purpose of the present manuscript was to describe the strategies we found helpful in recruiting and retaining children with CHC in a treatment trial of 24 to 48 weeks of therapy as well as two annual follow up visits after discontinuation of treatment. We learned that simply recruiting patients within our own centers was not sufficient to achieve target enrollment within the target time frame and that extra efforts were needed. These efforts are described as are the strategies utilized to achieve high retention rates (84% at the two year follow up).

METHODS

Enrollment process in the PEDS-C trial

PEDS-C (Pegylated Interferon +/- Ribavirin in Children with Chronic Hepatitis C Viral (HCV) Infection), is the first multi-center, double blind, placebo controlled, randomized clinical trial for children with CHC (Schwarz, et.al, 2011). The purpose of this trial was to determine the safety and efficacy of pegylated-interferon alfa-2a (PEG-2a) with ribavirin (RV) versus PEG-2a alone for the treatment of CHC in children. The study was conducted at 11 centers across the United States. The target enrollment was 114 children between the ages of 5 to 17 years to be enrolled over a 12 month period. Study participation was consistent with the Investigational Review Board (IRB) requirements at all the participating centers. The PEDS-C study was monitored closely by a Data Safety and Monitoring Board prior to initiation and during the course of the study. Consent forms were approved by the IRB of all the centers and met the requirement of a 6th-8th grade readability level. The consent form was written in simple language and included the statement: "this project has been explained to my child in my presence and in language he/she can understand." Assent

forms were required for children less than 14 years old to make accommodations for younger children and other children who may have variations in reading levels who we enrolled in our study. Children younger than 7 years old (ages 5 and 6 years) were informed about the study in simple language in the presence of parents but were not required to sign their names given their young age. For patients between the ages of 13 and 17 years, the following statement was added to the consent: "He/she has been encouraged to ask questions now and in the future about the research study."

Families were informed about the study by the site principal investigator and study coordinator. The majority of the study coordinators were experienced pediatric research nurses; there was also one pediatric nutritionist and one foreign medical graduate who served as coordinators. Parents and patients were able to ask questions and have them answered before they signed consent. No direct financial compensation was given to the research participants and families. The results of this trial were recently published.

The initial screening visit for recruitment of children in our study lasted approximately 2-3 hours. Eligibility of research subjects were determined based on these inclusion criteria: age 5 to 17 years with CHC infection documented by the presence of the hepatitis C virus in plasma on two occasions at least 6 months apart and chronic liver disease as indicated by inflammation and/or fibrosis consistent with CHC on a liver biopsy obtained within the past 24 months. Other details about inclusion and exclusion criteria are available at <http://www.ClinicalTrials.gov> (PEDSC). Eligible research subjects were seen at the clinical site within 35 days of screening, for their baseline visit. This visit lasted approximately 2-3 hours and included detailed quality of life questionnaires, growth and body composition measurements, physical examination and venipuncture for laboratory assessment. Parental instructions on giving injections and information on the study drugs were also provided during this visit.

Visit schedule and content

Once medication therapy was initiated, close monitoring was instituted. Research study visits were conducted at weeks one, three, five, eight and then every four weeks until the medication was discontinued by the physician or the medication administration protocol ended. Vital signs, a symptom-directed physical examination, history of adverse events, concomitant medications, compliance with study medications and blood samples were obtained at each visit. Compliance was assessed by a self-report patient diary (completed by either the patient or the care giver) and by vial and pill counts (completed by the site pharmacist or study coordinator). Depending on treatment and response, total therapy could last from 24-72 weeks. The protocol was designed for each center to enroll between 5 and 15 children, for a total recruitment of 114 subjects.

Recruitment and retention strategies

Recruitment and recruitment strategies occurred in two stages: 1) Initial (months 0 – 12), the original projected enrollment period and 2) Extra effort (months 13 – 18), the extended time necessary to achieve the enrollment goal of 114 subjects. Retention strategies were elaborated during the course of the study. The first child was screened in December of 2004. Enrollment was to be accomplished in 12 months. However, the last child was enrolled in June 2006 by using "extra effort" strategies to enhance enrollment.

RESULTS

Recruitment

During the initial phase (the 12 months originally planned for recruitment), 70 participants (61% of the goal) were recruited. The subsequent “extra effort” phase required employing additional efforts and another 6 months to complete the recruitment of 114 patients. Figure 1 shows screening and recruitment of the PEDS-C patients compared to our goal. Initial recruitment focused on existing clinic patients. The principal investigators also sent out IRB-approved letters to community physicians describing the study and encouraging referrals of patients and families that might be interested. Physician care, medication, laboratory evaluations, and supplies were provided free of charge. Other traditional resources for recruitment included the creation of a study website which families and referring physicians could access to gain more information about the trial. The study was also registered on the National Institute of Health (website at www.clinicaltrials.gov).

Our group of 11 pediatric hepatologists involved in the trial had originally estimated that we cared for approximately twice the number of children with CHC we needed to enroll in PEDS C. We therefore had not made special recruitment plans at the inception of the study. However, since only 61% of subjects were recruited in the initial year (Figure 1), extra effort strategies were implemented in November – December 2005 to enhance recruitment and meet the enrollment target. Increased community awareness of the study was accomplished through local radio shows by the principal investigator and contact with adult hepatologists at all sites by the investigators. A national presence was established at the annual meetings of the American Association of Study of Liver Disease and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, via a poster, a booth, and handouts. The trial was additionally advertised via the organization Parents of Kids with Infectious Disease, the Hepatitis Foundation International, and the American Academy of Pediatrics via “blast email.” All these efforts helped to increase awareness and widen our prospective patient population.

IRB-approved amendments were also made in the PEDS-C protocol to increase recruitment. The exclusion criteria were modified from “abnormal ceruloplasmin and alpha-1-antitrypsin” to “abnormally low ceruloplasmin or alpha-1-antitrypsin”, and the allowable interval between liver biopsy and screening was changed from 24 months to 36 months. Sites were also given permission to recruit more than 15 patients per site.

Additionally, an Exemption Committee was established for the rapid consideration of requested protocol exemptions for recruitment. The committee consisted of 4 Steering Committee site principal investigators and a member of the National Institute of Diabetes and Digestive and Kidney Diseases. The exemption request was submitted on a generic form and each voted upon by the committee within 1-2 days of submission. The exemptions were also submitted to the IRBs of all the participating sites and were approved. A total of 12 exemptions were requested and 10 were granted. Most were related to minor laboratory abnormalities, or biopsy and screening dates out of range by a few days. The protocol reflected any changes made on the basis of the exemptions which were also approved by the IRB of all participating sites in a timely fashion. The final strategies employed by the PEDS-C group were: allowing the option of using local laboratories for repeat laboratory testing, screening foster children for enrollment on a case by case basis with IRB approval from all the participating sites, and helping families with transportation by utilizing charity air transport. One patient enrolled at the University of California San Francisco site “commuted” from Hawaii to California through Miracle Flights and Angel Flights (services that uses volunteer pilots) as well as reimbursement for commercial airlines in order to fly patients to medical appointments that are required for treatment). These strategies made it

possible to recruit patients who were not local to any study sites, or in some cases, were otherwise initially not eligible.

Recruitment per study month is shown in Figure 2. Implementation of the extra effort strategies in November – December 2005 showed a boost in enrollment in March 2006 when 12 patients were recruited. By June of 2006, a total of 128 children, ages 5-18 years had been screened. Of these subjects, 12 were found to be ineligible and 2 withdrew prior to randomization. The goal of our study was to enroll 114 children in the first twelve months. With the extra effort strategies we succeeded in enrolling the 114 and randomizing them to treatment in the first 18 months, with 6-16 recruited per site.

Retention

A high retention rate of 84% was achieved in the PEDS-C study. Ninety-six of the original 114 randomized to therapy adhered to the study protocol as well as with the two years of follow-up (82% of those receiving PEG/RV and 86% of those receiving PEG plus placebo). Multiple strategies were used during the study to achieve this, including both traditional and innovative methods. Intensive ongoing education was provided for the participants and their families on the importance of remaining in the study for safety monitoring and to increase the success of the treatment. Principal investigators and study coordinators met with families at all visits to address any questions and concerns. The study sites also found that building close relationships with participants and their families, and making themselves available to the families outside of business hours proved to be helpful in patient retention. Having these close relationships built trust and fostered the family's comfort in sharing questions or concerns about the treatment. Personal relationships between the study staff and the participants and their families were particularly helpful in retention during our study.

The study sites also found that participant's guardians were highly motivated in continuing in the study and maintaining compliance to the study protocol. Other factors contributing to continuing in the study could be the stigma and parental guilt associated with a perinatally transmitted infection. The primary reasons for stigmatization in the pediatric population are similar to those in the adult population, including the limits imposed by a chronic disease as well as the fear (on the part of both parent and child) that the child will transmit the hepatitis C virus to others, and the assumption that the infected child has acquired disease because of illicit intravenous drug use (either by the child or secondarily, because the drug-abusing parent transmitted the infection to the child). Although stigma is usually considered in the negative context (e.g. having CHC can be associated with the above assumptions), in the case of our parent-child unit, fear that the child will be stigmatized for life unless the infection is eradicated may serve as a powerful motivation for the caregiver to seek treatment for the child. Several of the parents in the study were very proactive about getting their children treated because they themselves had been successful treated with pegylated interferon and ribavirin.

Some of the more innovative methods the study coordinators utilized to encourage retention of the child in the trial included allowing for flexibility in scheduling return study visits--within protocol guidelines--around the participant's and their family's school and work commitments. Study coordinators used close telephone call follow-up with families to ensure their understanding of what was expected with regards to return visits and compliance with study medication administration and dosage. Close contact was especially helpful when subjects needed to change their dose, missed doses, or took medication later than expected; subjects could call the coordinator at any time and obtain advice. Several of the investigator/coordinator teams attempted to be available around the clock. If an investigator was not going to be available by phone or pager, the site coordinator was able to contact any investigator in the PEDS-C group for emergency consultation.

Other factors

Another factor that insured the success of the study was a strong relationship between the research coordinators and data coordinating center, this provided cohesion to the study and allowed issues and problems to be dealt with immediately. Through constant contact with the study coordinator at the data coordinating center via email, phone calls, and monthly coordinator conference calls, problems and issues concerning the study were taken care of in real-time.

DISCUSSION

Various recruitment and retention strategies were developed for the PEDS-C study. Initial and extra effort strategies were employed to meet the recruitment goal in our large, multi center, complex pharmacotherapy trial in children with CHC. In spite of a high incidence of drug-related adverse events that included flu-like symptoms (88%), gastrointestinal symptoms (59%) and headaches (54%), the need for monthly study visits, frequent blood draws (sometimes weekly), and the great distances that some participants needed to travel, study-wide retention rate was remarkably high at 84%. Our recruitment goal was met six months after the estimated time of closing enrollment, a fact which further demonstrates the challenges in enrolling and keeping patients in pediatric trials.

Multiple strategies were used to educate and reduce family stress, explaining the high retention rate in spite of the high incidence of adverse events. These strategies also served to keep the patients and families engaged, involved, and motivated throughout the long treatment trial. It is felt that the high retention rate was due to the various traditional and creative methods employed by the study teams as well as the fact that the study coordinators were attentive, skilled in pediatric nursing as well as in the knowledge area of CHC, and readily available for their patients. We believe that the efforts of the study coordinators to retain patients in the study were also instrumental in achieving the high drug compliance rates previously noted; in the PEDS C study, patients reported taking 90% of the prescribed drug doses (Schwarz et. al., 2011).

The individual contribution of each of the recruitment and retention strategies employed cannot be assessed systematically. It was not clear whether any strategy worked better than the others because we do not know how much each factor worked towards enhancing enrollment. In future clinical trials it would be beneficial to create instruments to find out which recruitment and retention strategies would work the best, perhaps by creating a parent/child questionnaire as to whether a patient medication diary, flexibility in follow-up visits, reimbursement for travel, or other measures would be most likely to result in high recruitment and retention rates.

This was the first review of recruitment and retention strategies in the pediatric population with CHC. The significance of our study was two-fold: the first was that future pediatric trials in general might benefit from detailed planning as to a multi-pronged recruitment approach from the beginning instead of waiting several months into the trial when enrollment is waning; the second, specific to children with illnesses that require complicated therapeutic regimes such as PEG 2a and ribavirin, is that with energetic attention to the special requirements of the intervention trial (careful reexamination of inclusion and exclusion criteria, local laboratories for repeat blood drawing, some limited flexibility with visit schedule, as well as extra efforts to facilitate transportation to the site), high retention rates are possible.

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Abbreviations

(R and R)	recruitment and retention
C (CHC)	chronic hepatitis
(PEG-2a, ribavirin (RV)	pegylated-interferon alfa-2a
(IRB)	investigational review board

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Figure 1.
Screening and Enrollment of PEDS-C patients

Figure 2.
Monthly and cumulative recruitment in the PEDS-C study