Published in final edited form as:

Contemp Clin Trials. 2011 January ; 32(1): 10–15. doi:10.1016/j.cct.2010.10.004.

Experiences of Families with a Child, Adolescent, or Young Adult with Neurofibromatosis Type 1 and Plexiform Neurofibroma Evaluated for Clinical Trials Participation at the National Cancer Institute

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Abstract

Background—With increasing knowledge of the molecular pathways contributing to the progression of neurofibromatosis type 1 (NF1)-related plexiform neurofibroma (PN), the number of clinical trials for PNs has increased. However, little is known about experiences of families with children with NF1 participating in clinical trials.

Method—A 47-item anonymous survey, designed to assess experiences in research, was sent to parents with a child with NF1 and PNs who was evaluated at the National Cancer Institute (NCI) for a clinical trial.

Results—Sixty-four (85%) parents completed the paper or online questionnaire. Fifty-nine percent of the children were male; 44% were 11 years or older upon enrollment. Most parents reported understanding the purpose of the study, possible side effects, and their right to withdraw. Of respondents whose child had participated in a placebo-controlled trial, 100% said they understood the reason for the placebo at least somewhat. Seventy-four percent felt that study participation helped their child; most would “definitely” or “probably” participate in a future study, including a placebo-controlled trial, and particularly those assessing cognitive functioning or pain. Overall satisfaction with participation was high and correlated with fewer transportation problems, fewer study-related financial difficulties, and fewer school problems for the child ($p < .05$).

Conclusions—Most parents of children with NF1 who participated in research at the NCI reported a positive impact and would participate in future studies. Respondents identified several areas for improvement. This report may help plan future studies to optimize experiences of children and their families enrolled in clinical trials.

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Keywords

Clinical trials; research participation; Neurofibromatosis Type 1; children; families

Neurofibromatosis type 1 (NF1) is a genetic tumor predisposition syndrome (incidence 1:2500 – 1:3000) that is characterized by neurocutaneous findings, the development of tumors including benign nerve sheath tumors called plexiform neurofibromas (PNs), and neurocognitive deficits [1]. Research studies are essential for understanding the natural history of NF1 and the development of successful treatments for children and adolescents with NF1-related PNs. With increasing knowledge of the molecular pathogenesis of PNs, a very small but expanding number of medical treatment trials are open to enrollment for the treatment of individuals with PNs in the United States [2–4]. However, little is known about the factors that influence recruitment and retention in NF1 studies, including placebo-controlled trials (PCTs). Most clinical trials use a trial design and endpoints that are similar to those used in oncology clinical trials. However, while NF1-related PNs cause substantial morbidity [3,5], most PNs are not imminently life-threatening; thus, caregivers and patients may use different criteria for deciding whether to participate in clinical trials for NF1 compared to trials for children with refractory cancers.

Researchers have examined clinical trial participation among various pediatric populations with non-malignant conditions. For example, Dias et al. [6] surveyed 411 families participating in a pediatric clinical trial involving treatment for myopia progression. Responses to a 19-item questionnaire indicated that factors rated most positively included characteristics of the staff (e.g., staff friendliness, positive encouragement from staff) and the study (e.g., quality of care, convenience of appointments). The authors of the survey emphasize the importance of building positive relationships between staff and patients in maintaining high retention rates.

Only one study was found that addressed potential participation in clinical trials for patients with NF1. McQueen et al. [7] administered a 9-item survey to 59 adults with NF1 and 15 caregivers of pediatric patients. Results indicated that 80% of respondents would consider enrolling in a clinical trial. Among those willing to enroll, almost half stated a “definite” willingness to participate in a placebo-controlled study, and less than 5% reported being unwilling to consider participating in a PCT.

The National Cancer Institute (NCI) at the National Institutes of Health (NIH) in Bethesda, Maryland, has developed an active clinical trials program for NF1-related PNs consisting of both observational and experimental treatment studies. Patients are drawn from a national referral base. The NCI provides study-related evaluations and treatments at the NIH, as well as travel and lodging to participants and one accompanying parent, at no cost. The purpose of the current study was to examine the experiences of families with children with NF1 and PNs who were evaluated for enrollment, or who participated in a clinical trial at the NCI, and the willingness of families to participate in future studies.

Method

Members of the NF1 multidisciplinary team at the NCI developed an initial group of questions for the survey that included several items adapted from questionnaires used by other research groups [7,8]. This draft of the NCI survey was pilot-tested with three parents of children with NF1 during clinic visits. Edits were made based on their comments, and the resulting final version contained 47 items. The questions were designed to assess respondents' perceptions in five domains: their understanding of study participation (11

items), their reasons for participating (1 item with 6 response choices and an open-ended option), their general experience while enrolled on the study (19 items), their willingness to participate in a future study including a placebo-controlled trial (4 items), and their overall satisfaction with study participation (1 item). In addition, several questions assessed background information and demographic variables. The response format of the items included multiple choice, Likert scale (typically 4-point items), and open-ended questions. Reliability testing was not conducted due to the heterogeneity of the items.

Families were eligible for this survey if their child had been evaluated for participation in a past study at the NCI for their NF1, which could have included one of three multi-institutional treatment studies (one of which was a PCT) and one multi-institutional observational natural history study. The PCT enrolled 37 patients at the NCI, with NF1 and PNs, to a double-blinded cross-over design such that patients were randomized at enrollment (phase A) to receive the drug or placebo. Patients with disease progression on phase A were crossed over from drug to placebo or vice versa in phase B, and continued to be followed for progression. The other two treatment trials were a Phase I (10 patients at NCI) and Phase II (16 patients at NCI) investigation of the drug Pirfenidone. The natural history study was a 3-year multi-institutional protocol run through another research center. Twenty-four patients from the NCI enrolled on this study, the aim of which was to study the natural history of PNs in individuals not receiving medical treatment directed at their PNs, and to establish a reliable method of measuring PN growth to provide a basis for future therapeutic trials. Generally, patients on each of these studies participated in similar procedures while at the NCI (e.g., MRI scans, physical examinations, measurement of PNs). Parents of children who were evaluated for participation in a study but who did not enroll were instructed to skip certain sections of the survey that were not relevant to them. Since children of parent respondents could have participated in more than one study, parents were asked to answer survey items based on their experience with the most recent study in which the child was enrolled.

The NFI research staff at the NCI maintains a database of all past and present study participants, as well as patients who have been evaluated for potential participation, on any of the aforementioned protocols. Because the survey was anonymous, the NIH Office of Human Subjects Research reviewed and approved the project, and determined it was exempt from review by the Institutional Review Board. The survey was mailed to all families in the database with current contact information ($N = 75$). These families also were sent a letter explaining the purpose of the survey, and were given the option of completing the enclosed, anonymous survey and returning it by mail or doing the survey online. After several weeks, a reminder letter, along with another copy of the survey, was sent to all families again asking them to complete and return the questionnaire if they had not already done so.

Statistical Analyses

Descriptive statistics (e.g., means, percentages, frequencies) were computed for demographic and other survey items where appropriate. Pearson product moment correlations or analyses of variance (ANOVAs) were calculated to assess the relationships between the overall ratings of study satisfaction and positive and negative aspects of participation. An ANOVA was used to compare overall satisfaction between parents whose child participated in a PCT and those whose child participated in a treatment trial with no placebo group. Analyses were conducted with SAS statistical software, version 8 (SAS Institute, Cary, NC).

Results

Respondent Characteristics

Sixty-four (85%) of the 75 families returned the completed survey ($n = 54$ by mail and $n = 10$ online). Of those respondents, 86% were mothers and 14% were fathers. Slightly more than half of the children with NF1 were male (59%). At study enrollment, 25% of patients were less than 6 years of age, 33% were 6 to 10 years, and 42% were 11 to 24 years of age. Eighty-nine percent ($n = 57$) of children had entered a study at the NCI, while 11% had been evaluated for potential enrollment on a study but did not enroll (see Table 1).

Most families had learned about NF1 studies being conducted at the NIH through their local doctor (59%) or online (23%). More than half (58%) of the families had been involved with research at the NCI for more than two years. For 75% of respondents, no other family members had been diagnosed with NF1 other than the child evaluated.

Understanding of Study

Parents whose child entered a treatment study for his or her PNs ($n = 51$) were asked how well they understood various factors prior to enrollment. The majority reported that they thoroughly understood the main purpose of the study (86%, 95% Confidence Interval [CI] 77–95%), what medical procedures were involved (92%, 95% CI 84–99%), possible side effects (86%, 95% CI 77–95%), the time required for participation (86%, 95% CI 77–95%), and the right to stop the study at any time (96%, 95% CI 90–100%). Thirty-three respondents whose child had participated in a PCT were asked how well they understood the reason for the placebo, and 100% said they understood the reason “somewhat” or “a lot.” Moreover, 52% (95% CI 35–69%) of these parents said they “had no problem with [the experience of participating in a PCT]”, while 48% (95% CI 31–65%) reported finding it hard not knowing if their child was taking the study drug or the placebo.

Reasons for Participation

The most common reasons for initially enrolling on the study included to shrink the child’s tumors (77%, 95% CI 67–87%), to access medical care that otherwise would not have been available (72%, 95% CI 62–82%), and to help others (72%, 95% CI 62–82%). Less common reasons for enrollment included increasing one’s knowledge about NF1 (56%, 95% CI 44–68%) and meeting other families living with NF1 (28%, 95% CI 17–39%). In addition to the multiple-choice options on this item, parents were given the opportunity to write in other responses. One parent stated that a reason for their participation was “to make sure I was doing everything I could possibly do for my child.” Another parent commented that she had felt hopeless regarding her daughter’s condition, and they participated because “[the study] gave me hope.”

Experiences of Participation

Almost half (47%, 95% CI 35–59%) of respondents felt that study participation interfered with their family’s daily routine “some” or “a lot.” A few (6%, 95% CI 0 – 12%) reported that it interfered with their family relationships, although 75% (95% CI 65–85%) stated that participation impacted their family relationships in a positive way “some” or “a lot”. Most respondents reported that they did not have significant financial difficulties related to coming to the NCI (78%, 95% CI 68–88%), and that their child did not have notable difficulties from missing school due to coming to the NCI (77%, 95% CI 67–87). However, almost half (47%, 95% CI 35–59%) felt that their co-workers or supervisors were not always understanding about the time they had to take off from work.

With respect to interactions with research staff, 92% (95% CI 85–99%) of respondents agreed that the amount of contact was appropriate. Eighty-four percent (95% CI 75–93%) reported feeling “very comfortable” calling the research staff with questions, and 80% (95% CI 70–90%) reported that the staff members were “very easy” to reach.

When asked about the best parts of study participation, the most frequently endorsed options included the opportunity to help others (72%, 95% CI 62–82%), having access to medical care that would have been expensive outside the NCI (69%, 95% CI 58–80%), and the fact that they learned more about NF1 (58%, 95% CI 46–70%). Parents also cited the benefits of meeting other families living with NF1 (33%, 95% CI 22–44%), and their child’s tumors becoming more stable (25%, 95% CI 14–36%). Seventy-two percent (95% CI 62–82%) of respondents felt that study participation helped their child “some” or “a lot”. Several respondents provided additional comments about the best parts of participation in an open-ended section of this question. These comments referenced the fact that specific conditions (e.g., malignant tumors, other NF1-related complications) were identified that had not been found previously, and the availability and “caring” nature of the staff.

Worst parts of participation included having to take time off work (28%, 95% CI 18–38%), traveling to the NIH (25%, 95% CI 15–35%), the child having to miss school (25%, 95% CI 15–35%), and seeing no benefits to the child’s health (22%, 95% CI 12–32%). Factors endorsed less frequently were the child having to go through painful or uncomfortable medical procedures (14%, 95% CI 6–22%), the child having to take medicine (11%, 95% CI 3–18%), the child having to go through too many evaluations or procedures (9%, 95% CI 2–16%), and the child experiencing side effects from the medicine (6%, 95% CI 0–12%). In an open-ended part of this question, respondents were able to name other factors they considered to be the worst parts of participation. One parent noted that it was difficult to leave her other children while visiting the NIH. Additional factors specified by other parents included worrying that the child could be found ineligible to continue on study, the stress of waiting for medical test results, and having difficulty getting the child to take the study drug due to its unappealing taste.

Future Participation

Most respondents said they would “definitely” (84%, 95% CI 75–93%) or “probably” (9%, 95% CI 2–16%) participate in a future study at the NIH. A smaller but still substantial proportion of respondents said they would “definitely” (40%, 95% CI 28–52%) or “probably” (26%, 95% CI 14–36%) be willing to participate in a study with a placebo control group. Among respondents whose child had previously participated in a PCT, 84% (95% CI 72–96%) said they would “definitely” or “probably” participate in a PCT in the future. By contrast, among those whose child had participated in a study not involving a placebo group, only 54% (95% CI 31–77%) said they would “definitely” or “probably” participate in a PCT.

From a list of seven choices, respondents were asked to indicate areas they would like assessed in future studies. The majority expressed interest in studies assessing cognitive functioning (69%, 95% CI 58–80%), pain (63%, 95% CI 51–75%), scoliosis and other bone changes (61%, 95% CI 49–73%), and emotional/behavioral functioning (55%, 95% CI 43–67%). Respondents also expressed interest in studies assessing social skills (45%, 95% CI 33–57%), motor skills (44%, 95% CI 32–56%), and career/vocational skills (41%, 95% CI 29–53%). Among four future treatment studies, the most interest was expressed in a study targeting learning problems (55%, 95% CI 43–67%), followed by studies involving treatment for skin tumors (48%, 95% CI 35–59), NF1-related cancer tumors (41%, 95% CI 29–53%), and brain tumors (30%, 95% CI 19–41%).

Overall Satisfaction with Participation

On a Likert scale question assessing overall satisfaction with study participation (0 = very negative experience, 10 = very positive experience), the mean rating was 9.5 ($SD = .78$; 95% CI 8.0–10.0), and ratings ranged from 7 to 10. As shown in Table 2, higher overall satisfaction was significantly correlated with fewer transportation problems (e.g., airport shuttles), fewer financial difficulties related to study participation, and fewer school problems for the child resulting from study participation ($ps < .05$). Respondents' overall satisfaction was not related to the impact of study participation on family relationships, having long wait times before or between study appointments, whether the respondents' co-workers or supervisors were understanding about the time they took off work to come to the NIH, perceptions of whether study participation helped their child, disruptions to the family's routine, or the age of the child during study participation ($ps > .05$).

Respondents were divided into two groups based on whether their child had participated in the PCT or in a treatment study without a placebo control group. The mean satisfaction ratings were very similar across these groups ($9.48 \pm .80$, 95% CI 7.91–10, and $9.69 \pm .63$, 95% CI 8.45–10, respectively) and not significantly different from each other ($F = 0.71$, $p > .05$).

Suggestions for Improvements

In an optional open-ended question, respondents were asked what things could be improved about participating in a study at the NCI. Forty-one percent ($n = 26$) of parents provided comments. Suggestions included improvements in transportation ($n = 3$), increased communication between the NCI medical team and home physicians ($n = 2$), more contact from staff regarding scheduling upcoming appointments ($n = 2$), providing accommodations and/or covering travel costs for additional family members (a second parent or patient's siblings; $n = 2$), providing more information on new or upcoming studies ($n = 2$), providing more information about what to expect during the visits ($n = 1$), and decreasing long wait times for one particular clinic ($n = 1$). In addition, one parent commented that study visits were difficult because of the location of the NIH (being far from their home), and two parents whose children had participated in a placebo-controlled study expressed a desire to know whether their child was on placebo or the drug. (This was communicated to all parents when the study was completed and unblinded).

A number of parents offered positive comments about their experience when responding to this open-ended question. Specific factors cited included the "clinical experience" of the child, the lodging, the helpfulness of the information received throughout the study, and the friendliness and supportiveness of the staff.

Discussion

This report describes results of an in-depth survey of families of pediatric and young adult patients with NF1 and PNs who were evaluated for, or enrolled on, a clinical trial at the NIH. In general, most parents of patients with NF1 who participated in a clinical trial at the NCI felt they thoroughly understood important aspects of the research, including the purpose of the study, risks and benefits of participation, the time required, and their right to stop participating at any time. It is important to note that the survey assessed perceptions of understanding rather than actual understanding. Past research has found that patients often overestimate their knowledge about clinical trials in which they are participating [9,10]. Studies that have tested patients' actual knowledge suggest that some facets of the research are well understood whereas others are not. For example, Bergenmar et al [9] assessed understanding among patients enrolled in cancer clinical trials. Results indicated that

participants were highly knowledgeable about the voluntary nature of study, randomization, and their right to withdraw at any time, but less than half correctly answered items about the potential risks involved and the unproven nature of the trial. In order to clarify any misperceptions prior to patient enrollment, it may be helpful to assess patients' understanding of information provided during the consent process, either informally or with a brief set of questions formally built into the consent process. Specific recommendations for improving parents' or patients' understanding include providing audio and visual materials outlining the study [11], implementing structured decision aids [12], and improving the communication style of the medical staff (i.e., limiting medical jargon) [13].

In the current study, the overall experience of respondents' participation was extremely positive, even among those whose children participated in a PCT. Moreover, satisfaction among respondents whose child had participated in a PCT was not significantly different from those whose child had participated in a treatment study not involving a PCT. Of note, the vast majority of respondents whose child had participated in a previous PCT would consider participating in a future PCT. This finding is consistent with results from studies of adults with NF1 and caregivers of children with NF1 [7] and other disorders (e.g., autism [14]) who participated in a PCT. Thus, our study's extremely high satisfaction rate and willingness to consider participation in a future PCT, as well as the fact that the parents understood the reason for the placebo arm of the trial, suggest that use of a placebo-controlled design is feasible and that targeted enrollment can be successful. When considering our participants' positive responses to these questions, one should keep in mind that response bias is always possible in survey research, since parents who had a more positive experience may have been more inclined to complete the questionnaire.

Despite the high satisfaction rate, some problems were encountered that could be barriers to recruitment and/or retention. Financial difficulties relating to study participation were reported by 22% of respondents and were negatively correlated with overall satisfaction ratings. Although all direct study costs were covered by the NIH, parents may have incurred indirect costs resulting from time taken off work, or from insurance co-payments related to study procedures (i.e., lab work) done by medical clinics in the child's local community in between visits to the NIH.

A proportion (23%) of respondents reported that their child had "some" difficulties from missing school as a result of coming to the NCI for study appointments. The study team members make every effort to schedule visits when it is most convenient for families in terms of parents' work schedules and children's school schedules. Further efforts may need to be taken to encourage families to notify teachers in advance of the child's absences so that work can be prepared for the child to bring with them.

Helping these children keep up with their schoolwork is of particular importance for many of these families, given that learning problems are fairly common among children with NF1 [1,15,16]. Estimated rates of specific learning disabilities in this population have been reported as high as 42% [17], although differences in how learning disabilities are defined across studies have resulted in a wide range of estimates, making it difficult to reach a consensus. Of note, the most common area of interest reported by our respondents for both assessment and treatment in future studies involved cognitive functioning. While much has been learned about the cognitive profile of children with NF1, future studies are needed to identify subgroups of children who may be differentially at risk for learning problems and to evaluate the effectiveness of cognitive interventions.

The response rate for our survey was relatively high at 85%. Other recent survey studies conducted by mail with families of children with chronic illness have reported response rates

ranging from 49% [7] to 80% [18]. Our rate of response was aided by the second survey mailed to families and the availability of an online version of the measure. An additional five (8%) surveys were received after the second mailing. Further, ten (16%) of the surveys were completed using the online version, and these parents may not have returned the measure if that had not been an option. While we cannot be certain that parents did not complete the survey more than once, the cover letter clearly specified that respondents should disregard the second request if they had completed the survey already. Another potential reason for our high response rate was the fact that most eligible participants had enrolled in at least one research study at our institution and therefore had worked closely with the staff in the past and were familiar with the process of completing questionnaires for studies. Past experience with research has been found to relate to a more positive attitude toward research participation in the future among caregivers of children with sickle cell disease [19]. Thus, there may be an increased willingness to participate among our patients compared to individuals with less connection to the research process.

Finally, whereas this study assessed perceptions of one specific illness group, much of the information gained may be applicable to participants of clinical trials as a whole. For example, as in our study, parents of children with other conditions, including asthma [20], leukemia [21], and myopia [6], highly regarded factors such as staff friendliness and supportiveness, learning more about the child's disease, and the quality of care received. These are factors likely to help optimize recruitment and retention rates in clinical trials involving a wide variety of patient populations.

Conclusions

Increasing our knowledge about NF1 and the effectiveness of various treatments depends upon successful recruitment and retention in clinical trials. Despite a few negative experiences of participation, most parents in our survey reported a positive impact and would participate in future studies, including PCTs, and particularly those assessing cognitive functioning and pain as well as trials evaluating treatment for NF1-related learning problems. Specific recommendations include encouraging staff to build and maintain positive relationships with families; offering (or helping to locate) services or interventions such as online support networks for families or pill swallowing training for children; and helping families work with the child's school to minimize the impact of missing class. Researchers should plan future studies in accordance with these and other factors related to positive experiences of study participation to ensure optimum recruitment and retention for children with NF1 and their families, as well as participants of clinical trials in general.

Acknowledgments

The authors are grateful to the families who responded to this survey. We would also like to thank Jonathan Wiest, Ph.D. for his help with the development of the online version of the survey, and Sally Hunsberger, Ph.D. for her role as statistical consultant for specific computations.

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Table 1

Enrollment status of patients whose families responded to the survey ($N = 64$).

Enrollment Status of Patients	n	%
Evaluated but not enrolled	7	11
Enrolled		
Placebo-controlled trial (PCT)	33	52
Treatment trial (not PCT)	13	20
Natural history (non-treatment)	11	17

Table 2

Correlations between satisfaction ratings and other variables.

	Overall Satisfaction Rating	
	r	p
Transportation Problems	−.54	<.0001
Financial Difficulties	−.40	.001
Problems due to child missing school	−.30	.02
Problems due to parent(s) missing work	.06	.65
Interference with family routine	−.24	.053
Interference with family relationships	−.17	.17
Long wait times between appointments	−.12	.36
Feeling study participation helped child	.05	.73