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Recruitment of Infants with Sickle Cell Anemia to a Phase III Trial: Data from the BABY HUG Study

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Keywords

sickle cell; hydroxyurea; minorities; recruitment; infants

INTRODUCTION

An important aspect of research design is recruitment: how to enroll the number of subjects necessary to achieve the sample size requirements of a successful clinical trial, and how to estimate the size of the potential participant pool. Most estimates are based on anecdotal evidence, personal opinion, and guesswork by the protocol development team [1]. Less than one-third of 114 multi-center clinical trials identified in the United Kingdom recruited their original target within the originally specified time line, and an additional one-third received time extensions to achieve targeted enrollment [2]. However, extension of the recruitment period increases cost and may result in premature termination of the study for failure to accrue.

Sickle cell disease is the term applied to any clinically significant hemoglobin disorder that involves hemoglobin (Hb) S and is the result of a genetic mutation that causes the substitution of the amino acid valine for glutamic acid in the 6th position of the β-globin chain. Sickle cell anemia (HbSS) is the hemoglobinopathy in which the HbS gene is inherited from each parent. HbS molecules polymerize under hypoxic conditions resulting in red blood cell alterations

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which cause two important pathophysiologic characteristics of sickle cell anemia: vaso-occlusion and hemolysis. These properties are mitigated by the presence of HbF (fetal Hb), which declines rapidly from birth over the first year of life. Improved HbF levels are the major hematologic benefit from hydroxyurea treatment and the primary reason for the diminished frequency of the vaso-occlusive complications of sickle cell disease in treated subjects [3]. The Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) was a multi-center, randomized, double blinded, placebo controlled study of daily oral hydroxyurea (HU). In this study, hydroxyurea (or placebo) was given to very young children to determine if the drug is efficacious in preventing the normal decline in splenic function (associated with increased susceptibility to invasive pneumococcal infections) and renal function (associated with increased glomerular filtration rate and loss of urine concentrating ability). Both of these complications are prominent in the first years of life in persons with sickle cell anemia.

The study opened in October 2003 with a goal of recruiting 200 infants with sickle cell anemia (Hb SS) between 9 and 17 months of age. The study followed the participants for two years and required at least 40 clinic visits with a minimum of 33 blood tests and various examinations scheduled throughout the study period [4]. The primary endpoints were preservation of spleen and renal function. In response to slow recruitment, the study coordinators developed a screening log of all potential subjects born at each center after the date of study initiation, and sought to identify factors that affected recruitment of this very young racial and ethnic minority population. Because of the nature of the BABY HUG population, our results are particularly relevant to trials involving African-American children.

METHODS

As the study was being designed, BABY HUG investigators initially conducted meetings in their centers to assess community interest in a study of hydroxyurea in very young children with sickle cell anemia. A variety of methods were utilized to include as many families of such children as possible in discussions about the interest in and feasibility of a study of this kind. Centers provided informational group meetings, mailings, and one-on-one discussions during clinic visits to determine if families thought a study of hydroxyurea, including a placebo group, would be considered important. At all centers, the families' responses were overwhelmingly positive. They expressed a strong interest in learning more about the use of hydroxyurea in this age group.

Despite the initial enthusiasm from potential participant families, actual recruitment was slower than expected. Sixteen months after the study opened, BABY HUG study coordinators at the 14 participating institutions developed an IRB-approved patient log based on recruitment experience to date that recorded whether or not a potential patient's family was approached to participate in the BABY HUG trial. Coordinators from each site provided local data that was submitted to the Statistical and Data Coordinating Center and collated. These data were then analyzed as a whole, and also by individual site and by study coordinator.

Newborn screening data were used by the sites to determine the number of potentially eligible patients. Reasons for not approaching a family were categorized as "non-compliant with scheduled clinic visits", "social issues", "not meeting all inclusion criteria", and "other". The study was discussed with each family by the local Principal Investigator (PI) and/or BABY HUG study coordinator, after which the family was given as much time as needed to make a decision. Families who were approached received written and verbal information about the BABY HUG study, including an IRB-approved brochure that was available at all sites. The family had an opportunity to discuss the study with a research advocate (ombudsman), who was not part of the study team but whose role was to ensure that caregivers were fully informed

of the study requirements and that their participation was voluntary. Compensation was provided to families at each study visit for time spent and travel expenses.

During the recruitment phase, the study coordinators assessed whether each parent or legal guardian verbally agreed to participate or not and recorded the reason(s) for the choice. Answers were by free response, and more than one reason may have been described by a single family. After preliminary data of responses were reviewed, common themes emerged and five categories were used to code subsequent responses in a standardized manner. Reasons for initial affirmative responses were grouped into categories reflecting common themes: “perceive the child to be ill”, “ desire to aid research”, “ desire for closer follow-up”, “hope that the child would be randomized to receive hydroxyurea”, and “other”. Conversely, reasons for declining participation were grouped into the categories: “fear of research”, “transportation problems”, “ excessive clinic visits and/or lab draws”, “perception that the child was not ill”, “desire for hydroxyurea, not placebo”, and “other”. The study documented whether an informed consent was ultimately signed.

RESULTS

Between October 2003 and June 2007, the BABY HUG study coordinators at the 14 participating institutions identified 1106 potentially eligible infants less than 18 months of age with a diagnosis of HbSS or HbSβ^0thalassemia (Figure 1). Of these, 796 (72%) families were approached to determine if they would be interested in participating in the BABY HUG trial. Of the 310 who were not approached, 29 percent had not been keeping scheduled clinic visits reliably. Twenty seven percent were found to be ineligible for reasons that became apparent after additional medical record review and/or because of changes to their clinical status. These reasons included: a change in diagnosis from that reported on the initial newborn screening log, a previous splenectomy noted after review of records, and growth parameters below the eligibility criteria. In 19 percent of those not approached, study coordinators identified barriers to enrollment including guardianship disputes, parental health problems, and a variety of other social issues which might have compromised the family’s ability to provide daily medications and/or attend frequent clinic visits.

Of the families approached, 487 (61%) declined. The most common reason for declining participation (representing 25% of responses) was concern about the high frequency of required clinic visits, blood tests, and special studies. Fear or distrust of research participation was identified by 19 percent. Fourteen percent of the families had limited access to transportation; many were living long distances from the participating institutions. Ten percent perceived their child to be healthy and felt that medicine was not needed at this time, three percent moved away from their institution, and two percent wanted their child to receive hydroxyurea rather than possibly being randomized to receive placebo. However, 21 percent of families declining participation did not provide a reason for not participating before their child exceeded the maximum age of eligibility. Typically, these families did not return phone calls, did not return to the clinic to continue discussion about the study, or wanted to “think about” the information more.

Of the 796 approached, 309 (39%) of families stated they wanted their child to participate in the study. Of those who verbally agreed, 234 (76%) actually signed the informed consent and entered the screening phase of the BABY HUG study. A desire to aid research in sickle cell anemia was expressed by 51 percent of families agreeing to participate in the study. Fifty-one percent were interested because of the hope of receiving hydroxyurea for their child. Anticipation of closer follow-up through increased clinic visits also motivated 51 percent of the families. Sixteen percent perceived their child to be ill and hoped for clinical benefit from participation. Ultimately, 21 percent of the families of all potentially eligible infants (29 percent

of those families actually approached) signed informed consent. Demographic data on the families that consented to their infant's participation in BABY HUG have been recently published [5].

We retrospectively compared individual sites to identify factors leading to successful recruitment. The one center which failed to recruit any subjects joined the study late, had the fewest number of available patients, and had the fewest subjects approached. The 7 sites with the largest number of potential subjects (n=75-132) enrolled a total of155 (66.3%), compared with 79 (33.7%) at the 7 sites with the fewest potential subjects (n=23-71). Sites identified a mean of 73 (range 23 – 132) potentially eligible infants (Figure 2). However, the proportion consented in the larger sites (22%) and smaller sites (20%) was similar. As shown in Table 1, the number of subjects enrolled in the trial correlated with the number of families approached. In general, because the number approached was closely related to the number available, the number enrolled was also related to the number available (Table 1). When the enrollment rate (based on the number of months the study was open to recruitment at the site) was calculated, a similar relationship was found between the number of subjects available monthly, the rate of approaching families, and the rate of enrollment (Table 1). As shown in Figure 3, the proportion of families consented was directly related to the proportion approached (P=0.03). Additionally, the race of the study coordinator was not associated with successfulness in recruiting in this trial (Table 2).

DISCUSSION

A variety of barriers to participation in clinical trials have been identified. In general, our findings parallelled those in the literature. Protocol-related concerns include the complexity of the trial, opposition to randomization and the use of a placebo, the potential for negative side-effects, and fear or mistust of research or medical providers [6]. Our families greatest concerns in these areas were the frequency of clinic visits and lab tests and the fear or avoidance of research. Patient-related barriers have included lack of transportation, excessive distance from the clinical center, increased costs or effects on health insurance, lack of family support, and loss of control of decision-making [6,7]. We found similar barriers expressed as reasons to decline participation. Lower socioecomic status and membership in a racial/ethnic minority may be associated with a lack awareness of available trials and fewer opportunities to participate [8,9]. In general, our subjects were from a lower socioeconomic minority population, but we attempted to provide widespread awareness about the availability of the study through multiple methods including but not limited to individual and group meetings and letters to families and local primary care providers. Racial, ethnic and cultural differences between the patients and physicians may become barriers to communication and partnerships [10]. Matching racial/ethnic backgrounds of the recruiter and participants may improve study accrual [11], although this concept was not supported in the BABY HUG study.

The involvement of young children adds to the complexity of recruitment. Relatively little is known about the factors that influence parental consent. At least one parent must give consent, but an entire family may be involved in the decision to participate. In this study coordinators sometimes expressed frustration that some family members blocked participation but would not make themselves available for discussion with investigators. The perceived risks, benefits, and importance of the study have been identified as important components of parental decision-making [12]. A desire to help their child, to learn more about the disease, and to contribute to medical knowledge have been primary reasons for parental consent [13-16]. For example, a recent report identified that families of children with sickle cell disease who had favorable opinions of research participation perceived that their child's illness was moderate to severe and that more research is needed in sickle cell disease [17]. Similar considerations were

expressed by the families that chose to participate in our study. Conversely, financial stipends for participation do not seem to influence a parent's decision [14].

BABY HUG is notable for enrolling almost 200 minority infants (96% African American) after screening 1106 subjects to participate in a randomized, placebo controlled Phase III clinical trial.

In advance of study initiation, all BABY HUG sites reported strong community support for a clinical trial of hydroxyurea in this young age group to determine whether this drug could prevent the organ damage that affects those with sickle cell anemia. However, recruitment for the BABY HUG study was challenging on many levels, particularly since the study sought to enroll infants who in many cases had not yet experienced any complications from sickle cell disease. At the onset of the BABY HUG enrollment period, some centers adopted a strategy of being "selective" in the families they approached, believing that approaching fewer (but "more adherent") families would result in a higher proportion of successfully recruited children and a higher proportion of families who would be more likely to complete the trial. In fact, the opposite was found.

To assist the investigators in understanding the factors impacting recruitment, families were encouraged to express multiple reasons for their decision and responses were grouped into common themes. The desire to improve medical knowledge in sickle cell anemia, the hope that their child would be treated with hydroxyurea, and the anticipation that their child would receive more extensive clinical care were the strongest motivators for families choosing to participate. Initially there was a concern that children who were perceived to be severely affected would be disproportionately enrolled in the study. However, only 16 percent of parents enrolled hoping for special treatment of their "ill" child and only two percent declined the study because of concern about allocation to placebo through randomization. Conversely, 10 percent declined participation because they considered their child to be "healthy."

The burdensome frequency of clinic visits, blood testing, and special studies was the most commonly expressed reason for choosing not to participate in the BABY HUG study. However, a similar proportion of declining families did not express a reason; instead they failed to keep appointments to discuss the study until the child became too old to enroll. These families may have been uncomfortable in expressing their disinterest in the study, perhaps out of deference toward medical providers. Approximately one-fifth of families who were introduced to the study did not want their child to be a research subject or feared side effects of the study medication. In some cases there was conflict among family members with some agreeing and others disapproving of participation. While efforts were made to assist with transportation at all centers, longer distances to the site probably impacted recruitment. Some families were unable to commit the time and resources needed to travel to the BABY HUG sites at the increased frequency required by the study, even with the offered travel reimbursement.

Interestingly, sites that approached more patients were able to recruit more subjects, whereas sites which selected families based on a perception that they would have improved adherence to study demands actually tended to enroll fewer subjects (Figure 3). Overall, adherence to study expectations was good, suggesting that preconceived biases should not be applied in approaching subjects for participation in research [5].

There were potential limitations to this study. Coordinator responses were grouped into common themes to identify patterns but this classification of responses may have resulted in some misinterpretation of families' decision process. Additionally, of families that declined participation, twenty-one percent did so passively by not giving a reason or failing to respond to queries, so that definite information regarding their motivation was not available. Examining potential demographic differences between those families that chose to participate and those

who declined was not possible because those data were not collected on participants that did not consent to the study.

CONCLUSIONS

Families expressed a variety of mostly predictable reasons for choosing to participate or decline participation in BABY HUG. Based on our findings and those of others [17], recruitment should promote research participation as altruistic and socially desirable, particularly among racial and ethnic minorities. It should be recognized that families' desire for enhanced clinical care and the chance for access to new treatments are incentives for research participation.

Substantial numbers of potential subjects may be necessary for successful trial recruitment. Success rates for recruitment (~20%) were fairly constant from site to site in our study, suggesting that a major determinant of meeting recruitment goals is whether a large total pool of potential participants is available. This should be recognized during study development along with an emphasis on avoiding preconceived biases on whether a participant will be a "good" research subject or not.

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Figure 1.
Flow Chart of BABY HUG Recruitment

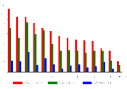

Figure 2.
Patients Available, Approached and Consented across 14 Sites

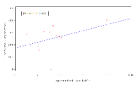

Figure 3.
Ratios of Consented/Approached and Approached/Available
Note: The green diamond at the bottom is an outlier and it is not included in our regression model.

Table 1

Correlation among Patients Available, Approached and Consented

	Correlation*	p-value
# consented vs # approached	0.879	<0.0001
# approached vs # available	0.925	<0.0001
# consented vs # available	0.717	0.0039
# consented monthly vs # approached monthly	0.828	0.0003
# approached monthly vs # available monthly	0.907	<0.0001
# consented monthly vs # available monthly	0.619	0.0182

*Pearson Correlation Coefficient is calculated.

Table 2

Patients Approached /Available, and Consented /Available Relating to Race of Coordinators across 14 Sites

Site Label	A*	B	C	D	E*	F	G*	H	I	J	K	L*	M	N
# available	132	116	116	103	92	86	75	71	68	66	65	49	44	23
# approached	92 (70%)	72 (62%)	104 (90%)	79 (77%)	87 (95%)	59 (69%)	45 (60%)	46 (65%)	45 (66%)	40 (61%)	44 (68%)	44 (90%)	24 (55%)	15 (65%)
# consented	24 (18%)	22 (19%)	42 (36%)	15 (15%)	29 (32%)	16 (19%)	7 (9%)	14 (20%)	16 (24%)	9 (14%)	12 (18%)	21 (43%)	7 (16%)	0 (0%)

* The coordinators of these sites are non-white.

T test p-value of sites with non-white/white coordinators with regard to # of approached/# of available: p=0.1428

T test p-value of sites with non-white/white coordinators with regard to # of consented/# of available: p=0.3607