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Recruitment & retention program for the NeuroNEXT SMA Biomarker Study: Super Babies for SMA!



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ABSTRACT

Background/Aims: Recruitment and retention of research participants are challenging and critical components of successful clinical trials and natural history studies. Infants with spinal muscular atrophy (SMA) have been a particularly challenging population to study due to their fragile and complex medical issues, poor prognosis and, until 2016, a lack of effective therapies. Recruitment of healthy infants into clinical trials and natural history studies is also challenging and sometimes assumed to not be feasible.

Methods: In 2011, our group initiated a two-year, longitudinal natural history study of infants with SMA and healthy infant controls to provide data to assist in the analysis and interpretation of planned clinical trials in infants with SMA. The recruitment goal was to enroll 27 infants less than 6 months of age with SMA and 27 age-matched healthy infants within the two-year enrollment period. A detailed recruitment and retention plan was

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developed for this purpose. In addition, a survey was administered to participant families to understand the determinants of participation in the study.

Results: All healthy infants were recruited within the study's first year and 26 SMA infants were recruited within the two-year recruitment period. Thirty-eight participant families responded to the recruitment determinants survey. Nearly half of respondents (18/38, 48%) reported that they first heard of the study from their physician or neurologist. The most common reason to decide to enroll their infant (22/38, 58%) and to remain in the study (28/38, 74%) was their understanding of the importance of the study. Thematic recruitment tools such as a study brochure, video on social media, and presentations at advocacy meetings were reported to positively influence the decision to enroll.

Conclusions: A proactive, thematic and inclusive recruitment and retention plan that effectively communicates the rationale of a clinical study and partners with patients, advocacy groups and the local communities can effectively recruit participants in vulnerable populations. Recommendations for the proactive integration of recruitment and retention plans into clinical trial protocol development are provided.

1. Introduction

Recruitment into clinical trials, particularly in vulnerable patient populations (ie: economically disadvantaged, racial and ethnic minorities, children, the elderly, prisoners and those with terminal illness) is a challenge that affects the cost and timeliness of delivering those potential therapies [1]. An analysis of studies registered in 2011 within the National Library of Medicine clinical trial registry demonstrated that 19% of the clinical trials closed or terminated due to failure to meet accrual goals [2].

Lack of awareness regarding to the availability of clinical trials is one factor for low enrollment [3]. This is often due to a lower priority placed on research by clinicians who are focused on clinical management [4,5]. There is also the belief by some practitioners that families will be overburdened by being asked to participate in research, despite evidence to the contrary [6]. On the other hand, altruism is a major factor for research participation reported by research participants [7]. Healthy volunteers and people enrolled in observational studies more generally state the benefits to enrollment are intangible and include feelings of enhanced self worth and knowing that “one has done a good deed” so long as the trial is not too overwhelming [8,9].

Spinal muscular atrophy (SMA) is a progressive, genetic motor neuron disease that affects 1 in 6000–10,000 births and is the leading genetic killer of infants [10]. SMA is characterized by progressive muscular weakness and in the most common and severe form (type 1), infants do not achieve sitting or higher level motor skills, and respiratory insufficiency and death often occur within the first two years of life [10,11]. This population presents clear challenges for recruitment; infants suffering from a terminal illness with, at the time of our study, no effective therapy. Recruitment in past SMA natural history

studies was variably successful in meeting recruitment goals for children older than 6 months and when done retrospectively [12–14]. However, even in a therapeutic trial, enrollment for infantile-onset SMA has been slow due to many patients being too weak to travel, or not interested if the trial includes a placebo arm [14].

The NeuroNEXT SMA Infant Biomarker Study was a prospective, longitudinal natural history study of infants with infantile-onset SMA begun in 2012 [15,16]. Between December 14, 2012 and September 10, 2014, 26 SMA and 27 healthy infants were enrolled marking a successful and on-time recruitment into the study (Fig. 1) [15]. The last study visit occurred in August, 2015. Twenty-three healthy infants (85.2%) completed the study. Two healthy infants (7.4%) discontinued because parents moved from a study site, and two were lost to follow up. Seven SMA infants (26.9%) completed the study. There were 12 deaths (46.2%) in the SMA cohort, and 7 infants (26.9%) withdrew from the study prior to the 24-month visit [16]. The success of the study has contributed to the interpretation of clinical trials in this population and to the approval of the first FDA-approved medication for SMA and promises to contribute to numerous clinical trials involving the study of motor function in infants [17–19].

Here, we report the details of the SMA Infant Biomarker Study recruitment and retention plan. In addition, we report the results of a questionnaire sent to participant families to determine factors that influenced recruitment and retention. Finally, we provide recommendations for the proactive integration of recruitment and retention plans into clinical trial protocol development.

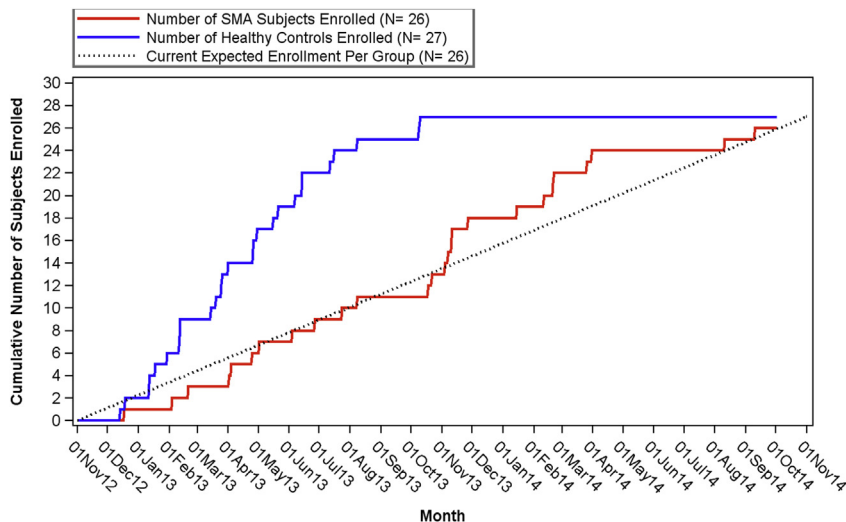


Fig. 1. Cumulative enrollment of the NeuroNEXT SMA Infant Biomarker Study Enrollment of 27 healthy control infants (blue line) and 26 infants with SMA (red line) exceeded expected 2-year enrollment estimate (dotted black line). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

2. Methods

2.1. Study design

The SMA Infant Biomarker Study was a prospective, multi-center, longitudinal natural history study in SMA and healthy infants designed to mimic a clinical trial [15,16]. The study was performed and supported by the NeuroNEXT Clinical Trial Network and originated from The Ohio State University Wexner Medical Center [20–22]. Parents or guardians of all participants provided written, informed consent approved by the NeuroNEXT central institutional review board [23] at each site. Fourteen sites within the NeuroNEXT Network enrolled subjects. Research coordinators who participated in this study are listed in Appendix 1. The protocol, patient demographics and baseline characteristics were published previously [15], and the primary outcomes of the study have been reported [16]. The study protocol was vetted by an experienced study coordinator (AB) to help reduce redundancies in data and ease of collection.

An informal pre-screening log was maintained at each enrolling center. Study tools were provided to sites to reduce study start-up

burden for research teams and to aid in uniform data collection. These included Case Report Forms, a detailed lab manual and educational study-related videos on how to process blood samples. The recruitment questionnaire and all recruitment materials utilized for this study were approved by the NeuroNEXT central IRB.

2.2. Recruitment strategy

Our recruitment and retention strategy involved 5 core components; 1) a thematic recruitment plan focused upon reciprocal altruism, 2) engagement of patient advocates and advocacy groups, 3) study team motivation and support measures, 4) measures to reduce potential burden for potential subjects and 5) engagement with participants after enrollment.

2.2.1. Thematic recruitment plan

We developed a marketing strategy and a brand focusing on reciprocal altruism to promote enrollment. Central to this was a partnership with an online company, Wry Baby™, whom we contacted and asked for assistance to build our thematic recruitment plan around their

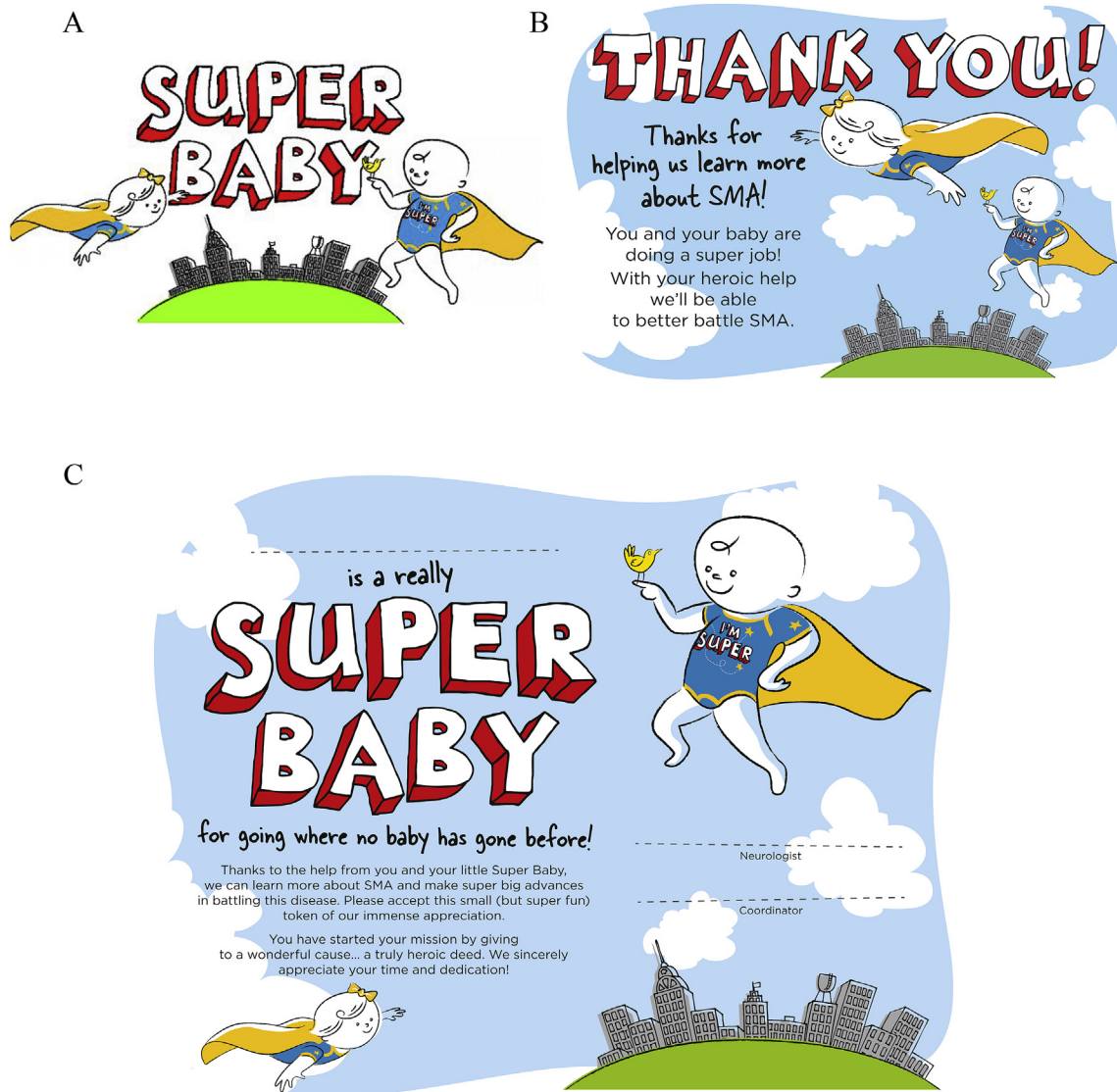


Fig. 2. Super Baby! Thematic Materials A. Artwork donated for the project was incorporated into all communications with participant families. B. Super Baby! thank-you notes with thematic fonts and colors sent after each study visit. C. Super Baby! diplomas with thematic fonts and colors presented to each participant family with actual Super Baby! onsie with cape. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

“Super Baby” baby onesie art work. The company donated their “Super Baby” onesie product and customized their artwork that was used in all recruitment materials to ensure a consistent branded identity (Fig. 2). All infants enrolled in the study received a complimentary “Super Baby onesie (Fig. 3). Also, the lead Principal Investigator for the SMA Infant Biomarker Study (SJK) was provided with a branded “You’re Super” Tee-Shirt with cape that was worn annually at the international Cur-SMA family conference attended by approximately 981 (in June 2013) and 1048 (in June 2014) individuals and family members affected by SMA to raise awareness of the study. This included presentations in the Family Research Q&A session and a family friendly poster session. As a result of the thematic material, the study also became known as the “Super Baby Study.”

Recruitment tools were employed that included a study-specific brochure (Appendix 2), a flyer, a webinar for coordinators to educate them about SMA and the importance of this study for future therapeutic trials, an SMA Biomarker YouTube video and a study-specific website (<https://www.neuronext.org/nn101-sma>). In addition, there were press releases and doctor referral letters. The coordinators at each site were instructed on how to use the tools and were given suggestions on whom to target. Anyone who was impacted by this disease was encouraged to share the YouTube™ video via social media. The SMA Biomarker YouTube™ recruitment video was produced to provide a brief background of SMA, the rationale for the study and a direct-to-community appeal

for recruitment that featured a parent of a child with SMA (<https://www.youtube.com/watch?v=f8xGDFj-DLU>).

The cost-efficiency of our strategy was high largely because the independent online vendor donated the thematic artwork and onesies. The video production was approximately \$5000. Printing for brochures (first and second printing) was ~\$800 and the expense of producing branded mugs, pens, cape costume and flyers was ~\$700. Thus, the expense for our materials was ~\$6500. This comes out to ~\$6500/54 enrolled participants = ~ \$120 expended for every participant enrolled. These costs do not include the time spent by the coordinator or investigator, however the budget outlay for recruitment materials was reasonable.

2.2.2. Advocates/advocacy

Prior to the finalization of the clinical protocol, the study collaborated with the CureSMA (formerly Families of SMA) advocacy network, Muscular Dystrophy Association (MDA), and individual SMA advocates. CureSMA representatives provided feedback on the draft recruitment materials prior to the study going live.

Once enrollment was open, Individual SMA advocacy parent blog sites were notified about the study and circulated study materials. We encouraged advocacy groups to use their blogs and Facebook™ pages to share recruitment materials and messages.

CureSMA and the MDA helped to circulate information about



Fig. 3. Super Baby! onesie. NeuroNEXT Biomarker Study infants wearing branded “I’m Super” onesie.

recruitment for the study once enrollment was open. Every new patient registered with CureSMA received a welcome packet of general SMA information that included the SMA Biomarker study brochure during the enrollment period. During this time period, 638 newly diagnosed packets were sent out to patients, and 206 of these packets were sent to families who had infants under six months of age. CureSMA and MDA also circulated cIRB-approved quarterly updates to ensure that people did not forget about the study. The study Principal Investigator (SJK) attended the annual, international CureSMA family meeting as an outlet to share study data directly with the families affected with SMA.

2.2.3. Site study team motivation and support

Research Coordinators, like physicians, focus on many different studies at one time. We made efforts to continue engagement with study coordinators throughout the study. We circulated YouTube™ videos produced by families that have been affected by SMA and provided participating centers information about their local CureSMA advocacy groups. Monthly coordinator calls were held to ensure consistency of protocol management across the sites and provide updates and success stories. We provided tokens of appreciation to sites for achieved study milestones. For example, after completion of enrollment of the control cohort, study specific, Super Baby branded pens were distributed to sites with a note stating, “I am but a pen and one day my ink will run out. I only hope I create something meaningful in the meantime.” During the study, an additional webinar demonstrating effective preclinical therapies in murine and porcine models was provided to study sites by a member of the protocol initiating team (WDA). Upon study completion, each SMA study team was awarded a “Super Baby” branded coffee mug with a motivational statement.

2.2.4. Eliminate potential burden for potential subjects

We created a toll free 1–800 number for participants to get information about the trial in a centralized manner. We offered participants a financial incentive of \$50 for participating at each visit. Additional funds were secured from CureSMA to reimburse families for travel expenses to ease subject financial burden and optimize reliability of study measures.

2.2.5. Engagement with participants after enrollment

Once a participant was enrolled, they received an “I’m Super” Branded Onesie (Fig. 3) and a branded Certificate of Achievement (Fig. 2C). Sites were provided “Super Baby” thank-you cards to mail to participants after study visits (Fig. 2B). The cards were personal notes of appreciation and gratitude signed by the study teams. In addition, a bi-annual newsletter was created to inform participants about the study updates and progress. After the study closed, participants received a newsletter summarizing the study findings.

2.2.6. NeuroNEXT network

NeuroNEXT is an NINDS sponsored initiative of 25 centers to improve research efficiencies by providing an infrastructure to facilitate rapid development and implementation of protocols in neurological disorders [19]. Fifteen of the 25 centers were selected to participate in this trial. The NeuroNEXT infrastructure improved study start-up efficiencies. Since this was the first funded NeuroNEXT study the sites were vested regarding recruitment and wanted to help the study succeed to prove value of the network. Having a central IRB and master contract helped minimize study start up time.

2.3. Participant questionnaire

To learn about factors that influenced enrollment, participants were asked about the study and their participation during the 9-month study visit. A survey was developed and then distributed through the NeuroNEXT Data Coordinating Center to all sites (Appendix 3). This survey was administered to families on the 9-month study visit.

3. Results

There were 38 surveys collected of the 39 families still enrolled at the 9-month study visit. Due mostly to the fatal nature of infantile-onset SMA, there were 14 participants who did not reach the 9-month study visit. Twelve surveys were from families of SMA infants and 26 surveys were from families of healthy infants.

3.1. Determinants for enrolling

When asked how the participant family initially received information about the study, nearly half of respondents reported that their doctor or neurologist provided the information (18/38, 48%). 29% reported first learning about the study from a friend or family member (11/38). Social media was accounted for by 19% of respondents (7/38). Only a single respondent reported that the YouTube™ SMA Biomarker video was the first contact about the study (1/38, 2%).

The most frequently reported reason for enrolling in the study was the importance of the research (22/38, 56%). Enrollment motivated by having a family member (17/38, 45%) or friend (5/38, 13%) with SMA was the next most common factor. The financial incentive was the least common motivator to enroll (1/38, 2%). Two respondents (5%) reported “other” and listed “research staff” and to “cure a horrible disease” as primary reason to enroll.

We sought to determine the impact of the recruitment tools employed for the study. Most respondents reported that they received or viewed the SMA Biomarker Brochure (23/38, 60.5%) and that it positively influenced their decision to participate (22/23, 95.7%). In general, respondents who viewed or received any of the recruitment tools also reported that they positively influenced participation.

3.2. Determinants for retention

Participants were asked what items motivated them to remain in the study. Many selected more than one item. It was reported most frequently that the importance of the research motivated the respondent (28/38, 73.7%). Retention motivated by having a family member (16/38, 42.1%) or friend (5/38, 13.2%) with SMA was the next most common factor. The influence of the study staff was reported in 26.3% of respondents (10/38). People selected to write in “other” determinants including the motivation to find treatments (2/38, 5%) and the ease of travel arrangements (1/38 3%) The least reported determinant selected for retention was to receive a financial incentive (1/38, 3%).

3.3. Determinants for not enrolling

During the enrollment period, we sought to determine factors leading potential participants to decline enrollment. Fifty-one families contacted or were seen at SMA Infant Biomarker Study recruitment sites during the recruitment period that expressed interest but did not enroll in the study. Reasons for not enrolling were collected in a pre-screening log kept by coordinators at each site. The leading reason for not enrolling was that the child was older than 6 months of age (11/51, 22%). The other reasons given were that the infant was too ill to participate (10/51, 20%), that the family wished to pursue therapy (8/51, 16%), that the study required an excessive commitment (7/51, 14%), that the study required excessive travel (6/51, 12%), that the family disliked the study procedures (5/51, 10%). The remainder (4/51, 8%) did not report a specific reason for not enrolling.

4. Conclusion

We successfully met our recruitment targets in a prolonged natural history study involving two challenging and vulnerable pediatric populations and enrolled the healthy infant cohort in less than one year. One important reason for this success was likely due to the timing of the

study itself. In 2011, clinical trials to deliver therapies based on very promising preclinical results in animal models were being planned, and there was much excitement in the SMA community about these trials. It was therefore easier to persuade the community that a well-characterized natural history study, designed to match the design of these clinical trials, would be meaningful and would aid in getting potential therapies to the “finish line”. Nevertheless, we had to communicate this meaningfulness effectively to members of the community and to our clinical study teams at every enrollment site. We largely attribute the success of this study to a proactive and thoughtful recruitment and retention plan.

Our study recruited approximately 40% of the infants registered with the advocacy group CureSMA who would meet eligibility criteria during the recruitment period (Jill Jarecki, personal communication). This highlights another key to the success of the recruitment plan; namely, partnership with disease-specific advocacy groups that permit widespread outreach to affected families. It was important to involve these groups early during protocol planning and design to ensure they felt a part of the study. Thus, when recruitment started, advocacy groups already had some study ownership and support.

There were lessons learned throughout the study that could have improved recruitment and an understanding of the determinants of recruitment and retention. We found that there was sometimes a loss of communication between participants and study sites when the study visits were six months apart. We recommend developing a communication plan to include formal reminders when study intervals are prolonged, as they were in our study. Regarding the recruitment and retention survey, we recommend incorporating this into the screening visit. We had chosen to do it at the 9-month study visit in order to minimize the burden and duration of the screening visit. We found, however, that due to infant mortality in the SMA cohort, not all subjects returned for the 9-month visit. Moreover, we found that the person who enrolled the participant in the study was not always the person who brought the participant to later visits. Thus, it is possible that responses were either second hand, or did not reflect the feelings of the enrolling parent.

Drawing from our experience, we recommend the follow key features to include in a successful recruitment and retention plan for future studies in vulnerable (and non-vulnerable) populations:

1. Have a Recruitment plan in place *prior* to starting a study. Do not wait until recruitment is lagging.
2. Do not count on clinic referrals as the only source of participants.
3. Include all possible referral sources (advocacy groups, patient advocates) when designing the protocol/recruitment plan so they are invested in the protocol.
4. Consider research coordinator burden. Provide them with tools to ensure visits are done per the protocol in a uniform manner. Avoid design elements that require redundant data. Provide training videos along with manuals for procedures that are specific to your trial. Remember there are different learners at centers and visual aids can help promote clean data capture.
5. Commend sites that do well in the recruitment of the study to boost morale.

One of the remarkable aspects of the NeuroNEXT SMA natural history study is that it marks the last time that the clinical course of untreated SMA infants will likely be reported. With the stunning advent of effective disease-modifying therapies, it is likely not ethical or feasible to perform future clinical trials in infants with SMA that have a placebo arm [17,18]. No recruitment and retention strategy for an untreated natural history study in SMA would be successful now given these advances. The lessons learned through our experience with recruitment and retention in the NeuroNEXT study, however, can be applied to any vulnerable population for whom there is a compelling argument to obtain rigorous, prospective natural history data. Ultimately, effective communication, delivered through a thoughtful

recruitment and retention plan tailored to a specific population, is the key to successful patient engagement without which no clinical study would be possible.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.conctc.2018.07.002>.

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