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### Authors

Figoni, Andrew  
Bauer, Andrea  
James, Michelle

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## Potential barriers to randomized clinical trials in infants with brachial plexus birth palsy

Andrew Figoni<sup>a</sup>, Andrea Bauer<sup>b</sup>, and Michelle James<sup>b</sup>

<sup>a</sup>University of California Davis School of Medicine

<sup>b</sup>Shriners Hospitals for Children - Northern California, Sacramento, California, USA

### Abstract

Randomized clinical trials (RCTs) are the gold standard for comparing medical treatments. However, pediatric surgical RCTs are uncommon. We sought the opinions of parents whose children had undergone reconstructive nerve surgery regarding participating in research studies. Twenty-nine of 30 parents indicated they would enroll their child in a research study, and 24 of these would enroll in a surgical RCT. However, the most common reason for willingness to participate was a desire to help their child, demonstrating a fundamental misunderstanding of RCTs. The burden is on the researcher to ascertain the subject's level of understanding before consenting to randomization.

### Keywords

Brachial Plexus Birth Palsy; Surgical Randomized Clinical Trial; Randomization; Nerve Graft

### Introduction

Brachial plexus birth palsy (BPBP) occurs in 1.5 per 1,000 live births in the United States [1]. Roughly two thirds of infants with this condition will spontaneously recover by 6 months [2]. For those with post-ganglionic nerve rupture, microsurgical nerve repair may restore some function in the affected limb.

Although sural nerve autograft is currently considered the 'gold standard' of peripheral nerve gap repair after post-ganglionic nerve rupture in brachial plexus birth palsy, other microsurgical repair techniques have been recently described [3], including acellular nerve allografts or synthetic collagen conduits. Allografts and collagen conduits eliminate the sensory deficit and scarring associated with sural nerve harvesting [4]. While it is important to determine if one of these techniques is superior, comparing surgical techniques in clinical trials is challenging.

The goal of this study was to determine the feasibility of patient accrual for a surgical RCT comparing different nerve grafts for BPBP treatment in infants. We proposed to estimate this using a modification of prospective preference assignment, by interviewing the parents of

children who had previously received microsurgical treatment in infancy, because they already understood the difficult decision-making involved in consenting for reconstructive surgery for their infant.

## Methods

We drafted a questionnaire containing questions pertinent to RCTs in the hypothetical case of testing alternatives to sural nerve grafting. After IRB approval, 46 potential participants meeting the inclusion criteria were identified during a search of hospital records. Participants met inclusion criteria if they were parents of children aged one month to 21 years with BPBP who had undergone microsurgical intervention in infancy; potential subjects were excluded from this study if they were unable to understand either English or Spanish. Thirty-one parents were contacted and asked to participate, while 15 could not be contacted. One parent who initially agreed to participate could not be reached subsequently to arrange a visit. Eight participants were interviewed in person, while the remaining 22 were interviewed via telephone. The questionnaire was available in English and Spanish, and interviews were conducted with a Spanish interpreter when necessary.

Before administering the questionnaire, the subjects received an information sheet explaining BPBP, the different microsurgical treatment options, the concept of randomization, and the purpose of this study. Specifically, the information sheet introduced the idea of two alternatives to sural nerve grafting. The first alternative, a processed allograft nerve, was described as “nerve tissue from a deceased human donor.” The second alternative, a nerve conduit, was described as “a man-made nerve tube.”

Once parents completed the questionnaire, demographic data was collected from the medical record and entered into a Research Electronic Data Capture (REDCap) database for statistical analysis [10]. REDCap is a secure, web-based application designed to support data capture for research studies, providing an interface for validated data entry, automated export procedures, and procedures for importing data from external sources.

This study was approved by our local institutional review board, and informed consent was obtained from all individual participants included in the study. Use of REDCap was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health (NIH), through grant UL1 TR000002.

## Results

Aggregate answers to the questions are listed in Table 1. When asked whether they would enroll their child in a research study of any kind, twenty-nine of 30 parents (97%) indicated that they would, while one indicated that she would not. Common themes to the free response portion of this question were identified and classified (Table 2). Nine parents would consider enrolling their child in a research study out of a desire to help their own child, while six indicated a desire to help other children. Three parents expressed a desire to increase the understanding of BPBP in general. Five parents gave other reasons or did not give a reason; several parents gave more than one reason (Figure 1).

When asked about whether they would be interested in a surgery that used an alternative to sural nerve harvest, twenty-five parents of 29 (86%) said they would consider such an alternative when the surgeon did not know which operation would be better for the child. One parent whose child underwent nerve transfers instead of sural nerve autograft did not answer the question, while the parents of two other children who did not have sural nerve autografts opted to answer, and indicated that they would prefer the operation that did not leave a scar. Four parents (14%) would not consider the alternative surgery. Of these four parents, two would choose whatever option the surgeon recommended, one would want more information about the outcome and the number of times the surgery had been performed at the hospital, and one gave no reason for declining. In total, four parents indicated discomfort with the use of alternate nerve sources—two with the use of synthetic nerves, one with the use of cadaveric nerves, and one with the use of both types. These parents cited unfamiliarity with synthetic and donor nerves and outstanding questions among the reasons for their discomfort.

As a follow up to this hypothetical situation, parents were asked for their opinion about another hypothetical scenario in which the alternate surgery was only available through an RCT. Of the 25 parents who initially indicated interest in the alternative surgery, 24 indicated a willingness to participate in this RCT. Common motivations included a desire to help their child, a desire to help future patients, and the lack of a leg scar. One of these 25 declined without giving a reason. The parent who initially declined this alternative option because he would want more education indicated that he would enroll his child because, if an RCT was taking place, he thought that enough positive information on the surgery would be available.

When asked what investigators could do to address the concerns of parents with respect to randomized clinical trials, the most common response was to provide as much information as possible regarding all of the potential treatment options included in the study. In general, parents wanted to know the risks and benefits, expected outcomes, sources of funding, and clinical success rates of the treatment arms.

Eleven parents provided additional comments; five expressed gratitude to the hospital for their child's care. Other comments included a recommendation for Caesarean section to prevent this type of injury; a request to physicians to value the benefits of physical therapy; suggestions for more conversations about realistic expectations of surgery and methods to develop trusting physician-patient relationships; an expression of happiness with the overall procedure; and comments on the importance of future research and prevention of BPBP.

## Discussion

The highest level of evidence is obtained from RCTs, but these are rarely performed in orthopaedic surgery. A 2003 study found that between 1966 and 1999, 671 out of 36,293 orthopaedic articles described RCTs (1.85%) [5]. Even rarer are pediatric surgical RCTs. Moss *et al.* identified 134 articles presenting the results of pediatric RCTs, comprising 0.17% of the 80,377 articles reviewed in their study. Similar to the findings of other studies, they identified patient / parent reluctance to enroll as a significant barrier to conducting these

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trials [6-8]. Specific barriers to patient enrollment and retention discussed by Campbell *et al.* included a lack of comprehension and support of randomization and participant burdens due to lengthy office visits. These barriers, they concluded, decrease the accuracy and validity of studies, and, therefore, should be minimized.

Prospective preference assignment, a method for improving the efficiency of RCTs, was described in 2002 [9]. Prospective preference assignment entails interviewing potential study participants prior to officially enrolling them in order to evaluate their motivations, thus providing information useful for maximizing enrollment. We used a variation of this technique of prospective preference assignment to assess parental willingness to enroll their child in a hypothetical surgical RCT, and found that 83% were willing to do so. In contrast, Campbell and colleagues tracked enrollment statistics for an RCT comparing the outcomes of three treatment options for hemiplegic upper extremity cerebral palsy, including one surgical and two non-surgical treatments [6]. Twenty-seven of 65 (42%) of the eligible patients approached agreed to participate. Ten out of the 37 (27%) potential patients who refused cited not wanting randomization of their child's treatment as their reason for refusing. Only one parent responding to our questionnaire cited a similar concern. This may suggest that parents are more willing to accept randomization between different surgical treatments than randomization between surgical and non-surgical treatments. It also may suggest that while parents will respond positively in a hypothetical situation, the response rate to an actual study may be much lower.

Another explanation for parents' willingness to participate in our hypothetical RCT is that they did not fully understand the concept of randomization. Although we initially explained this concept, we did not test their understanding of it. Our finding that nine parents would enroll their child in a trial in order to help their child directly supports this conclusion.

This study has weaknesses. These include a small sample size that may obscure differences between populations. However, among our study group, we had reasonable response rate of 65%, which indicates that our results may at least accurately reflect the opinions of this population.

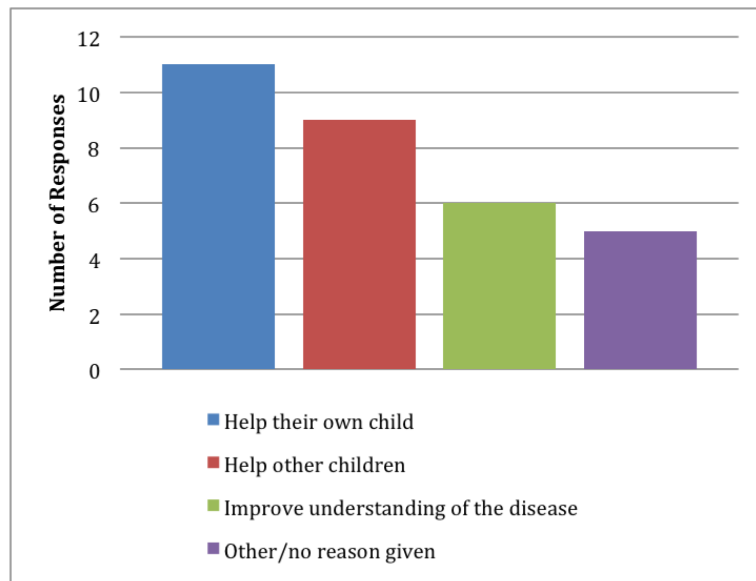
Another weakness is the potential for selection bias, since we chose to study a population of parents whose children had already undergone surgery. Our rationale was to query parents who were more likely to understand the difficult process of surrogate surgical decision-making. However, these parents had grown to trust our institution and surgeons (five parents indicated gratitude towards the hospital for the care provided to their child). Their gratitude may have contributed to their willingness to participate in this hypothetical RCT. We attempted to minimize this bias by using a researcher who was not part of their child's care team.

Asking a parent to enroll their child in an RCT is not an easy task. Patients desire treatment options, yet they want a medical professional to provide an expert opinion [6, 11]. Randomization removes choice and recommendation and is thus a strong barrier to enrollment. As a result, accruing subjects remains a challenge in pediatrics. A thorough discussion is a critically important part of the recruitment process. This discussion should

focus on education on the concept of randomization, included treatment arms, potential risks, and expected outcomes, while simultaneously addressing common parental concerns. We believe that designing a study with specific input from parents will better address these concerns; however, it is apparent that the concept of randomization is difficult for parents to apply to their child. In order to obtain true informed consent, it may be necessary to not only explain this concept, but to test parents on their understanding of it before obtaining consent. Although randomization may be the “gold standard” for obtaining information about the effects of treatment, this methodology is difficult for parents to reconcile with their need to trust their surgeon to provide the best treatment for their child.

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**Fig. 1. Reasons for Enrollment in a Research Study of Any Kind**

Reasons given by parents for agreeing to participate in a research study. The numbers displayed here are higher than total study numbers because some parents chose more than 1 reason for participating.

**Table 1**

## Responses to Questionnaire

	Yes	No
Would you ever consider enrolling your child in a research study of any kind?	29 (96.7%)	1 (3.3%)
If you had the option of a different surgery to improve your child's arm and hand function without a scar on the leg, but the surgeon did not know which surgery was better for your child, would you consider it? <sup>a</sup>	25 (86.2%)	4 (13.8%)
If this other surgery were available to you and your child ONLY if you participated in a randomized clinical research study, would you be part of the study? <sup>b</sup>	24 (88.9%)	3 (11.1%)

<sup>a</sup>Only 27 children underwent sural nerve harvesting and therefore had scars on their legs.

<sup>b</sup>Not all participants responded to this question.



**Table 2**

Illustrative quotes of reasons for enrollment

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Help their own child	“Anything to help my son.”
Help similarly affected children	“Because it could help other children.”
Increase the understanding of BPBP	“We may be able to learn from it.”

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