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# BRIEF REPORT
# The Benefits and Challenges of Preconsent in a Multisite, Pediatric Sickle Cell Intervention Trial

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Enrollment of patients in sickle cell intervention trials has been challenging due to difficulty in obtaining consent from a legal guardian and lack of collaboration between emergency medicine and hematology. We utilized education and preconsent in a pediatric multisite sickle cell intervention trial to overcome these challenges. Overall, 48 patients were enrolled after being preconsented. Variable Institutional Review Board policies related to preconsent validity and its allowable duration decreased the advantages of preconsent at some sites. The utility of preconsent for future intervention trials largely depends on local Institutional Review Board policies. Preeducation may also benefit the consent process, regardless of site differences. Pediatr Blood Cancer 2016;63:1649–1652. © 2016 Wiley Periodicals, Inc.

**Key words:** consent; preconsent, pediatric hematology/oncology; sickle cell disease

## INTRODUCTION

Intervention trials in children with sickle cell disease (SCD) hospitalized for acute pain are frequently hindered by several barriers to enrollment. These barriers have resulted in the early termination of studies due to poor enrollment,[1–3] potentially delaying advances in treatment. One barrier is the ability to obtain consent, particularly at night and during weekends, due to limited research staff availability.[2,3] Additionally, waiting for legally authorized representatives (LARs) to be available on the inpatient floor instead of completing consent in the emergency department (ED) can delay or preclude consent.[4,5] Another barrier is a lack of trust between families and providers,[3,6–8] which is accentuated by the lack of a relationship between emergency medicine physicians and families. Minority families in particular may have preexisting mistrust of research that can only be mitigated by a provider with whom the family shares a strong relationship.[9,10] Stress associated with the ED environment can be tense and upsetting for families,[11] who may be unwilling or unable to focus on research studies.[12] Finally, obtaining assent in children with SCD after they received opioids may be problematic due to decreased levels of consciousness and attention.[13,14]

Preconsent—informed consent given in advance of an eligible ED visit—has been suggested as a way to overcome these barriers.[6,15,16] Children with SCD and other chronic conditions are seen, accompanied by an LAR, at regular intervals in the outpatient setting. Thus, clinic visits represent an opportunity to educate families about an ongoing study in a controlled environment, outside of the stressful ED. Preconsent may then facilitate enrollment for inpatient clinical trials. We incorporated a preconsent process in a multisite, randomized clinical trial conducted within the Pediatric Emergency Care Applied Research Network. In the intravenous Magnesium for Sickle Cell Vasoocclusive Crisis (MAGiC) trial,[17,18] the preconsent process was jointly conducted by research staff from the ED and investigators in hematology who had an established relationship with patients with SCD and their families. Here, we describe our

Abbreviations: ED, emergency department; IRB, Institutional Review Board; LAR, legally authorized representative; MAGiC, Intravenous Magnesium for Sickle Cell Vasoocclusive Crisis; SCD, sickle cell disease

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preconsent process, the benefits and challenges of preconsent in the MAGiC study, and suggest key items to consider when deciding whether to preconsent in future intervention trials. Institutional Review Board (IRB) approval was obtained as part of the parent trial.

## METHODS

In the MAGiC study, four of eight enrolling sites adopted a preconsent process. The other four sites cited past experience, an understanding of the limits of preconsent gained from participating sites, and resource limitations as factors for declining to institute a preconsent process.

The preconsent process was similar across the sites. Sites worked with their hematology clinics to identify patients likely to be eligible based on inclusion/exclusion criteria (e.g., HbSS or HbS$\beta^0$ genotype, not on chronic transfusion therapy, no history of stroke) or frequency of recent hospitalizations. The preconsent process was identical to the standard consent with the exception that the preconsent introduction was given by the clinic hematologist as opposed to the enrolling research staff in the ED. In both scenarios, the introduction was followed by a full, informed-consent discussion and signing of the consent document. When a preconsented child returned for an eligible ED visit, willingness to participate was verbally confirmed and key study procedures reviewed. All signed consents were kept in the ED, so information was readily accessible.

## RESULTS

In total, all eight sites randomized 208 patients into the trial.[8] Among the four preconsenting sites, 177 (77%) of all approached patients were first approached for consent in the ED, whereas 53 (23%) were previously preconsented (Table I). Of the 177 patients who were not preconsented, 72 (41%) were randomized compared to 48 (91%) of the preconsented patients ($P < 0.001$).

Altogether, sites preconsented 134 patients: 48 (36%) were subsequently approached and randomized, five (4%) were approached but did not wish to be randomized at that time, and the remaining 81 (60%) never had a qualifying ED visit during the study period. Preconsented patients comprised 23% of all randomized patients and 40% (48/120) of randomized patients among the preconsenting sites. Analysis by time of day revealed that 33% (16/48) of the preconsented patients presented between 10 pm and 6 am compared to 38% (27/72) of patients who were not preconsented ($P = 0.641$). The percentage of preconsented patients who were subsequently enrolled ranged by site from 24 to 56%.

A major finding reported by site research staff was IRB variability in the duration of the validity of the signed preconsent document. At the two sites with the most stringent IRB consent requirements, signed consents expired at the annual continuing review, even if the consent had been signed only 1 month before. This expiration forced these sites to reconsent if not enrolled prior to the date of the continuing review. This made preconsenting in the last quarter of the year unlikely to yield successful preconsent. Additionally, one of these sites' IRBs invalidated all signed preconsents if any part of the protocol was updated, even if it did not change the consent form, while the other site invalidated all preconsents if any part of the consent form changed. IRBs at the two remaining sites considered signed consents to be valid until the subject reached the age of majority as long as no significant changes occurred in the risks/benefits or study procedures. Finally, there were institutional differences related to the need for LAR presence at subsequent enrollment after preconsent. At one site, the LAR needed to be in the ED to sign an additional, shorter consent form prior to randomization (although no patients were actually unable to enroll due to this restriction), whereas, at the other three sites, enrollment was allowed without an LAR.

Among the two sites with the greatest number of preconsented subjects, 18 of 70 (25.7%) patients at the site with the more stringent IRB were randomized compared to 14 of 32 (43.8%) patients at the less stringent site ($P = 0.069$). Both sites had a similar proportion of their preconsented patients randomized on nights/weekends. The number of preconsented patients across sites reflected the size of the sickle cell program at each site.

## DISCUSSION

In a multisite, sickle cell intervention trial, preconsent in the clinical setting provided a means to address several barriers to enrollment in the ED. In this study, preconsent facilitated enrollment in the absence of an LAR, highlighted to families the collaboration between ED and hematology, and provided a comfortable, less stressful, setting in which to obtain consent.

When comparing randomization rates between those preconsented and not, the proportion of preconsented patients who were randomized was more than double that of those who were not preconsented, with more than 90% of approached preconsented subjects being randomized into the trial. By comparison, a recently completed treatment trial of acute SCD pain crisis by Telen et al. randomized 76 patients during 31 months of enrollment across 22 sites, averaging 0.11 patients per site per month.[19] The MAGiC study randomized 208 patients during 36 months across eight sites, averaging 0.73 patients per site per month.

Approaching families at clinic visits as part of the MAGiC preconsent process was also a form of preeducation. The study was introduced by the hematologist and consent discussions occurred with the research staff. Even if consent was not obtained, families were educated about the study and general research concerns may have been eliminated. While preconsent is a longer and more thorough process than preeducation, preconsent may not be worthwhile at all sites.

Local IRB policies greatly influenced the degree to which sites were able to benefit from the preconsent process. Although not statistically significant, the difference in randomization rates between the two sites with the most stringent and most flexible IRB consent policies highlights the importance of the IRB when evaluating the potential effectiveness of preconsent.

We believe that preconsent is a valuable strategy to address barriers to enrollment in sickle cell acute intervention trials. However, investigators should have a clear understanding of the regulatory requirements adopted by their local IRBs to determine whether that particular site would benefit from a preconsent process.

**TABLE I. Number of Subjects Approached and Randomized by Site**

| Site | Consent type | Approached[1], n | Randomized, n (% of approached) |
|---|---|---|---|
| Site A | Standard | 79 | 25 (31.6) |
| | Preconsent | 22 | 18 (81.8) |
| Site B | Standard | 35 | 20 (57.1) |
| | Preconsent | 15 | 14 (93.3) |
| Site C | Standard | 42 | 16 (38.1) |
| | Preconsent | 7 | 7 (100.0) |
| Site D | Standard | 21 | 11 (52.4) |
| | Preconsent | 9 | 9 (100.0) |
| Site E | Standard | 52 | 28 (53.8) |
| Site F | Standard | 60 | 24 (40.0) |
| Site G | Standard | 49 | 23 (46.9) |
| Site H | Standard | 19 | 13 (68.4) |

[1]Approached at an eligible ED visit (additional subjects approached for preconsent at each of the four preconsenting sites are not included because these subjects never had a subsequent eligible visit).

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